SECTION 1

Symptomatology

**Chapter 1. Dysphagia**

Dysphagia, originating from the Greek words ‘dys’ (difficulty) and ‘phagia’ (to eat), refers to the sensation that food is stuck in its passage from the mouth to the stomach. Dysphagia becomes more common with age and affects up to 15% of persons aged more than 65 years.

Definitions

1. **Dysphagia** is the perception of impediment to the normal passage of swallowed material. Dysphagia refers either to the difficulty someone may have with the initiation of a swallow (usually described as oropharyngeal or "high" dysphagia) or to the sensation that foods and/or liquids are somehow being obstructed in their passage from the mouth to the stomach (usually described as oesophageal or "low" dysphagia).

2. **Odynophagia** is painful swallowing.

3. **Globus sensation** is a sensation of a lump lodged in the throat.

4. **Heartburn** is a sensation of burning discomfort behind the breastbone.

Types of Dysphagia

1. **Oropharyngeal dysphagia (transfer dysphagia)**

Oropharyngeal dysphagia refers to difficulties in the passage of food from the mouth to the oesophagus and is also known as transfer dysphagia. Oropharyngeal dysphagia occurs due to either mechanical or neuromuscular disorders that affect the pharynx and upper oesophageal sphincter. Dysphagia occurs within 1 sec of swallowing and is associated with cough, nasal twang, nasal regurgitation, dysarthria or hoarseness of voice.

2. **Oesophageal dysphagia**

Oesophageal dysphagia refers to disorders in the passage of a bolus from the upper oesophagus to the stomach. Oesophageal dysphagia occurs due to either mechanical or neuromuscular disorders that affect the oesophageal body. Patients are able to initiate the swallowing but complain of difficulty in transporting food down the oesophagus. In young patients, oesophageal dysphagia is most often caused by peptic stricture, eosinophilic oesophagitis and corrosive ingestion. In older people, it is usually caused by oesophageal cancer, peptic stricture, stricture following ablative therapy for Barrett's oesophagus.

Causes

Oropharyngeal Dysphagia

In young patients, oropharyngeal dysphagia is often caused by muscle diseases, webs or rings. In older people, neuro-logical disorders like stroke, Parkinson disease and dementia are responsible for majority of causes of oropharyngeal dysphagia. Within 3 days of stroke, 42–67% of patients present with oropharyngeal dysphagia. Among these patients, half aspirate and one-third develop pneumonia that requires treatment. The severity of dysphagia is directly proportionate with the severity of the stroke. Up to 50% of Parkinson patients show some symptoms consistent with oropharyngeal dysphagia and while around 95% are found to have abnormalities on video esophagography.

Oesophageal Dysphagia

In young patients, oesophageal dysphagia is most often caused by peptic stricture, eosinophilic esophagitis and corrosive ingestion. In older people, it is usually caused by oesophageal cancer, peptic stricture and stricture following ablative therapy for Barrett's oesophagus **(Table 1.1)**. Rates of reflux-induced stricture have been decreasing across the globe as proton-pump inhibitors became widely available. Eosinophilic oesophagitis is increasingly being recognized as a major cause of dysphagia both in children and adults.

Odynophagia

Odynophagia results from either oropharyngeal lesions (e.g., malignancy, foreign body ingestion or mucosal ulceration) or oesophageal lesions (e.g., corrosive ingestion, infections, radiation oesophagitis or mucosal ulcerations secondary to pill oesophagitis).

ClinicaL History

It is very vital to differentiate oropharyngeal dysphagia from oesophageal dysphagia. Dysphagia occuring within 1 sec

of swallowing or swallowing associated with coughing, drooling, aspiration or nasal regurgitation suggests oropharyngeal dysphagia. While dysphagia occuring more than 1 sec after swallowing associated with retrosternal pain or regurgitation of unchanged food suggests oeso-phageal dysphagia. Once oesophageal dysphagia is suspected, the history helps to differentiate mechanical causes of dysphagia from neuromuscular causes of dysphagia **(Table 1.2)**.

**Oropharyngeal Dysphagia Mechanical Obstruction**

Retropharyngeal abscess Benign stricture

Zenker diverticulum Neoplasm

Cricopharyngeal bar Webs and rings

Cervical oesophagus Vascular compression

**Neuromuscular Disorders Motility Disorders**

Cerebrovascular stroke Achalasia cardia

Parkinson's disease Spastic oesophagus

Motor neuron disease Scleroderma

Polymyositis Chagas disease

Myasthenia gravis

**Miscellaneous Miscellaneous**

Sjogren syndrome Diabetes

Alzheimer disease Gastroesophageal reflux

Mediastinal abnormality

1. ***Type of food causing dysphagia***

n Dysphagia to solids suggests mechanical obstruction.

n Dysphagia to liquids and solids suggests motility disorders.

n Structural lesions of the esophagus usually produce solid food dysphagia with progression to liquid dysphagia once luminal narrowing becomes severe.

2. ***Progressive or intermittent***

n Progressive dysphagia - Neoplasm, peptic stricture

n Intermittent dysphagia - Mucosal ring/web, eosino-philic oesophagitis

3. ***Location***

n Poor sensitivity to localize the site of pathology

n Usually the lesion is at or below the perceived location of dysphagia.

4. ***Aggravating factors***

n Dysphagia aggravated by either hot or cold liquids indicates spastic oesophageal disorder.

5. ***Relieving factors***

n Dysphagia relieved by repeated swallowing, raising the arm over the head or Valsalva manoeuvre indicates motility disorder.

6. ***Associated features***

n Heartburn indicates reflux disease or scleroderma.

n Angina-like chest pain indicates diffuse oesophageal spasm.

n Swallowing with a gurgling noise, swelling in the neck and coughing of food debris may indicate the presence of a Zenker diverticulum.

n Nocturnal regurgitation with cough or chest infection indicates achalasia cardia.

n Significant weight loss, anorexia or rapidly worsening dysphagia favours oesophageal malignancy as the likely cause.

n Hoarseness of voice is secondary to recurrent laryngeal nerve dysfunction.

n Odynophagia following ingestion of pills like doxy-cyline, aspirin and potassium suggests pill oesophagitis.

Physical Examination

1. Patients over 40 yrs, thin built with pallor indicates malignancy.

2. Koilonychia suggests postcricoid web as the cause of dysphagia (Plummer-Vinson syndrome).

3. Careful inspection of mouth, pharynx and neck mainly for motor and sensory function of the cranial nerves, masses, adenopathy or spinal deformity.

4. Oral thrush suggests candidial infection as a cause of dysphagia or odynophagia.

5. Signs of bulbar or pseudobulbar palsy mainly in patients with suspected oropharyngeal dysphagia.

6. CREST syndrome for scleroderma.

7. Left supraclavicular lymph node indicates malignancy.

8. Hepatomegaly in case of suspected oesophageal cancer suggests liver metastasis.

9. Respiratory system examination for evidence of aspiration pneumonia in case of oropharyngeal dysphagia and suspected tracheo-esophageal fistula secondary to oesophageal malignancy.

**Major tests for evaluating oropharyngeal dysphagia are**:

1. ***Video fluoroscopy****, also known as the "modified barium swallow"*

n This is the gold standard for evaluating oropharyngeal dysphagia.

n Swallowing is recorded on video during fluoroscopy, providing details of the patient's swallowing mechanics.

n It may also help to predict the risk of aspiration pneumonia.

n Video fluoroscopic techniques can be viewed at slower speeds or frame by frame and can also be transmitted via the internet even at remote places.

2. ***Upper endoscopy***

n Nasoendoscopy is the gold standard for evaluating structural causes of dysphagia, e.g., lesions in the oropharynx and inspection of pooled secretions or food material.

n It is not a sensitive investigation of detecting abnormal swallowing function.

n It fails to identify aspiration in 20–40% of cases when followed up with video fluoroscopy, due to the absence of a cough reflex.

3. ***Fibreoptic endoscopic evaluation of swallowing (FEES)***

n FEES is a modified endoscopic approach that involves visualizing the laryngeal and pharyngeal structures through a transnasal flexible fibreoptic endoscope while food and liquid boluses are given to the patient.

4. ***Pharyngoesophageal high-resolution manometry***

n This is a quantitative evaluation of the pressure and timing of pharyngeal contraction and upper oesophageal relaxation.

n It can be used in conjunction with video fluoroscopy to allow a better appreciation of the movement and pressures involved.

n It may have some value in patients with oropharyngeal dysphagia despite a negative conventional barium study.

n It may be useful when surgical myotomy is being considered.

5. ***Automated impedance manometry (AIM)***

n This is a combination of impedance and high-resolution manometry.

n Pressure-flow variables derived from automated analysis of combined manometric/impedance measurements provide valuable diagnostic information.

n When they are combined to provide a score on the swallow risk index (SRI), these measurements are a robust predictor of aspiration.

6. ***Water swallow test***

n It involves the patient drinking 150 mL of water from a glass as quickly as possible, with the examiner recording the time taken and number of swallows. The speed of swallowing and the average volume per swallow can be calculated from these data. It is reported to have a predictive sensitivity of >95% for identifying the presence of dysphagia, and it may be complemented by a "food test" using a small amount of pudding placed on the dorsum of the tongue.

**Major tests for evaluating oesophageal dysphagia are**:

1. **Barium contrast oesophagram (barium swallow)**

n Barium oesophagrams taken with the patient supine and upright can outline irregularities in the oesophageal lumen and identify most cases of obstruction, webs and rings.

n A barium examination of the oropharynx and oesophagus during swallowing is the most useful initial test in patients with a history or clinical features suggesting a proximal oesophageal lesion.

n Oesophageal disorders like primary achalasia **(Fig. 1.1)** diffuse oesophageal spasm **(Fig. 1.2)** and complexity of corrosive oesophageal stricture **(Fig. 1.3)** can be diagnosed with barium swallow study.

n A timed barium oesophagram is very useful for evaluating achalasia before and after treatment.

2. **Endoscopic evaluation**

n High-resolution video endoscopy can be used to detect subtle changes, such as the typical whitish islands in eosinophilic oesophagitis.

n Oesophageal malignancy **(Fig. 1.4)**, corrosive stricture **(Fig. 1.5)**, peptic oesophageal stricture **(Fig. 1.6)** and oesophageal rings **(Fig. 1.7)**, post cricoid web **(Fig. 1.8)** can be identified easily.

n Biopsy can be taken by video endoscopy in case of confirmation of the diagnosis of eosinophilic oesopha-gitis, oesophageal neoplasm, Barrette's oesophagus, etc.

n Mediastinal lymph node compression can be diagnose via endoscopic ultrasound (EUS) examination

3. **Conventional and high-resolution manometry (HRM) oesophageal manometry**

n Manometry is indicated when an oesophageal cause of dysphagia is suspected after an inconclusive barium swallow and endoscopy.

n The three main causes of dysphagia that can be diagnosed using oesophageal manometry are achalasia, scleroderma and oesophageal spasm.

n Performed either solid-state or perfusion techniques.

n High-resolution manometry (HRM, up to 36 pressure sensors spaced 1 cm) of the oesophagus is a new technique that provides a more precise assessment of oesophageal motility than conventional techniques (widely spaced sensors). HRM uses a high-resolution catheter to transmit intraluminal pressure data that are subsequently converted into dynamic oesophageal pressure topography (EPT) plots. The standard HRM protocol consists of a baseline phase and a series of 10 wet swallows in the supine or reclined position.

n The Chicago Classification (CC, version 3.0) diagnostic algorithmic scheme allows hierarchical categorization of esophageal motility disorders.

CC has clarified the diagnosis of achalasia and of distal oesophageal spasm.

n High-resolution impedance manometry (HRIM) catheters embed impedance sensors between high-resolution circumferential pressure sensors, enabling concurrent assessment of bolus transit in relation to manometric changes.

4. **Radionuclide oesophageal transit scintigraphy**

n Little value in era of video endoscopy and high-resolution manometry.

n The patient swallows a radiolabeled liquid (e.g., water mixed with technetium Tc-99m sulfur colloid or radiolabeled food), and the radioactivity in the oesophagus is measured.

Management of Oropharyngeal dysphagia

The goals of treatment are to improve the movement of food and drink and to prevent aspiration. The cause of the dysphagia is an important factor in the approach chosen.

The management of complications is of paramount importance. In this regard, identifying the risk of aspiration is a key element when treatment options are being considered. For patients who are undergoing active stroke rehabilitation, therapy for dysphagia should be provided to the extent tolerated. Simple remedies may be important, e.g., pros-thetic teeth to fix dental problems, modifications to the texture of liquids and food stuffs or a change in the bolus volume.

1. **Swallowing rehabilitation and re-education**

n Appropriate postural, nutritional and behavioural modifications can be suggested. Relatively simple manoeuvres during swallowing may reduce oropharyngeal dysphagia.

n Specific swallowing training includes strengthening exercises and biofeedback by a specialist in swallowing disorders.

2. **Nutrition and dietary modifications**

n Softer foods, possibly in combination with postural measures, are helpful.

n Oral feeding is best whenever possible. Modifying the consistency of food to thicken fluids and providing soft foods can make an important difference.

n Adding citric acid to food improves swallowing reflexes, possibly due to the increased gustatory and trigeminal stimulation provided by acid.

n Adjuvant treatment with an angiotensin-converting enzyme inhibitor to facilitate the cough reflex may also be helpful.

3. **Alternative nutritional support**

n A fine-bore soft feeding tube passed down under radiological guidance should be considered if there is a high risk of aspiration or when oral intake does not provide adequate nutritional status.

n Percutaneous endoscopic gastrostomy (PEG) involves passing a gastrostomy tube into the stomach via a percutaneous abdominal route under guidance from an endoscopist, and if available this is usually preferable to surgical gastrostomy.

n Jejunal tube feeding should be used in the acute setting and percutaneous gastrostomy or jejunostomy tube feeding in the chronic setting.

4. **Surgical treatments** aimed at relieving the spastic causes of dysphagia, such as cricopharyngeal myotomy, have been successful in up to 60% of cases, but their use remains controversial. On the other hand, open surgery and endoscopic myotomy in patients with Zenker diverticulum is a well-established therapy.

Management of Oesophageal dysphagia

Management of oesophageal dysphagia is directly towards the aetiology. Management of various aetiologies has been discussed in various chapters.

Grading of Dysphagia

n Ia Able to take all foods

n Ib Able to take soft foods

n II Able to take blenderized foods

n III Able to take clear liquids only

n IV Not able to swallow even saliva

Physiology of Swallowing

The act of swallowing has four phases **(Fig. 1.9)** viz:

1. Oral preparation phase

2. Oral transfer phase

3. Pharyngeal phase

4. Oesophageal phase

An abnormality of any of the phases results into dysphagia. The entire process of swallowing is organized in the nucleus tractus solitarii (NTS) and the neighbouring reticular substance. Motor neurons involved in the swallowing sequence lie in the trigeminal, facial and hypoglossal nuclei (for oropharyngeal phase), the nucleus ambiguus of the vagus (for oesophageal striated muscle) and dorsal motor nucleus of vagus (DMNV, for oesophageal smooth muscle).

Pattern of OEsophageal Peristalsis

1. **Primary peristalsis**: Propulsion of food bolus into the stomach with minimal resistance.

2. **Secondary peristalsis**: Propulsive oesophageal body contractions generated by retained food in the oesophagus.

3. **Tertiary contractions**: Uncoordinated, non-propulsive motor activity that is observed in neuromuscular oesophageal disease.

Further Reading

1. Blackwell Z, Little Johns P. A review of the management of dysphagia: a South African perspective. *J Neurosci Nurs* 2010;42:61–70.

2. Spechler SJ. AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology* 1999;117:233–54.

3. Lind CD. Dysphagia: evaluation and treatment. *Gastroenterology Clin North Am* 2003;32:553–75.

4. Cook IJ, Kahrilas PJ. AGA technical review on management of oropharyngeal dysphagia. *Gastroenterology* 1999; 16:455–78.

5. Chen CL, Orr WC. Comparison of esophageal motility in patients with solid dysphagia and mixed dysphagia. *Dysphagia* 2005;20:261–5.

**Chapter 2.**

**Nausea and Vomiting**

Nausea and vomiting are one of the common manifestations of systemic illness. They are common and distressing symptoms with a number of underlying causes. Control of the primary disease activity improves symptoms of nausea and vomiting.

Definitions

1. **Nausea** is unpleasant sensation of being about to vomit.

2. **Vomiting (emesis)** is the forceful expulsion of gastrointestinal contents due to contractions of gut and thoraco-abdominal wall musculature. Retching differs from vomiting in the absence of expulsion of gastric content.

3. **Regurgitation** is the effortless return of gastroesophageal contents into the mouth.

4. **Rumination** is the repeated regurgitation of stomach contents, which are often re-chewed and then re-swallowed.

5. **Hiccups** are recurring, involuntary spasm of the diaphragm associated with characteristic sound due to violent sucking of air through approximated vocal cords.

6. **Early satiety** is the sensation of gastric fullness before a meal is completed.

Causes

1. Gastrointestinal disorders: Peptic ulcer disease, bowel obstruction, gastroparesis, hepatitis, cholecystitis, appendicitis, pancreatitis, gastroenteritis.

2. Drugs: NSAID, chemotherapeutic agents, digoxin, antibiotics, theophylline, etc.

3. Systemic illness

4. Sepsis, myocardial infarction, renal failure, electrolytes imbalance.

5. Central nervous system: Head trauma, raised intracranial pressure, epilepsy, stroke, meningitis, motion sickness.

6. Endocrine disorders: Diabetes, Addison’s disease, thyrotoxicosis.

7. Psychogenic vomiting

Clinical History

1. **Onset**

n Acute onset vomiting indicates infections, drugs, toxins, head trauma or visceral pain.

n Chronic vomiting indicates partial mechanical obstruction, motility disorders, endocrinopathy, metabolic disorders, brain tumour or psychogenic cause.

2. **Relation to meals**

n Vomiting within 5 min after food indicates psychogenic vomiting.

n Vomiting more than 1 hr after food suggests gastro-paresis or gastric outlet obstruction.

n Vomiting of materials eaten 12 hrs before indicates gastric outlet obstruction or proximal small bowel obstruction.

3. **Time of day**

n Early morning vomiting indicates pregnancy, uraemia, alcoholism or raised intracranial pressure.

4. **Associated abdominal pain**

n Relief of abdominal pain by vomiting suggests antral or small bowel obstruction.

n Vomiting has no effect on pancreatitis, appendicitis or cholecystitis pain.

5. **Content of vomitus**

n Bilious vomiting excludes gastric outlet or proximal duodenal obstruction.

n Old food in the vomitus suggests gastric outlet obstruction or severe gastroparesis.

n Undigested food indicates achalasia or Zenker diverticulum.

n Presence of blood indicates peptic ulcer disease, malignancy or portal hypertensive bleeding.

n Voluminous acidic vomiting suggests gastrinoma.

n Feculent odour indicates distal intestinal or colonic obstruction, bacterial overgrowth or gastrocolic fistula.

6. **Projectile vomiting**

n Vomiting without hypersalivation or nausea indicates raised intracranial pressure or pyloric obstruction.

7. **Associated symptoms**

n Fever indicates systemic infection or inflammation.

n Weight loss indicates malignancy or gastric outlet obstruction. Patient with psychogenic vomiting usually maintains stable weight.

n Headache, altered mentation, convulsion or diplopia indicate intracranial cause for vomiting.

n Vertigo, tinnitus and deafness indicate vestibular dysfunction.

n Abdominal distension, abdominal pain and constipation indicate small bowel obstruction.

n Prior abdominal surgery indicates mechanical obstruction or post gastrectomy syndrome.

n History of nonsteroidal anti-inflammatory drugs.

Physical Examination

1. Assessment of intravascular fluid loss.

2. Fever suggests inflammation or infection.

3. Loss of dental enamel in oral cavity examination suggests bulimia.

4. Icterus indicates hepatobilliary disease.

Abdominal Examination

1. Abdominal distension indicates ileus or intestinal obstruction.

2. Abdominal tenderness is noted in inflammation, infection and luminal distension.

3. A succussion splash on side-to-side movement is found in gastric outlet obstruction and gastroparesis.

4. Look for any mass, hepatomegaly or splenomegaly.

5. An absence of bowel sounds indicates ileus, whereas hyperactive, high-pitched bowel sounds with a distended abdomen suggests mechanical intestinal obstruction.

Neurological Examination

1. Impaired mentation, focal neurological deficit, neck stiffness and papilledema suggest central nervous system disease.

2. Autonomic and peripheral neuropathy may be associated with gastrointestinal motility disorders.

Diagnostic Procedures

1. ***Blood chemistry***

n Leucocytosis indicates inflammation, whereas anaemia is due to either blood loss or chronic inflammation.

n Hypokalaemia and elevated blood urea nitrogen with normal creatinine in patient with dehydration.

n Metabolic alkalosis may result from loss of hydrogen ions in the vomitus and contractions of the extracellular space from dehydration.

n Other endocrine and metabolic parameters in suspected cases.

n Amylase, lipase and liver chemistry in suspected pancreatic or hepatobilliary disorders.

2. ***Imaging studies***

n Plain radiograph of abdomen shows small intestinal air-fluid levels with absent colonic air suggests obstruc-tion, while diffuse distension indicates ileus.

n Ultrasound abdomen or spiral CT abdomen for suspected hepatobilliary and pancreatic disorders.

n Contrast radiography of small intestine (barium meal follow through or enteroclysis) for partial obstruction; it may precipitate acute obstruction.

3. ***Endoscopy study***

n Upper endoscopy for suspected gastric outlet obstruction. Biopsy can be obtained from suspicious lesions during endoscopic procedure. Retained food in absence of obstruction indicates gastroparesis, whereas excessive gastric contents without any food indicates Zollinger-Ellison syndrome.

n Colonoscopic examination with biopsy may be needed in suspected ileocecal tuberculosis or Crohn’s disease causing luminal narrowing.

4. ***Functional studies***

n Functional studies are required once luminal obstruction is excluded by either endoscopy or barium study.

n Gastroparesis is diagnosed by delayed emptying of either solid (99mTC – sulphur colloids in eggs) or liquid (111In – DTPA in water) on scintigraphy.

n Electrogastrography (EGG) measures electrical pace-maker activity of the stomach through electrodes affixed to the abdomen.

n Antroduodenal manometry for suspected intestinal pseudo-obstruction.

Management

1. Intravenous fluid resuscitation is the most important in patients with moderate-to-severe dehydration secondary to persistent vomiting.

2. Threshold for hospitalization should be lower in chronic debilitating patients and very young or old patients.

3. Medical management for vomiting should be directed at the underlying illness.

4. Many patients benefit from medications that suppress vomiting (antiemetic and prokinetic agents; Chapter 60).

Drugs used to treat nausea and vomiting belong to either central antiemetic agents or peripheral prokinetic agents; some of these drugs share both actions. Commonly used central antiemetic agents are dopamine D2 receptor antagonist, anti-histamines and anti-muscarinic agents, and serotonin antagonists. Gastric prokinetic agents are serotonin 5HT4 receptor agonists and motilin receptor agonists.

Dopamine antagonists are metoclopramide, prome-thazine and prochlorperazine. This group of drugs are useful for migraine-associated nausea, postoperative nausea and vomiting and chemotherapy and radiotherapy-induced

nausea and vomiting. Selective serotonin antagonist are ondansetron, granisetron, dolasetron and are useful to control nausea and vomiting associated with radiotherapy or chemotherapy or following surgery or gastroenteritis. Antihistamines and anticholinergics are cyclizine, cinnarizine, meclizine and scopolamine (antimuscarinic agent) and are useful in vestibular mediated nausea and for motion sickness. Gastric prokinetic agents include serotonin 5HT4 receptor agonists and motilin receptor agonists. Cisapride, cinitapride and tegaserod are the examples of serotonin 5 HT 4 receptor agonists. Erythro-mycin is an example of motilin receptor agonist. Indications for erythromycin are to treat acute nausea and vomiting associated with gastroparesis (diabetic, postsurgical or idiopathic) and to clear the stomach of retained food, secretions and blood from the stomach before doing upper endoscopy.

Pathophysiology of Vomiting

Multiple afferent and efferent pathways exist, which induce vomiting; the following are the major components of these pathways:

1. The area postrema in the floor of the fourth ventricle, which contains a “chemoreceptor trigger zone (CTZ)” that is sensitive to many humoral factors, including neurotransmitters, peptides, drugs and toxins.

2. An area in the medulla known as the nucleus tractus solitarius (NTS), which may serve as a central pattern generator for vomiting; information from humoral factors via the area postrema and visceral afferents via the vagus nerve may converge at this site.

3. The central pattern generator presumably projects to the various motor nuclei to elicit the sequential excitation and inhibition that controls the vomiting reflex.

The presence of gastrointestinal and multiple non-gastro-intestinal trigger areas can result in vomiting with numerous disorders. Five principle neurotransmitter receptors mediate vomiting: muscarinic M1, dopamine D2, histamine H1,

5-hydroxytryptamine (5-HT3, serotonin) and neurokinin

1 (NK1, substance P).

Studies of vomiting in dogs reveal that gastric content is expelled as a result of gastric and lower oesophageal sphincter relaxation, retrograde contraction in the proximal small bowel and antrum, abdominal muscle contraction, and initial cricopharyngeus contraction followed by relaxa-tion seconds before vomiting. Retching occurs when the glottis closes and respiratory muscles counteract abdominal muscle contraction to prevent the expulsion of gastric content.

Gastric Outlet Obstruction

Pyloric stenosis can occur from malignancy or peptic ulcer disease. Inflammatory oedema associated with ulcers may

respond to acid suppression therapy and nasogastric suction. However, fibrotic strictures may persist after ulcer healing. Treatment of benign fibrotic strictures can be accomplished surgically or endoscopically. The endoscopic approach is the least invasive; however, there is a risk of perforation and recurrence is common after long-term follow-up if the natural history of the underlying ulcer disease is not altered. Periampullary neoplasm, eosinophilic duodenitis, and pancreatic fluid collections also can lead to gastric outlet obstruction.

Eosinophilic Gastroenteritis

Benign eosinophilic infiltration of the gut is uncommon, but its diagnosis is especially important as steroid therapy is usually effective. The disease can occur from the oesophagus to the colon, and the symptoms depend on the extent and layer(s) of bowel involved. Gastric mucosal disease is typically associated with nausea and vomiting.

Cyclic Vomiting Syndrome

Cyclic vomiting syndrome (CVS) is characterized by repeated episodes of nausea and vomiting that last for hours to days and is separated by symptom-free periods of variable length. It has been most often described in children in whom symptoms often begin in the early school years and stop spontaneously at puberty. In adults, the disorder consists of episodes of nausea and vomiting lasting for 3–6 days in a patient-specific stereotypic pattern.

Chronic Idiopathic Intestinal Pseudo-obstruction

Chronic intestinal pseudo-obstruction is usually secondary to an underlying disorder affecting neuromuscular function that suggests mechanical bowel obstruction of the small or large bowel in the absence of an anatomic lesion that obstructs the flow of intestinal contents.

Rumination Syndrome

The rumination syndrome is a behavioural disorder that is most commonly identified among mentally disadvantaged children although it is increasingly recognized among adolescents and adults of normal mental capacity. The behaviour consists of daily, effortless regurgitation of undigested food within minutes of starting or completing ingestion of a meal.

According to the Rome IV criteria, the diagnosis of rumination syndrome requires the presence of all of the

following for at least 3 months (with symptom onset at least 6 months prior to diagnosis):

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing.

2. Regurgitation is not preceded by retching.

Criteria that are supportive of rumination syndrome, but are not required, include the following:

n Effortless regurgitation events are usually not preceded by nausea.

n Regurgitant contains recognizable food that might have a pleasant taste.

n The process tends to cease when the regurgitated material becomes acidic.

Further Reading

1. Hasler WL, Chey WD. Nausea and vomiting. *Gastroenterology* 2003;125:1860.

2. American Gastroenterological Association. American Gastroenterological Association medical position statement: nausea and vomiting. *Gastroenterology* 2001; 120:261.

3. Scorza K, Williams A, Phillips JD, Shaw J. Evaluation of nausea and vomiting. *Am Fam Physician* 2007;76:76.

4. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. *Gastroenterology* 2016;150:1380.

5. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. *Am Fam Physician* 2004;69:1169–74.

**Chapter 3.**

**Abdominal Pain**

Acute abdominal pain is a common medical condition for which patients seek emergency medical care. Chronic abdominal pain is often challenging for the clinician. Chronic abdominal pain can be benign and self-limited or a harbinger of a serious life-threatening condition. Diagnosis of func-tional GI disorder is generally considered once potential causes of organic chronic abdominal pain have been confidently excluded.

Definitions

1. **Acute abdominal pain** - Pain of less than a few days duration that has worsened progressively until the time of presentation is clearly “acute.”

2. **Chronic abdominal pain -** Pain that has remained unchanged for months or years can be safely classified as chronic. It is a pain of unknown origin usually labeled after 6 months. Pain that does not clearly fit either category might be called subacute and requires consideration of a broader differential than acute and chronic pain.

3. **Primary hyperalgesia** *is the shift in the stimulus response curve, suggestive of decrease in the stimulus intensity to elicit response.*

Causes of Acute Abdominal Pain

Abdominal Causes

1. Abdominal wall

n Trauma or infection of muscle

n Traction of mesentery

2. Inflammation of parietal peritoneum

n Peritonitis secondary to perforated viscus

n Pancreatitis

n Cholecystitis

n Pelvic inflammatory diseases

3. Hollow viscera obstruction

n Small or large intestinal obstruction

n Biliary tree obstruction

n Ureteric obstruction

4. Vascular causes

n Thrombosis or embolism

n Vascular rupture

n Sickle cell anaemia

5. Distension of visceral surface

n Hepatic or renal capsules

6. Functional disorders

n Irritable bowel syndrome

n Functional dyspepsia

Metabolic Causes

1. Diabetic ketoacidosis

2. Porphyria

3. Lead poisoning

4. Uraemia

Extra-abdominal Causes

1. Coronary artery disease

2. Radiculitis

3. Torsion of testicle

4. Pneumonia, pulmonary infarction

5. Herpes zoster

Causes of Chronic or Recurrent Abdominal Pain

1. ***Structural diseases***

n Chronic pancreatitis

n Inflammatory bowel diseases

n Chronic mesenteric ischaemia

n Abdominal malignancies

n Pelvic inflammatory diseases

2. ***Functional disorders***

n Irritable bowel syndrome

n Functional dyspepsia

n Functional abdominal pain syndrome

n Functional biliary pain (gallbladder or sphincter of Oddi dysfunction)

Types of Pain

1. **Parietal pain**

n Parietal pain is steady and aching in character and is located directly over the inflamed area.

n Parietal pain is localized pain because of somatic nerve supplying parietal peritoneum.

n Pain of peritoneal inflammation is aggravated by pressure or changes in tension of the peritoneum. Thus, patient with peritonitis lies quietly in bed, as movement aggravates the pain.

3. **Visceral pain**

n Visceral pain is a dull, poorly localized pain as visceral supply is multisegmental.

n Visceral pain occurs due to stimuli to visceral noci-ceptors.

4. **Referred pain**

n Pain in areas remote to the diseased organ is called referred pain.

n Convergence–projection hypothesis of referred pain:

Convergence of both visceral afferent nociceptors and somatic structures on a single spinal segment of dorsal root ganglion.

n The brain has no way of knowing the actual source of input and mistakenly “projects” the sensation to the somatic structure.

n Thus pathology beneath diaphragm causes referred pain to shoulder and lower neck.

Clinical History

1. **Onset**

n *Abrupt onset*: Mesenteric infarction, perforated viscus, ruptured aortic aneurysm.

n *Acute onset*: Pancreatitis, appendicitis, cholecystitis, etc.

n *Chronic onset*: Chronic pancreatitis, irritable bowel syndrome.

2. **Site**: Site of abdominal pain and associated conditions are listed in **Table 3.1**.

Right upper Cholecystitis

quadrant Liver abscess

Left upper Splenic infarct

quadrant Colonic ischaemia

Inflammatory bowel disease

Pancreatic diseases

Central Pancreatitis

Biliary colic

Peptic ulcer disease

Intestinal colic

Right lower Appendicitis

quadrant Mesenteric adenitis

Amoebic colitis

Pelvic inflammatory disease

Inflammatory bowel disease

Left lower Diverticular disease

quadrant Inflammatory bowel disease

Pelvic inflammatory disease

Colonic ischaemia

3. **Characters**

n *Biliary colic*: It is a visceral pain, which is steady rather than intermittent, usually in the epigastrium and right upper quadrant, increases over a period of 15 min to 1 hr and then remains at plateau for 1 hr or more, and then slowly resolving within 6 hrs.

n *Pancreatic pain*: Dull, continuous pain mainly in epigastrium lasting for several hours, radiating to back, aggravated by food and relieved by sitting up or leaning forward.

n *Intestinal colic*: It is crescendo-decrescendo type of pain, poorly localized in periumbilical area and associated with nausea and vomiting.

n *Ureteric colic*: It is severe, colicky pain starting in the loin and radiates to groin, hypogastrium, genitalia or medial side of the thigh. This may be accompanied by burning micturition or hematuria.

n *Pain of gastric ulcer*: It is gnawing, burning or cramping in character, poorly localized in upper abdomen. It is aggravated by food and relieved on empty stomach or by antacids.

n *Pain of duodenal ulcer*: It is intense, burning or hunger like pain in upper abdomen. It is more on empty stomach and relieved by food.

4. **Aggravating factors**

n Pain of gastric ulcer and chronic mesenteric ischaemia is aggravated by food.

n Coughing and body movements aggravate pain of peritonitis.

n The pain of nerve root compression may worsen with some movement.

5. **Relieving factors**

n Sitting up and leaning forward position gives pain relief in patient with pancreatitis (exact reason is not known, but this position reduces pressure on celiac ganglion).

n Pain of duodenal ulcer is relieved by meal.

n Vomiting may give a transient relief of pain in intestinal colic.

n Passage of stool may reduce abdominal cramps in patient with colitis

6. **Associated symptoms**

n Vomiting is common associated symptom in many conditions like pancreatitis, cholecystitis, ureteric colic, appendicitis, intestinal obstruction, etc.

n Haematemesis indicates pain of peptic ulcer disease.

n Associated diarrhoea indicates acute gastroenteritis or inflammatory bowel disease.

n Associated jaundice suggests cholecystitis, pancreatic cancer or liver abscess.

Past medical, surgical and social history

1. Recurrence of a similar pain can often be seen in cases of nephrolithiasis, diverticulosis or gallstone disease. Acute abdominal pain in patients with a history of atrial fibrillation may be highly sensitive for mesenteric ischaemia.

2. Nonsteroidal anti-inflammatory drug (NSAID) use in elderly patients was associated with an increased risk of upper gastrointestinal (GI) bleeding or peptic ulcer.

3. Previous abdominal surgery may suggest small bowel obstruction as the cause for pain.

4. History of smoking puts patients at a higher risk of developing an abdominal aortic aneurysm. Illicit drug use is also an important risk factor associated with acute mesenteric ischaemia.

5. History of vaginal bleeding, discharge, prior ectopic pregnancies may be useful clues in diagnosis. Ectopic pregnancies have proven to be associated with a prior history of intrauterine device (IUD), history of infertility and tubal ligation.

General Examination

1. Patients who are pale, confused or in severe distress tend to have a more sinister pathology. Atypical presentations can be seen in certain patient populations such as elderly patients who might not mount an adequate clinical signs.

2. If patients appear ill with unstable vital signs, such as hypotension, volume resuscitation should be started immediately in conjunction with assessing for life-threatening pathologies requiring immediate surgical intervention.

- Fever: It is suggestive of infection or inflammation and may be absent in elderly and immunocomp-romised patients.

-Blood pressure: Hypotension may indicate sepsis, haemorrhage and severe dehydration.

- Heart rate: Tachycardia is suggestive of pain, sepsis, haemorrhage and volume depletion from third spacing and may be absent in patients on beta-blockers.

- Respiratory rate: Tachypnea can indicate metabolic acidosis with respiratory compensation or increased pain. Nonspecific findings are seen in cardiac/pulmonary diseases.

Abdominal Examination

Inspection

1. A proper and thorough inspection can give valuable clues.

2. Patients with peritonitis are usually quiet in the bed as

even slight movement exacerbates pain whereas patient with renal or intestinal colic is usually restless.

3. Scars of previous surgery should be noted, which indicate adhesion as a cause of intestinal obstruction.

4. “Step ladder” pattern of visible peristalsis indicates small bowel obstruction.

5. Periumbilical and flank discolouration by ecchymosis (Cullen’s and Gray Turner’s sign) indicates intraperitoneal haemorrhage. Vesicular rash in dermatome distribution indicates herpes zoster.

6. Inspection of hernial orifice may reveal femoral hernia as the cause of the intestinal obstruction.

7. In male patients, external genitalia should be examined as pain from testicular torsion or epididymitis may be referred to abdomen.

Palpation

1. Palpation should be performed gently, beginning with the quadrant most remote from the patient’s pain, moving towards the painful area.

2. Positive Murphy’s sign is supportive of a diagnosis of cholecystitis.

3. Rebound tenderness at McBurney’s point suggests appendicitis.

4. Generalized severe abdominal tenderness is indicative of diffuse peritoneal inflammation.

5. Significant abdominal pain in the absence of physical examination finding in an elderly person may be a clue to mesenteric ischaemia.

6. Carnett test: This test can distinguish intra-abdominal discomfort from abdominal wall pain. Increased tenderness upon raising the head or testing abdomen suggests superficial abdominal wall source.

7. Psoas sign: Positive if pain is elicited with passive hip extension.

8. Obturator sign: Positive if pain is elicited with passive internal/external rotation of the right hip.

9. Rovsing sign: Positive if pain is elicited in RLQ when the examiner exerts pressure on the LLQ.

Auscultation

1. Bowel sounds are probably the least helpful in majority of cases, because reflex ileus can occur with virtually all painful abdominal conditions.

2. High-pitched, tinkling bowel sounds are suggestive of small bowel obstruction.

3. Silent abdomen indicates generalized peritonitis.

4. An abdominal bruit suggests potential vascular pathology.

Digital Rectal/Vaginal Examination

1. A rectal examination should be performed in all cases. It is especially useful in acute GI bleed, colon cancer, intussusceptions, ischaemic colitis, perirectal abscess, rectal foreign body, stool impaction.

2. In women, a pelvic examination should be performed to check for pelvic masses, cervical motion tenderness and discharge.

3. Presence of blood on rectal examination raises the possibility of malignancy, ischaemia, ulcer or inflammation. Perianal fistulae, fissures and abscess suggest Crohn’s disease. Right-sided tenderness on rectal examination may indicate appendicitis.

Diagnostic Procedures

1. ***Biochemistry***

n Leucocytosis indicates inflammation, whereas anaemia may be secondary to gastrointestinal blood loss or lead poisoing (normocytic, normochronic).

n Elevated sedimentation rate is secondary to inflammation.

n Renal profile including electrolytes to assess fluid status.

n Hyperamylasemia is seen in pancreatitis, viscus perforation and mesenteric ischaemia. Lipase estimation is more specific for pancreatitis.

n Liver profile for suspected hepatobilliary diseases.

n Diagnostic paracentesis in the presence of ascites to exclude spontaneous bacterial peritonitis.

2. ***Abdominal plain radiography***

n Supine and upright abdominal plain radiography is essential in all patients with acute abdominal pain.

n Pneumoperitoneum indicates hollow viscus perforation, whereas multiple air-fluid level suggests small intestinal obstruction.

n Plain radiograph also detects calcified gallstones, renal stones and pneumobilia.

3. ***Ultrasound abdomen/CT scan***

n Ultrasound abdomen is very useful for detection of cholelithiasis, biliary dilatation, ectopic pregnancy, ascites and ovarian cyst.

n CT scan abdomen is more sensitive for pancreatic disease, retroperitoneal collections, inflamed or ischaemic intestinal wall and choledocholithiasis.

4. ***Other imaging studies***

n EUS, ERCP and MRI may give complementary information.

n ERCP is very useful in patients with choledo-cholithiasis and cholangitis.

n Diagnostic laparoscopy can be performed when with all non-invasive modalities fail to reach the diagnosis.

Differential diagnosis of unstable patient

1. GI bleed

2. Ruptured abdominal aortic aneurysm

3. Massive pulmonary embolism

4. Perforated viscus

5. Ruptured ectopic pregnancy

Management

1. Management is towards specific cause.

2. As functional abdominal pain or irritable bowel syndrome has no cure, all efforts should be directed to enhance the good quality of life. Low-dose tricyclic antidepressant, non-opiod analgesic and mebevirine might help in these patients.

Who Require Urgent/Emergent Evaluation

Patients in whom there are concerns for life-threatening causes of abdominal pain should be referred to the emergency department.

These include those with:

1. Unstable vital signs

2. Signs of peritonitis on abdominal examination (e.g., abdominal rigidity, rebound tenderness and/or pain that worsens when the examiner lightly bumps the stretcher).

3. Concern that the abdominal pain is from a life-threatening condition (e.g., acute bowel obstruction, acute mesenteric ischaemia, perforation, acute myocardial infarction, ectopic pregnancy).

These patients may require analgesics, which can be administered without compromising their assessment.

Pathophysiology of Pain

Gastrointestinal viscera are relatively insensitive to stimuli such as light touch, cutting or even burning compared to somatic structure. Two stimuli for gastrointestinal viscera:

1. Noxious: Actual damage to the organ or tissue.

2. Nociceptive: Reflex response resulting in the pain response.

Two types of fibres (nociceptors):

1. Unmyelinated: C-polymodal class (PMNs) fibres – sensitive to mechanical, chemical or thermal stimuli; located in muscle layer, serosa and mesentery.

2. A-delta fibres: Myelinated fibres, respond mainly to mechanical or thermal stimuli, located in the mucosa.

*During inflammatory states, C-fibres also occur in mucosa.*

Neural pathway of abdominal pain involves three levels, which are as follows **(Fig. 3.1)**:

1. First-order neurons from the viscus, pass via sympathetic ganglia into dorsal horn of the spinal cord.

2. Second-order neurons arise from dorsal horn of spinal cord and cross to opposite side, and in lateral columns, run upwards in spinothalamic and spinoreticular tract. They terminate in PVL (posteroventrolateral) nucleus of thala-mus and reticular formation.

3. Third-order neurons from thalamus to somatosensory cortex (sensory-discriminative components) and from reticular formation to limbic system connecting anterior cingulated gyrus and frontal cortex (motivational-affective component).

n Visceral peritoneum is supplied by C-fibres and parietal peritoneum is by A -type of fibres. Most common stimulus for pain in hollow viscus is stretch. In intestine, biliary tract and ureter, sensory fibres are found within the muscular wall. Distension of the hollow viscus or forceful muscular contraction will lead to pain.

n In solid organs like liver, nociceptive fibres are limited to the capsule of the liver. So mass of the liver usually does not cause pain, until it is increases in size causing stretching of Glisson capsule or traction on the organ.

Functional abdominal pain

Functional abdominal pain and functional abdominal pain syndrome in children (Rome III) has now been substituted

for Functional Abdominal Pain-Not Otherwise Specified

in Rome IV criteria. The frequency required for pain is changed from weekly to 4 times a month to align with other functional abdominal pain disorders (FAPD).

Centrally Mediated Disorders of Gastrointes-tinal Pain (Rome IV)

This category includes two disorders: **centrally mediated abdominal pain syndrome (CAPS)**, formerly in Rome III, functional abdominal pain syndrome, and the new **narcotic bowel syndrome/opiate-induced hyperalgesia**.

**Centrally mediated abdominal pain syndrome** has a strong central component and relative independence from motility disturbance or evidence for visceral hypersensi-tivity. Symptom-related behaviour in patients with CAPS that can facilitate their identification include the expression of pain of varying intensity through verbal and nonverbal methods, urgent reporting of intense symptoms, minimizing a potential role for psychosocial contributors, frequently seeking for health care, request for narcotic analgesics, focusing their attention on complete symptom relief, taking limited personal responsibility for self-management and requesting diagnostic studies. CAPS is typically associated with psychiatric comorbidities, but there is no specific profile that can be used for the diagnosis, and some degree of gastrointestinal dysfunction may be present.

**Narcotic bowel syndrome/opiate-induced gastro-intestinal hyperalgesia** is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids.

Gallbladder and Sphincter of Oddi Disorders

This category includes biliary pain, functional gallbladder disorder and functional biliary sphincter of Oddi disorder. Biliary pain can occur in the absence of recognized organic causes and some patients are cured by removal of the gallbladder or ablation of the sphincter.

Abnormal biliary manometry and hepatobiliary scintigraphy are helpful to support the diagnosis.

Abdominal Migraine

Diagnostic Criteria\*

*Must include* ***all*** *of the following*:

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hr.

2. Intervening periods of usual health lasting weeks to months.

3. The pain interferes with normal activities.

4. The pain is associated with two of the following:

n Anorexia

n Nausea

n Vomiting

n Headache

n Photophobia

n Pallor

5. No evidence of an inflammatory, anatomic, metabolic or neoplastic process considered that explains the subject’s symptoms.

\*Criteria fulfilled two or more times in the preceding 12 months.

**Abdominal pain mimics**: Medical conditions that abdo-minal pain without abdominal abnormality can be a diagnostic challenge.

Diabetic Hypercalcaemia Sickle cell

ketoacidosis Porphyria disease

Angioedema Henoch-Schonlein Systemic lupus

purpura erythematosus

Polyarteritis Mushroom Alcohol

nodosa intoxication intoxication

Metal poisoning Opioid withdrawal Atypical acute

coronary syndrome

Pulmonary Congestive heart Herpes zoster

embolism failure

Abdominal Heat stroke

epilepsy

Further Reading

1. Lyon C, Clark DC. Diagnosis of acute abdominal pain in older patients. *Am Fam Physician* 2006;74:1537.

2. Bender J. Approach to the acute abdomen. *Med Clin North Am* 1989;73:1413.

3. Drossman DA. Chronic functional abdominal pain. *Am J Gastroenterol* 1996;91:2270–81.

**Chapter 4. Dyspepsia**

Dyspepsia is a heterogeneous group of symptoms located in the upper abdomen. There is overlap of symptoms of peptic ulceration, reflux disease and gastric dysmotility. The most prevalent causes underlying dyspeptic symptoms are PUD and GERD. The term uninvestigated dyspepsia refers to dyspeptic symptoms in persons in whom no diagnostic ingestions tests have yet been performed.

Definitions

1. **Dyspepsia** is defined as discomfort centered in the upper abdomen characterized by abdominal fullness, early satiety, bloating or nausea.

2. **Definition of Functional dyspepsia (Rome IV Criteria)**: Patients with one or more of the following symptoms including; 1, bothersome postprandial fullness, 2, early satiation, 3, epigastric pain, and 4, epigastric burning for the previous 3 months with symptom onset at least 6 months prior to diagnosis are told to have functional dyspepsia, if they have no evidence of structural disease, including upper endoscopy that can explain their symptoms.

3. **Uninvestigated dyspepsia**: There are the patients with dyspepsia in whom no diagnostic investigation has yet been performed and in whom a specific diagnosis that explains the dyspeptic symptoms has not been determined.

Causes

1. Gastrointestinal tract disorders

n Peptic ulcer disease

n Gastric or esophageal neoplasm

n Gastroparesis

n Irritable bowel syndrome

n Malabsorption

n Infiltrative disorders

2. Pancreaticobiliary disorders

n Cholelithiasis

n Chronic pancreatitis

n Pancreatic or gallbladder neoplasm

3. Systemic disorders

n Diabetes mellitus

n Thyroid and parathyroid disorders

n Renal and heart failure

4. Drugs

n NSAIDs

n Antibiotics

n Steroids

n Iron

n Diuretics

Clinical History

1. Onset: Acute onset of dyspepsia indicates food intolerance, medications, peptic ulcer disease.

2. Age: Age more than 45 years indicates more chances of organic cause of dyspepsia.

3. Recent change in character of chronic symptoms suggests organic cause of dyspepsia.

4. Alarming symptoms like weight loss, bleeding, dysphagia or protracted vomiting suggest organic etiology for dysphagia.

5. Associated with abdominal pain indicates pancrea-ticobiliary or infiltrative gastrointestinal disorders.

6. Medications and dietary history.

Physical Examination

1. The physical examination in patients with dyspepsia is usually normal, except for epigastric tenderness. The presence of epigastric tenderness cannot accurately distinguish organic dyspepsia from functional dyspepsia. Abdominal tenderness on palpation should be evaluated with the Carnett sign to determine if it is due to pain arising from the abdominal wall rather than due to inflammation of the underlying viscera. The presence of increased local tenderness during muscle tensing (positive Carnett’s sign) suggests the presence of abdominal wall pain. However, if the pain is decreased (negative Carnett’s sign), the origin of pain is not from the abdominal wall and likely from an intra-abdominal organ, as the tensed abdominal wall muscles protect the viscera.

2. Pallor suggests organic cause for dyspepsia.

3. Signs of malabsorption syndrome in case of suspected chronic pancreatitis, a cause of dyspepsia.

4. Lymph nodes in left supraclavicular fossa suggests gastrointestinal tumour, a cause of dyspepsia.

5. Thorough abdominal examination to identify case of dyspepsia.

Diagnostic Procedures

Usually diagnostic procedures are not required in all dyspepsia patients. Age more than 45 yrs, alarming symptoms such as anorexia, weight loss or anaemia merits ingestions to identify the cause of dyspepsia. Routine biochemical tests, abdominal sonogram and upper endoscopic evaluation are frequently ordered tests for patients with dyspepsia.

Test and treat for *Helicobacter pylori*

The rationale for *H. pylori* testing in patients with dyspepsia is based on the recognition of *H. pylori* as an aetiologic factor in peptic ulcer disease. Testing for *H. pylori* should be performed with a urea breath test or stool antigen assay. Serologic testing should not be used due to their low positive predictive value.

Patients who test positive for an infection with *H. pylori* should undergo treatment with eradication therapy. Most dyspeptic patients who are *H. pylori* positive and who are treated with appropriate antibiotic therapy persist with dyspeptic symptoms; the number needed to treat to successfully relieve dyspeptic symptoms is estimated at 1 in 14.

Management

Options for a patient who do not have risk factors for organic dyspepsia includes the following:

1. Do a diagnostic endoscopy

2. Use non-invasive test for *H. pylori*

3. Use empirical antisecretary medications

Management of Functional Dyspepsia

Try following measures in patients with mild or intermittent symptoms:

1. Reassurance and education is very essential.

2. Make a confident and positive diagnosis.

3. Eat small meals more frequently.

4. Avoid meals with high fat content.

5. Discourage spicy food.

6. Reduce coffee consumption.

7. Avoid smoking and alcohol.

8. Avoid NSAID and aspirin.

9. Treat anxiety and depression if present.

Drug therapy can be tried in patients with severe symptoms or for those who do not respond to reassurance and lifestyle changes.

1. **Acid suppression therapy** - A Cochrane review has studied the efficacy of acid suppressants in functional dyspepsia. Twelve randomized controlled trials of H2 antihistamines versus placebo found that these drugs

were effective for the treatment of functional dyspep-sia. Ten trials studied PPIs. Again, there was a significant benefit over placebo although this was modest. There was significant heterogeneity between studies, with no obvious explanation, but no funnel plot asymmetry. A subgroup analysis conducted according to predominant symptom showed that PPIs were most beneficial in patients with reflux-type symptoms and more effective than placebo in patients with epigastric pain. However, they were no more effective than placebo in those with dysmotility-like functional dyspepsia.

2. ***H. pylori* eradication** - The benefit of eradication therapy is less pronounced in functional dyspepsia than in peptic ulcer disease, but treatment is still more effective than placebo. In a Cochrane review of 21 placebo-controlled trials, the Number Needed to Treat (NNT) for improvement in symptoms after eradicating *H. pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry.

3. Try **prokinetic agents** with good safety record for patients with postprandial fullness and early satiation. Therapy with a single drug is preferable than combining PPI with prokinetic agent.

4. Trial of **low-dose tricyclic antidepressant** can be considered in patients who fail above measures.

**High-dose tricyclic antidepressant** can be tried if they have features of anxiety or depression.

5. A **referral to psychiatrist or psychologist** should be arranged for patients with obvious co-existing psychiatric illness, a history of physical or sexual abuse.

Newer drugs

Drugs that can improve gastric fundal relaxation and that modify the visceral analgesia are newer concepts in the treatment of functional dyspepsia. Many of such drugs are still investigational drugs.

Pathophysiology of dyspepsia

Approximately 70–80% of patients with epigastric pain have functional dyspepsia. Although the causes of this disorder have not been completely understood thus far, gastro-duodenal dysmotility and sensitivity to both distension and acid have been proposed as the possible causes of this disorder. Functional dyspepsia is a multifactorial disease, and thus, any individual treatment is effective only in a small proportion of patients.

The causes of the central nervous system abnormalities, dysmotility and hypersensitivity seen in patients with functional dyspepsia are poorly understood. Several hypotheses have been proposed, including a subtle increase

in the levels of inflammatory mediators in the upper gastro-intestinal tract. Results of recent studies indicate that an increase in the number of eosinophils in the duodenum is responsible for the various conditions associated with functional dyspepsia. Thus, increase in immune activation and inflammation may cause neuromodulation that leads to dysmotility, hypersensitivity and changes in the central nervous system. The cause of this immune activation is uncertain, but it is most likely to be an infective process. Among the various infective agents, *Helicobacter pylori* infection may lead to immune activation of the upper gastrointestinal tract. This finding is consistent with the finding that dyspepsia is more common after an episode of acute gastroenteritis.

Classification and diagnostic criteria

The Rome IV criteria define functional (idiopathic or nonulcer) dyspepsia as the presence of one or more of the following: postprandial fullness, early satiation, epigastric pain or burning and **no**evidence of structural disease to explain the symptoms. These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis and a frequency of at least 3 days per week.

Postprandial Distress Syndrome

Diagnostic Criteria\*

*Must include* ***one or both*** *of the following*:

1. Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week.

2. Early satiation that prevents finishing a regular meal, at least several times per week.

\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Supportive Criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present.

2. Epigastric pain syndrome may coexist.

Epigastric Pain Syndrome

Diagnostic Criteria\*

*Must include* ***all*** *of the following:*

1. Pain or burning localized to the epigastrium of at least moderate severity, at least once per week

2. The pain is intermittent

3. Not generalized or localized to other abdominal or chest regions

4. Not relieved by defecation or passage of flatus

5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Supportive Criteria

1. The pain may be of a burning quality, but without a retrosternal component.

2. The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting.

3. Postprandial distress syndrome may coexist.

Further Reading

1. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; 127:1239–55.

2. Talley NJ, American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005;129:1753.

3. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006;4:CD001960.

4. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in non-ulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004;127:1329–37.

5. Nicholas J Talley, Alexander C Ford. Functional dyspepsia. *N Engl J Med* 2015;373:1853–1863.

6. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology* 2016;150:1380.

**Chapter 5.**

**Diarrhoea**

Diarrhoea is a universal human experience particularly in developing and under-developed world. Majority of acute diarrhoea are self-limiting. But some cases of diarrhoea last for more than few days or is complicated by signs of inflammation like abdominal pain, fever, arthropathy, skin lesions and rectal bleeding. Three or more bowel movements per day is considered as abnormal. Upper limit of stool weight in Western countries is around 200 g/day.

Definitions

1. **Diarrhoea** is defined as an increase in the frequency, decrease in stool consistency and increase in stool volume.

2. **Acute diarrhoea** refers to an illness of less than 2 weeks duration.

3. **Chronic diarrhoea** refers to an illness of greater than 4 weeks duration.

4. **Steatorrhea** is an increase in stool fat excretion of >7% of dietary fat intake.

5. **Maldigestion** is defined as defective hydrolysis of nutrients.

6. **Malabsorption** is defined as a defective mucosal absorption.

Causes

Acute Diarrhoea

1. Infection

n Bacteria

n Virus

n Protozoa

2. Drug induced

n Clindamycin

n Ampicillin

n Amoxicillin

n Colchicine

n Aminophylline

n Cephalosporines

Chronic Diarrhoea

Common causes are listed in **Table 5.1**.

**Chronic Watery Diarrhoea**

**Osmotic diarrhoea Secretory diarrhoea**

n Osmotic laxative n Bacterial toxins

(e.g., Mg2+, PO43-) n Bile acid malabsorption

n Lactose n Inflammatory bowel

malabsorption disease

n Stimulant laxatives

n Vasculitis

n Disordered motility

- Diabetic diarrhoea

- Post vagotomy

- Irritable bowel

syndrome

n Endocrine diarrhoea

- Gastrinoma

- Hyperthyroidism

- VIPoma

- Carcinoid syndrome

n Tumours

- Colon carcinoma

- Villous adenoma

n Idiopathic secretory

diarrhoea (Brainerd’s

diarrhoea)

**Chronic inflammatory diarrhoea**

n Inflammatory bowel disease

n Infectious colitis

- Pseudomembranous colitis

- CMV infection

- Tuberculosis

n Radiation colitis

**Chronic fatty diarrhoea**

***Maldigestion***

n Pancreatic exocrine dysfunction

n Inadequate luminal bile acid

***Malabsorption***

n Diffuse mucosal diseases

n Bacterial over growth syndrome

n Ischemic colitis

n Short bowel syndrome

Pathophysiology

Diarrhoea is the reversal of the normal process of absorption of water and electrolytes in the gastrointestinal tract. Such a reversal may be because of an osmotic force that acts in the lumen to drive water into the gut or the result of an active secretory state induced in the enterocytes. Osmotic diarrhoea occurs after the ingestion of non-absorbable disaccharides like lactulose and sorbitol or lactose in lactose malabsorbers. In osmotic diarrhoea, the stool output is proportional to the intake of the unabsorbable substrate and is usually not massive; diarrhoeal stools promptly regress with discontinuation of the offending nutrient, and the stool ion gap is high, exceeding 100 mOsm/kg. The ion gap is obtained by subtracting the concentration of the electrolytes from total osmolality (assumed to be 290 mOsm/kg), using the following: ion gap = 290 – [(Na + K) × 2].

In secretory diarrhoea, the ion transport processes in the epithelial cells are turned into a state of active secretion. The most common cause of acute-onset secretory diarrhoea is a bacterial infection of the gastrointestinal tract. Several mechanisms are involved in this process. After colonization, enteric pathogens may adhere to or invade the epithelium and produce enterotoxins. The pathogens also trigger the release of cytokines, which, in turn, contribute to the activated secretion by inducing the release of agents such as prostaglandins or platelet-activating factor. Features of secretory diarrhoea are high diarrhoeal output, a lack of response to fasting and a normal stool ion gap (i.e., 100 mOsm/kg or less). Nutrient absorption is usually intact in secretory diarrhoea.

Clinical History

1. Onset of diarrhoea

n Abrupt diarrhoea indicates acute gastroenteritis.

n Insidious onset diarrhoea more favours the case of chronic diarrhoea.

2. Duration of diarrhoea

3. Character of stool

n It is very important to know whether stool is watery, bloody or fatty (steatorrhea).

n Large, pale, bulky stool requiring frequent flushing in toilet suggests steatorrhea. Sometimes patient may give history of oil drops in the stool.

4. Small bowel versus large bowel diarrhoea

n It is important to know whether diarrhoea is small bowel or large bowel diarrhoea.

n Large quantity, offensive stool associated with steatorrhea without blood or tenesmus suggests small bowel diarrhoea. Patients with small bowel diarrhoea have periumbilical pain.

n Small, frequent, non-offensive stool with blood and tenesmus suggests large bowel diarrhoea. Patients with large bowel diarrhea have hypogastric pain.

5. Floating of stool in the toilet water indicates high fat content or high gas content.

6. Explosive diarrhoea (passage of stool with excess gas) is classical of carbohydrate malabsorption.

7. Diarrhoea improving with fasting indicates osmotic diarrhea.

8. Abdominal pain

n Presence of abdominal pain is suggestive of inflammatory bowel disease, ischaemia or irritable bowel syndrome.

n Periumbilical pain suggests small bowel involvement while hypogastric pain suggests large bowel involvement.

9. Fever and weight loss suggest inflammatory bowel disease, lymphoma or infections like tuberculosis.

10.Previous surgery to gastrointestinal tract.

11.Clinical history of systemic disease like diabetes, thyroid disease and autoimmune diseases.

12.History of current medications, alcohol and caffeine used by the patients should be noted.

13.A detailed dietary history is important in chronic diarrhoea with special attention to “artificial sweetener,” fibre intake, fruit juices.

14.Factitious diarrhoea caused by surreptitious laxative ingestion should be considered in every patient with diarrhoea.

Physical Examination

Following may be observed in patients with acute diarrhoea:

1. **Dehydration**

n Dehydration is the most important aspect in acute diarrhoea.

n Assess severity of dehydration in every patient with acute diarrhoea.

n Signs of dehydration: Poor skin turgor, dry mucous membranes, sunken eyes, lethargy, depressed consciousness, sunken anterior fontanel in children, lack of tears and delayed capillary refill.

2. **Borborygmi**: Significant increases in audible or palpable peristaltic activity.

3. **Perianal erythema**

n Frequent stools can cause perianal skin breakdown, particularly in young children.

n Secondary carbohydrate malabsorption often results in acidic stools.

n Secondary bile acid malabsorption can result in a severe diaper dermatitis that is often characterized as a “burn.”

**Physical examination for chronic diarrhoea is described Ch. 30**.

Skin Changes in Chronic Diarrhoea

1. Carcinoid syndrome – Flushing

2. Celiac sprue – Dermatitis herpetiformis

3. Mastocytosis – Urticaria pigmentosa

4. Addison’s disease – Hyperpigmentation

5. Amyloidosis – Waxy papule

6. Glucagonoma – Migratory necrolytic erythema

Diagnostic Procedure

Diagnostic procedures are discussed in detail in Ch. 30. In the present chapter, only discussion about stool examination is given.

Stool Analysis

Stool analysis (either spot stool sample analysis or quantitative stool collection tests) is one of the most important investigations in patients with chronic diarrhoea.

Spot Stool Analysis

1. **Stool leucocytes** - Presence of fecal leucocytes indicates enteroinvasive infection. Presence of fecal leukocytes eliminates possibility of enterotoxigenic *E. coli*, vibrio species and viruses.

2. **Qualitative fat estimation**

n Sudan III stain identifies the presence of fecal fat in semi-quantitative way.

n Method: A sample of stool is placed on a glass slide to which few drops of glacial acetic acid and Sudan III stain are added (glacial acetic acid improves fat extraction and separation of the lipid layers). The slide is heated to boiling and examined while still warm for presence of orange fat globules.

n Up to 100 globules with a diameter less than 4 µm per high-power filed are considered to be normal.

n This test has sensitivity of 78% and specificity of 70%.

n Stool steatrocrit test has not been evaluated in patients with chronic diarrhoea.

3. **Fecal culture** - Fecal culture is not indicated routinely in immunocompetent patients as bacterial infection rarely causes chronic diarrhoea.

4. **Rotavirus and adenovirus antigens** can be identified by enzyme immunoassay and latex agglutination assay of the stool. Presence of blood in the stool leads to high false-negative rate.

5. **Tests for protozoa** - Fecal ELISA test for Giardia-specific antigen and detection of Strongyloides larvae and cysts and ova of *E. histolytica.*

6. **Fecal pH** – Fecal pH less than 5.3 indicates carbohydrate malabsorption.

7. **Fecal osmotic gap** – Formula to calculate osmotic gap:

Osmotic gap = 290 – 2 (Na+ + K+)

n <50 mOsm indicates secretory diarrhoea

n >125 mOsm indicates osmotic diarrhoea

Quantitative Stool Collection

1. Quantitative estimation of fecal fat (van de Kamer method)

n A 72-hr quantitative stool collection test is the gold standard for evaluating steatorrhea.

n Steatorrhea is defined as excretion of fat more than 7 g/day on a 100 g/day fat diet. In the presence of diarrhoea, value more than 14 g/24 hrs is considered significant.

2. Analysis for laxative – Analysis for laxative should be done in all patients of diarrhoea of unknown origin.

Management

Acute Diarrhoea

1. **Fluid resuscitation** is the most important treatment in severe diarrhoea, diarrhoea in infants and in elderly patients. Oral rehydration treatment (ORT, **Table 5.2**) is the mainstay of therapy in patients with mild-to-moderate dehydration, whereas intravenous crystalloids are indicated in patients with severe dehydration. ORT with a glucose-based oral rehydration solution is the most physiologic way to provide rehydration and maintain hydration in children with acute diarrhoea. The ideal ORT solution has a low osmolarity (210–250 mmol/L) and low sodium (50–60 mmol/L) content. Not all commercial ORT formulas promote optimal absorption of electrolytes, water and nutrients.

2. **Zinc supplementation** is very important in children with viral diarrhoea.

3. Antibiotics are indicated for cholera, salmonellosis, shigellosis and traveler’s diarrhoea. Probiotics and prebiotics have little role to play in the management of acute diarrhea in adult.

4. **Bismuth subsalicylates (BSSs)** can be administered to control the rates of passage of stool and may alleviate bouts of mild-to-moderate illness in patients with travelers’ diarrhoea. In patients receiving antibiotics for traveler’s diarrhoea, adjunctive loperamide therapy can be administered to decrease the duration of diarrhoea and improve the chances of curing the diarrhoea.

**Composition 1975 2003**

Sodium 90 75

Potassium 20 20

Chloride 30 30

Base 80 80

Glucose 111 75

Osmolarity >300 245

5. **Rifaximin**: Nonabsorbed (< 0.4%), is a broad-spectrum antibiotic specific for enteric pathogens of the gastrointestinal tract (i.e., gram-positive, gram-negative, aerobic and anaerobic). Rifaximin is indicated in patients with *Escherichia coli* (enterotoxigenic and enteroag-gregative strains)-associated travelers’ diarrhoea.

6. **Viral diarrhoea** does not require any specific therapy.

7. **Loperamide** and **diphenoxylate** are the commonly used as antimotility drugs. Loperamide has lesser central opioid effects than diphenoxylate. Further, diphenoxylate combines with atropine, which has no antidiarrhoeal effectiveness and may have undesirable side effects. Loper-amide exerts its effect via two mechanisms; the first inducing segmental contraction of the gut, which slows the intraluminal movement of fluids and enables increased absorption. Second mechanism includes inhibition of calmodulin, which leads to reduced mucosal secretion. The recommended dose of loperamide for adults with diarrhoea is 4 mg initially followed by 2 mg. Loperamide in combination with an antibacterial drug is very useful in the self-treatment of traveler’s diarrhoea; the combination is very effective because the antibacterial drug decreases the number of diarrhoea stools passed and the antibiotic agent cures the enteric infection.

8. **Starch-based ORT**: Contains starch instead of glucose, which produces a “slow release” effect of the glucose molecules. Starch-based ORT acts when the enzyme amylase (the secretion of which is not affected in diarrhoea) cleaves the starch (glucose polymer) into glucose.

Vaccines

1. **Rotavirus vaccine**: Rotavirus vaccine (RotaTeq) is a pentavalent vaccine that contains 5 live reassortant rotaviruses and is administered as a 3-dose regimen against G1, G2, G3 and G4 serotypes, the 4 most common rotavirus group A serotypes.

In addition, this vaccine contains attachment protein P1A (genotype P).

RotaTeq is administered in a 3-dose series starting from the age of 6–12 weeks and the treatment is completed before the age of 32 weeks.

2. ***Salmonella typhi* vaccine** is recommended for individuals travelling to countries with a high risk of infection. Live-attenuated, killed whole-cell and capsular polysaccharide vaccines of *S. typhi* are available.

3. ***Vibrio* species vaccine** is available, but this vaccine protects only 50% of immunized persons for 3–6 months. Thus, use of this vaccine is not indicated.

Chronic Diarrhoea

1. Management of chronic diarrhoea is directed to the underlying cause.

2. Lactose restriction in lactase deficiency, gluten-free diet in celiac disease, appropriate therapy for IBD, pancreatic enzyme supplementation for chronic pancreatitis, long-term antibiotics and folic acid for tropical sprue and octreotide for hormone-secreting tumours (like carcinoid, VIPoma, etc).

3. The opiate derivatives like loperamide, diphenoxylate and codeine are the most common non-specific agents used in patients with diarrhoea.

4. Low dose of tricyclic antidepressant or serotonin antagonist for diarrhoea predominant IBS.

Clinical Classification of Chronic Diarrhoea

Clinical history and stool examination define the type of diarrhoea, thus help the clinician to make a roadmap for further evaluation of the aetiology of diarrhoea.

1. **Osmotic vs secretory diarrhoea**

n Osmotic diarrhoea comprises small number of patients with chronic diarrhoea. But for clinician it is important to know the osmotic type of diarrhoea to avoid unnecessary workup for secretory diarrhoea. Osmotic diarrhoea usually ceases with fasting. Measurement of fecal electrolytes and fecal osmotic gap is the most important diagnostic test to confirm osmotic diarrhoea.

n Leading causes of osmotic diarrhoea are ingestion of magnesium salts, lactulose, artificial sweetener like sorbitol, lactose by lactase-deficient individuals.

n Infection is the most common cause of secretory diarrhoea.

2. **Watery vs fatty vs inflammatory diarrhoea**: This is the most useful classification of chronic diarrhoea, based on gross appearance of stool and simple laboratory testing.

n Watery diarrhoea is characterized by its fluidity and the absence of blood or pus. It is due to defect in water absorption (secretory diarrhoea) or ingesting of poorly absorbed substances (osmotic diarrhoea).

n Fatty diarrhoea (steatorrhea) is characterized by greasy, bulky and often light colored stools, due to defective digestion or absorption of fat in the small intestine.

n Inflammatory diarrhoea is characterized by the presence of blood and pus, due to inflammatory or neoplastic process in the gut.

3. **Painless versus painful small bowel diarrhoea** **(Tables 5.3 and 5.4)**: Chronic diarrhoea with abdominal pain and without abdominal pain helps to identified probable aetiology of chronic diarrhoea.

Tropical sprue Thyrotoxicosis

Celiac sprue MCT, VIPoma, somatostatinomas

Lactase deficiency Abetalipoprotenemia

Osmotic diarrhoea Lymphangietasia

Villous adenoma Diabetic diarrhoea

**Infective Inflammatory Malignancy others**

Tuberculosis IBD Lymphoma IBS

Giardiasis Whipple’s Carcinoid Addison’s disease disease

*C. jejuni* Eosinophilic Zollinger-

gastroenteritis Ellison

syndrome

*Yersinia* IPSID

Strogylodosis Ulcerative

jejunoileitis

Further Reading

1. Mark S Riddle, Herbert L DuPont, et al. Connor. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. *Am J Gastroenterol* 2016;111:602–22.

2. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice Guidelines for the Management of Infectious Diarrhea. *Clin Infect Dis* 2001;32:331–51.

3. Farthing M, Salam MA, Lindberg G, et al. Acute diarrhea in adults and children: a global perspective. *J Clin Gastroenterol* 2013;47:12–20.

4. Operario DJ, Houpt E. Defining the causes of diarrhea: novel approaches. *Curr Opin* *Infect Dis* 2011;24:464–71.

**Chapter 6.**

**Constipation**

Chronic constipation is a common medical issue. The prevalence of constipation is higher in women than in men (2:1) and the prevalence increases with age. In the past, constipation was often defined solely by reduced stool frequency (e.g., <3 bowel movements/week). Constipation is a syndrome that is defined by bowel symptoms (difficult or infrequent passage of stool, hardness of stool or a feeling of incomplete evacuation) that may occur either in isolation or secondary to another underlying disorder such as a degenerative neurological disease.

Classifications of Constipation

Based on Duration

1. **Acute constipation**: Adynamic ileus often accompanies acute intra-abdominal disease and various traumatic conditions.

2. **Chronic constipation**: As per the American College of Gastroenterology (ACG), constipation is considered “chronic” if these symptoms are present for 3 months. Straining more that 25% of defecation, lumpy or hard stool, sensation of anorectal obstruction, manual manoeuvres to facilitate bowel movement and fewer than 3 bowel movements per week. Lack of physical activity, low-fibre diet and age-related low colonic activity leads to chronic constipation in elderly.

Based on Aetiology

1. **Primary (functional or idiopathic) constipation**: Primary constipation may be caused by either slow colonic motility or pelvic floor disturbances.

2. **Secondary constipation**: Secondary constipation is caused by medical condition like diabetes mellitus, colorectal carcinoma, drug induced, anorexia nervosa, etc.

Based on Pathophysiology

1. **Slow-transit constipation**: This is characterized by increased transit of stool through the colon. This delay may be caused by a primary dysfunction of the colonic smooth muscle (myopathy) or its nerve innervation (neuropathy).

2. **Dyssynergic or obstructive defecation**: This is also known as “anismus” or “pelvic floor dyssynergia.” This is characterized by either difficulty or inability to expel stool from the anorectum. Many patients with dyssynergic defecation may also have associated prolonged colonic transit.

3. **Constipation-predominant irritable bowel syndrome**

Causes

1. Structural causes

n Colonic neoplasm

n Colonic stricture

n Rectocele

n Pelvic floor weakness

n Rectal prolapse

2. Endocrine causes

n Diabetes mellitus

n Hypothyroidism

3. Metabolic disorders

n Uraemia

n Hypokalaemia

n Hypocalcaemia and hypercalcaemia

4. Infiltrative disorders

n Amyloidosis

n Scleroderma

5. Neurological causes

n Dysautonomia

n Multiple sclerosis

n Spinal cord disease

n Parkinson’s disease

6. Psychological

n Anorexia nervosa

7. Drugs

n Opioids

n Calcium channel blocker

n Aluminum-containing antacid

n Antidepressant

n Iron

Clinical History (Ask patient to maintain 2 weeks Bowel Diary)

1. Infrequent stool (usually 3 or less movements per week).

2. Absence of urge to pass stool.

3. Ineffective straining.

4. Requires digitations.

5. Sense of incomplete evacuation.

6. Rome foundation recommends usage of Bristol stool form chart to characterize what kind of stool the patients often passes **(Fig. 6.1)**.

7. Need to change the posture indicates pelvic floor dyssynergia.

8. Associated rectal prolapse, bleeding per rectum, fecal incontinence or perianal pain.

9. Associated with bloating or abdominal discomfort.

10. Requirement of laxative or enema.

11. Stool evacuation by vaginal or perianal pressure indicates pelvic floor dysfunction.

Physical Examination

1. Pallor indicates malignant bowel lesion causing constipation.

2. Abdominal examination particularly for tenderness, distention, mass and bowel sounds.

3. Anorectal inspection may reveal anal fissure, skin tags, skin excoriation or haemorrhoids.

4. Anocutaneous reflex and perianal sensation - Can be assessed by gentle stroking of the perineal skin in all four quadrants using a cotton bud or a blunt needle. The absence of the anocutaneous reflex should suggest neuropathy.

5. A careful digital rectal examination - Anal stenosis, rectal neoplasm, fecal impaction or rectal stricture.

6. Digital rectal examination to identify dyssynergic defecation - Once patient is asked to bear down, the examiner should perceive relaxation of the external anal sphincter together with perineal descent. Pelvic floor dyssynergia indicates in absence of this relaxation.

Diagnostic Procedures

1. ***Biochemistry***

n Blood chemistry is mainly for endocrine (diabetes and hypothyroidism) or metabolic parameters (electrolytes and renal functions).

n Fecal occult blood test

2. ***Imaging studies***

n *Plain abdominal radiography*: Limited utility (dilated loops, abundance of stool and gas).

n *Barium enema*: Little role to play in the present scenario. It is useful to identify colonic abnormalities like redundant sigmoid colon, megacolon, megarec-tum, stenosis, extrinsic compression or intraluminal masses.

n *Defecography*: Defecography outlines anatomic and functional changes of the anorectum. Around 150 ml of barium paste is instilled into the rectum and ask the patient to evacuate in the sitting position while video fluoroscopic images are recorded. The most common findings include rectocele, intussusceptions, poor activation of levator muscles, prolonged retention or inability to expel the barium.

n *Colonic transit study*: Colonic transit time is typically measured using either of these two methods: (a) inges-tion of radiopaque markers followed by radiography of the abdomen performed at different times or (b) radionuclear scintigraphy. In the first method, a single capsule containing 24 radiopaque markers (Sitzmarks; Konsyl Pharmaceuticals, Fort Worth, TX) is ingested on day 1 and a plain abdominal radiograph is performed on day 6. Retention of more than five markers on day 6 is considered to be abnormal and indicative of slow transit constipation. Up to two-thirds of patients with dyssynergic defecation may also retain markers, and thus the diagnosis of slow transit constipation should only be made after excluding dyssynergia. Colonic transit scintigraphy is a non-invasive method of quantitative evaluation of total and regional colonic transit. Both studies are not standardized and will not differentiate regional transit time.

n *Magnetic resonance imaging*: Endoanal MRI and dynamic pelvic MRI (MR defecography) can be useful to evaluate dynamic pelvic floor motion and global pelvic floor anatomy. Endoanal MRI may reveal changes in the external anal sphincter that are not identifiable by an endoanal ultrasound.

3. ***Endoscopy***

n *Flexible sigmoidoscopy or colonoscopy*: Direct visualization of the colon is indicated in patients to identify colonic malignancy, solitary rectal ulcer syndrome and inflammatory bowel disease. According to the American Society of Gastrointestinal Endoscopy (ASGE), colonoscopy is recommended in patients with chronic constipation only if they have rectal bleeding, haeme-positive stool, iron-deficiency anaemia, rectal prolapse, weight loss, obstructive symptoms and in patients older than 50 years who

have not undergone colon cancer screening. Flexible sigmoidoscopy may be sufficient in younger patients to exclude distal disease.

n *Anorectal endosonography*: Morphological information regarding the anal sphincters and puborectalis muscle in patients with chronic constipation.

n *Wireless motility capsule*: This method is used to assess regional gastric emptying and small bowel transit times. Useful in patients who has refractory constipation to conservative measures and laxatives. This test will differentiate slow from normal colonic transit. Well tolerated, good compliance and no risk of radiation exposure.

4. ***Anorectal and colonic manometry***

n Anorectal and colonic manometry provides assessment of the pressure activity in the colon, rectum and anal sphincters along with an assessment of colon tone, colon and rectal compliance, rectal sensation and anorectal reflexes. Manometry helps to detect abnormalities like reason for dyssynergic defecation and Hirschsprung’s disease.

5. ***Balloon expulsion test***

n The balloon expulsion test (BET) is a simple bedside test to assess function of the pelvic floor.

Management

1. **Bowel training**:Colonic activity is greatest following meal and after walking.Patients should be encouraged to attempt defecation first thing in the morning, when the bowel is more active, and 30 min after meals, to take advantage of the gastrocolic reflex.

2. **Dietary fibre intake**:Increased dietary fibre intake leads to bulky stool leads to decreased colonic transit time. The daily recommended fibre intake is 20–30 g daily such as fruits, bran, nuts and vegetables. Wheat, psyllium and methylcellulose are fibre supplements.

3. **Fluid intake**: At least 8 glass of water intake per day is mandatory. Patients are advised to decrease their consumption of coffee, tea and alcohol.

4. **Regular exercise**:Prolonged bed rest and immobility are often associated with slow bowel transit.

5. **Bulk laxative**: Bulk laxatives include psyllium seed (e.g., Metamucil), calcium polycarbophil (e.g., FiberCon), wheat dextrin (e.g., Benefiber) and methylcellulose (e.g., Citrucel). They are natural or synthetic polysaccharides or cellulose derivatives that primarily exert their laxative effect by absorbing water and forming stool bulk for increase colonic activity. Side effects are minimal except bloating. They may be used alone or combined with high-fibre diet.

Results of a systematic review showed that psyllium increases stool frequency in patients with chronic constipation, but sufficient evidence was not obtained for other types of fibres, including calcium polycarbophil, methylcellulose and bran.

6. **Osmotic laxatives** (poorly absorbed/non-absorbed sugars): (a) Low-dose polyethylene glycol (PEG; 17g/day) is effective and well tolerated in older patients. High-dose PEG (34 g/day) is associated with side effects such as abdominal bloating, cramping and flatulence, and older adults may be more susceptible to these side effects. (b) Lactulose increases stool frequency, decrea-ses the severity of symptoms of constipation and reduces the need for other laxatives in older adult patients. (c) Sorbitol was as effective as lactulose, less expensive and better tolerated in older adult patients with constipation. (d) Saline laxatives such as magnesium hydroxide/milk of magnesia and magnesium citrate are less indicated in older adults and should be used with caution because of the risk of hypermagnesemia specifically in patient with renal failure.

7. **Stimulant laxatives** (Senna, Bisacodyl/Dulcolax) enhance colonic transport and motility by affecting electrolyte transport across the intestinal mucosa. Hyponatremia, abdominal cramps, hypokalaemia and dehydration are side effects of long-term use. The long-term safety data of stimulant laxatives are scant.

8. **Stool softeners, enemas and suppositories**: Stool softeners (Docusate) prevent constipation by making the stools less hard; they do not directly affect the bowel movements. Bisacodyl or glycerin suppositories or enemas can be used in hospitalized older adults with dyssynergic defecation.

9. **Prokinetics**: Prucalopride acts as a selective agonist of the 5-HT4-receptor and stimulates gastrointestinal motility. Potential adverse effects, particularly at the initiation of therapy, include headache, nausea and diarrhoea. Unlike other 5-HT4 agonists such as tegaserod or cisapride, prucalopride has not been associated with any cardiac side effects. Other 5-HT4 agonists such as velusetrag or naronapride improve gastrointestinal motility and have proven efficacy in chronic constipation.

10. **Secretagogues**: (a) Linaclotide is a first-in-class selective guanylate cyclase C (GC-C) agonist with secretory and visceral antinociceptive properties. It binds locally to GC-C receptors on the surface of intestinal epithelial cells and increase intracellular cyclic GMP (cGMP) levels. On the one hand, this leads to activation of the cystic fibrosis transmembrane conductance regulator (CFTR) with stimulation of water, bicarbonate and electrolyte secretion

into the intestinal lumen, leading to soft stool and increased stool frequency. Antinociceptive properties are thought to be mediated by cGMP. Various doses (145 g and 290 g) of linaclotide has been evaluated in a large clinical trial both for chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C). (b) Plecanatide, another GC-C agonist has efficacy and safety similar to that of linaclotide. (c) Lubiprostone, selective chloride channel (ClC-2) activator in the apical membrane of the gastrointestinal epithelium that increases intestinal water secretion. An increase in the secretion of chloride leads to an increase in the levels of intraluminal fluid in the gut, which facilitates transit in the intestine and thereby improves constipation. (d) Colchicine may be effective in chronic constipation as found in randomized controlled trial at dose of 0.6 mg three times a day. Myopathy is knows side effect of colchicine.

Peripherally Acting -Opioid Antagonists (PAMORA) for Opioid-Induced Constipation

Opioids play a significant role in the management of chronic pain. The mechanism of action of opioids is based on activation of central and peripheral nervous -opioid receptors. Opioid receptors play a crucial role in the neural regulation of intestinal motility and secretion. Peripheral nervous -opioid receptors action is responsible for opioid-induced constipation (OIC). Thus, modern treatment concept is to selectively block the opioid effects on intestinal -opioid receptors and thus reduce/prevent gastrointestinal side effects without disturbing central effects of opioids. Oral prolonged-release (PR) naloxone is a systemic opioid antagonist; limits its action to the intestinal -receptors because of a high first-pass-effect in the liver. PR-naloxone is currently available in a fixed-combination tablet with the opioid pain agent oxycodone. This fixed-combination has proven efficacy in pain therapy with concomitant reduction/prevention of OIC. The introduction of true peripherally acting -opioid antagonists (PAMORA), which do not pass the blood-brain barrier, has therefore markedly improved the treatment options of OIC. PAMORAs can be combined with all types and administration routes of opioid pain medication. Currently available PAMORAs are naloxegol, an oral tablet, and methylnaltrexone, as a subcutaneous application. In addition, a new oral PAMORA, naldemedine, has shown good efficacy and tolerability in recent clinical trial.

Biofeedback Treatment

Biofeedback therapy is a painless noninvasive method of cognitively retraining the muscles of the pelvic floor and the abdominal wall. Biofeedback therapy should be considered

in patients with pelvic floordysfunction, particularly dyssynergic defecation.

Fecal Impaction

Fecal impaction is the result from the person’s inability to sense and respond to the presence of stool in the rectum. Lowered sensory perception of the rectum and decreased mobility are common causes of fecal impaction. Digital rectal examination is sufficient to make the diagnosis of fecal impaction. Impacted faces in the proximal rectum and sigmoid colon may be diagnosed by ultrasound of abdomen. The impacted fecal bolus is removed manually using enemas followed by oral administration of PEG solution to evacuate the remaining fecal load from the colon. After management of an acute impaction, the potential causes of constipation should be identified, eliminated and treated using appropriate laxatives.

Rome IV criteria for functional constipations

Following criteria should be present for at least 3 months and onset of symptoms should be at least 6 months prior to diagnosis.

1. Must include 2 or more of the following:

n Straining during more than one-fourth (25%) of defecations.

n Lumpy or hard stools (Bristol stool form scale 1 or 2) more than one-fourth (25%) of defecations.

n Sensation of incomplete evacuation more than one-fourth (25%) of defecations.

n Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defaecations.

n Manual manoeuvres to facilitate more than one-fourth (25%) of defecations (such as digital evacuation or support of the pelvic floor).

n Fewer than 3 spontaneous bowel movements per week.

2. Loose stools are rarely present without the use of laxatives.

3. Patient should have insufficient criteria for IBS.

Criteria for pelvic floor dyssynergia

1. Patient must meet diagnostic criteria for functional chronic constipation.

2. Patient must show dyssynergia during repeated attempts to defecate during manometric, EMG or radiological evidence of pelvic floor dysfunction.

3. Evidence of adequate straining during defecation.

4. Evidence of incomplete evacuation.

Further Reading

1. Locke GR, Pemberton JH, Phillips SF. AGA technical review on constipation. *Gastroenterology* 2000;119:1766–78.

2. Anthony Lembo, Michael Camilleri*.* Current concept: chronic constipation. *N Engl J Med* 2003;349:1360–68.

3. Rao SSC, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol* 2005;100:1605–15.

4. Brandt LJ, Prather CM, Quigley EMM, et al. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol* 2005;100 (suppl 1):S5–S22.

5. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol* 2005;100:936–971.

6. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med* 2014; 370:2387.

7. Larkin PJ, Sykes NP, Centeno C. The management of constipation in palliative care: clinical practice recommendations. P*alliat Med* 2008;22:796–807.

8. Tack J, Drossman DA. What’s new in Rome IV? *J Neurogastroenterol Motil* 2017;29: e13053.

9. Taghavi SA, Shabani S, Mehramiri A, et al. Colchicine is effective for short-term treatment of slow transit constipation: a double-blind placebo-controlled clinical trial. *Int J Colorectal Dis* 2010; 25:389–94.

**Chapter 7.**

**Fecal Incontinence**

Fecal incontinence (FI) affects all age group people, but it is more prevalent in middle-aged women and older adults. The social stigma and embarrassment attached to fecal incontinence make it difficult for the patients to seek treatment. Urinary incontinence is sometimes associated with fecal incontinence. Structurally and functionally impaired anorectal region leads to FI.

Definitions

1. **Fecal incontinence** is defined as involuntary passage of stool through the anus for at least 3 months.

2. **Anal discharge** is the passage of small amounts of mucus, pus or blood from the anus.

3. **Tenesmus** is painful, ineffectual desire to defecate.

Causes

1. ***Structural disorders***

n Congenital anomalies of anorectum

n Rectal prolapse

n Postoperative

n Childbirth injury

n Fistula

n Radiation

n Ulcerative colitis

*Fecal incontinence in last two conditions occurs due to reduced sphincter tone and reduced rectal compliance.*

2. ***Neurological***

n Dementia

n Stroke

n Multiple sclerosis

n Cauda equina lesions

n Polyneuropathy due to diabetes mellitus

3. ***Muscular disorders***

n Myasthenia gravis

n Myopathy

n Muscular dystrophy

Clinical History

1. Duration of fecal incontinence.

2. Four FI instruments – Wexner (Cleveland Clinic), Vaizey (St. Mark’s), Rockwood and the Fecal Incontinence and Constipations Assessment (FICA) are used in clinical studies to rate the severity of FI. **(Table 7.1)**

3. Incontinence occurs only with the liquid stool or also with the solid stool.

4. Does it happen accidentally or patient is aware of incontinence?

5. How long patient can defer the defecation?

6. Presence of physical barrier like toilet situated upstairs

7. Does patient require help to reach the toilet?

8. Associated with bleeding PR or tenesmus suggests inflammatory bowel disease

9. Recent history of childbirth or perineal surgery

Physical Examination

1. Inspection of perianal and perineal area: Look for fissure, fistula, prolapse or ballooning of rectum.

2. Elicit cutaneoanal contractile reflex.

3. Per rectal examination to see resting anal tone (maintained by internal sphincter supplied by autonomic nerves) and squeeze pressure (maintained by external sphincter supplied by somatic S2–4 [pudendal] nerves).

4. Palpate puborectalis muscle in the posterior midline as transverse bar. Digital examination may disclose dys-synergia, which is associated with contraction or failure to relax the puborectalis and/or anal sphincter muscles and reduced perineal descent when patients try to expel the examining finger.

5. After examination in the lateral position, patients should be examined in the seated position on a commode (or while squatting) if the history and/or examination suggest a rectal prolapse, pouch of Douglas hernia or excessive perineal descent that may not be appreciated in the lateral position.

Diagnostic Procedures

1. ***Anorectal manometry***

n Measurement of basal and squeeze pressure in the anal canal. Resting pressure is a function of the internal anal sphincter while squeeze pressure is due to contraction of the external anal sphincter and pubo-rectalis muscle.

n Normal resting pressure is 40 mmHg. Squeeze pressure >80 mmHg.

n This technique is used to evaluate rectal sensation, rectoanal inhibitory response and rectal compliance.

2. ***Rectal balloon manometry***

nIt can be performed using a three-balloon probe or using a balloon mounted at the end of a perfused or transducer-based anal manometry.

nIt provides information about rectal sensation, rectal compliance, rectoanal contraction and rectoanal inhibitory reflex.

3. ***Defecation proctography***

nThis technique is used to evaluate the rectoanal angle, pelvic floor muscles and causes of obstructed defecation.

nIn this method, the anal verge is identified using radiopaque markers, and then, a small amount of barium is injected into the rectum. Then, the patient is asked to sit on a commode. Patient is asked to defecate after a transient increase in the abdominal pressure and squeezing.

nThe angle formed between the axes of the rectum and anal canal is measured.

4. ***Anal ultrasonography***

nThis method shows the anatomy of the internal anal sphincter more accurately than that of the external anal sphincter.

nThree-dimensional endoanal ultrasound may improve accuracy.

5. ***MRI***

nMRI is the only imaging modality that can visualize both anal sphincter anatomy and global pelvic floor motion in real time without radiation exposure.

6. ***Pudendal nerve terminal motor latency (PNTML)***

n Prolonged conduction time is considered indicative of pudendal nerve damage.

7.  ***Electromyography (EMG)***

n EMG to assess muscle activity in the anal sphincter includes surface, needle and single-fibre methods. EMG findings are characterized as normal, neurogenic, myogenic or nonspecific.

8. ***Evoked potentials, positron emission tomography and functional MRI***

n Less data available about their clinical utility.

Management

Initial management of fecal incontinence consists of supportive care and medical therapy.

1. Supportive care - Supportive measures include avoiding foods (fructose, lactose, caffeine, etc) or activities known to worsen symptoms and improving perianal skin hygiene. Maintaining symptom diary to identify factors that cause diarrhoea and incontinence is important. The anoderm should be kept clean and dry. Incontinence pads and application of zinc oxide cream to the perianal skin are useful. Biofeedback using instrumental learning is useful in patients with fecal incontinence. In biofeedback training, the process is external anal sphincter contractions in response to rectal distension. Biofeedback training is inexpensive, quick and safe.

2. Medical therapy - Aim of medical therapy is to reduce stool frequency and improving stool consistency. No specific medication has been proven to be of benefit for fecal incontinence, except for antidiarrhoeal drugs in patient’s diarrhoea. Bulk laxative helps in patients with low volume loose stool with incontinence. Enemas and suppository help to the patient with fecal impaction due to neurological conditions.

3. Surgical therapy - Occlusive balloon that obstruct the recto-anal junction leads to decrease in the number of incontinent episodes. This device should be used in patients who want to avoid surgery.

Transanal electrostimulation or implanting electrodes into S3 or S4 foramina reduces incontinence. Dynamic

graciloplasty or an artificial anal sphincter device may be used to treat refractory fecal incontinence. Diversion of the fecal stream with a colostomy or ileostomy is the definitive therapy for patients with intractable symptoms.

Various Surgical Interventions in Patients with Fecal Incontinence

1. Total pelvic floor repair

2. Transposition of gracilis muscles

3. Thiersch procedure (anal encirclement)

4. Injection of bulking agents around the anal canal

5. Development of artificial anal sphincter

6. Rarely fecal diversion by either colostomy or ileostomy

Mechanism of Defecation

Three physioanatomical events during defecation:

1. **Rectoanal angle**: It is an angle formed between axes of rectum and anal canal. It is usually 90°. Puborectalis muscles maintain it. During defecation, puborectalis muscles relax.

2. **Rectoanal inhibitory reflex**: Relaxation of internal anal sphincter following rectal distension, maintained by a local spinal reflex.

3. **Rectal accommodation reflex**: Relaxation of rectum to accommodate large volume of stool to maintain low intraluminal pressure. Mucosa in the anal canal is extremely sensitive for tactile perception.

During voluntary inhibition, rectal accommodation reflex maintains low intraluminal pressure and tonic contraction of puborectalis muscles, which prevent passage of stool or gas

into the anal canal. Anal sphincter weakness is the most

frequently observed cause for fecal incontinence. External anal sphincter weakness may be due to one or more of the following reasons: sphincter damage, neuropathy, myopathy or reduced corticospinal inputs.

Anal resting pressure is maintained by the internal anal sphincter. Structural disturbance (perianal procedure) or functional disturbances (scleroderma) are leading cause of thinning of the internal anal sphincter.

Proctalgia Fugax

Proctalgia fugax is defined as a sudden severe pain in the rectal area, which lasts for a few seconds to several minutes, and then disappears completely. It is more common in women than men. The pain is localized to the rectum in the case of 90% of the patients. Patients describe the pain as cramping, gnawing, aching or stabbing and may range from uncom-fortable to unbearable. It is described as “harmless, unplea-sant and incurable.” Spasm of the anal sphincter, pudendal nerve compression and neuropathy are proposed patho-genesis of proctalgia fugax. Because the disorder is harm-less, treatment normally consists only of reassurance and explanation. Drugs like beta adrenergic agonist, clonidine, amylnitrite or nitroglycerine have been used for the manage-ment of this condition.

Rome IV Criteria for Chronic Proctalgia

Diagnostic Criteria\*

*Must include* ***all*** *of the following:*

1. Chronic or recurrent rectal pain or aching unrelated to defecation.

2. Episodes last from seconds to minutes with a maximum duration of 30 min.

3. There is no anorectal pain between episodes.

4. Exclusion of other causes of rectal pain such as ischemia, inflammatory bowel disease, cryptitis, intramuscular abscess, anal fissure, haemorrhoids, prostatitis, coccygodynia and major structural alterations of the pelvic floor.

\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Levator Ani Syndrome

Levator ani syndrome is also called levator spasm, pubo-rectalis syndrome and pelvic tension myalgia. This pain is often described as a vague, dull ache or pressure sensation high in the rectum and is often worse with sitting than with

standing or lying down. Examination showed contracted levator ani muscles. Treatment includes electogalvanic stimulation; biofeedback training; muscle relaxants, such as methocarbamol, diazepam and cyclobenzaprine; digital massage of the levator ani muscles and sitz baths.

Diagnostic Criteria\* of Levator Ani Syndrome

Must include all of the following:

1. Chronic or recurrent rectal pain or aching

2. Episode last 30 min or longer

3. Tenderness during posterior traction on the puborectalis

4. Exclusion of other causes of rectal pain

\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to the diagnosis.

Further Reading

1. Bharucha AE. Fecal incontinence. *Gastroenterology* 2003; 124:1672–85.

2. Fernandez–Fraga X, Azpiroz F, Malagelada J. Significance of pelvic floor muscles in anal incontinence. *Gastroenterology* 2002;123:1441–50.

3. Jorge J, Wexner S. Etiology and management of fecal incontinence*. Dis Colon* *Rectum* 1993;36:77–97.

4. Law P, Kamm M, Bartram C. Anal endosonography in the investigation of faecal incontinence. *Br J Surg* 1991;78: 312–314.

5. Melchior C, Bridoux V, Touchais O, et al. MRI defaeco-graphy in patients with faecal incontinence. *Colorectal Dis* 2015;17:O62–O69.

6. Mimura T, Kaminishi M, Kamm M. Diagnostic evaluation of patients with faecal incontinence at a specialist institution*. Digest Surg* 2004;21:235–241.

7. Jakob Duelund-Jakobsen, Jonas Worsoe, et al. Management of patients with faecal incontinence. *Therap Adv Gastroenterol* 2016;9:86–97.

**Chapter 8.**

**Gastrointestinal Bleeding**

Upper gastrointestinal bleeding (UGIB) is a common cause for hospital admission and is associated with a mortality of around 10%. Prompt clinical assessment and resuscitation are keys in the initial management. Advanced age and severe coexistent comorbidities are associated with high mortality. Initiation of endoscopic evaluation should be as early as possible, preferably within 24 hrs of admission. The source of bleeding cannot be recognized in 10–15% of patients with UGIB; either the lesion is hard to identify (such as a Dieulafoy’s lesion), obscured by a retained blood clot at endoscopy or the lesion has already healed by at the time of endoscopy.

Definitions

1. **Haematemesis** is vomitus of red blood or “coffee-ground” materials.

2. **Melena** is black, tarry, foul-smelling stool. The black, tarry character of melena is caused by degradation of blood in the more proximal intestine including proximal colon. Melena should not be confused with the greenish character of ingested iron or the black, non-foul- smelling stool caused by ingestion of bismuth.

3. **Haematochezia** is passage of bright red or maroon blood per rectum.

4. **UGIB** is bleeding from above the ligament of Treitz.

5. **Obscure GI bleed** is defined as overt GI bleeding where bi-directional endoscopy (upper endoscopy and colonoscopy) does not show aetiology of bleeding.

6. **Occult GI bleed** is identification of GI bleeding in the absence of overt bleeding by special examination of the stool (e.g., guaiac testing).

Overall mortality of UGIB has remained stable over recent decades and is still 6–14% in most studies. About 18% of the total mortality is directly related to GI haemorrhage while majority of deaths are caused by concurrent comorbidities. Pulmonary disease (24%), multiorgan failure (24%) and terminal malignancy (34%) are the most common comorbidities. The risk of mortality increases with rebleeding. The incidence of rebleeding in patients with UGIB shows a wide range from 5% to more than 20% depending on various factors.

Causes of Gastrointestinal Bleeding

UGIB

1. Peptic ulcer disease (PUD)

2. Variceal bleeding related to portal hypertension

3. Mallory-Weiss tear

4. Portal hypertensive gastropathy

5. Oesophagitis or oesophageal erosion

6. Arteriovenous malformation

7. Duodenitis/gastritis/erosions

8. Oesophagogastric tumours

9. Aortoduodenal fistula

10.Dieulafoy’s lesion

Lower Gastrointestinal Bleeding

1. Haemorrhoids

2. Inflammatory bowel disease

3. Neoplasm

4. Vascular ectasia

5. Diverticular disease

6. Ischaemic or radiation colitis

7. Colonic ulceration

Obscure Gastrointestinal Bleeding

*(Both upper endoscopy and colonoscopy negative)*

1. Small bowel vascular ectasia

2. Small bowel adenocarcinoma

3. Small bowel stomal tumour

(GIST, gastrointestinal stomal tumour)

4. Meckel’s diverticulum

5. Ectopic varices

6. Haemobilia

7. Aortoenteric fistula

Occult Gastrointestinal Bleeding

*(Only fecal occult blood test positive)*

1. Gastrointestinal cancer

2. Colonic adenoma

3. Crohn’s disease

4. Vascular ectasia

5. Dieulafoy’s lesion

6. Worm infestation

7. Gastrointestinal ulcer (at any site)

8. Portal hypertensive gastropathy or colopathy

Initial Assessment and Resuscitation

Assessment of severity of gastrointestinal bleeding is the most important as initial management **(Table 8.1)**.

**Haemodynamics % Blood loss Bleed type**

Normal <10% Minor

Postural hypotension or 10–20% Moderate

postural tachycardia

Shock (resting hypotension) 20–25% Severe

Intensive care admission is indicated in haemodynamically unstable patients. Oxygen supplementation should be given liberally. Close monitoring of vital signs and urine output should be monitored. Decisions about blood transfuse is often difficult. The threshold for blood transfusion depends on the underlying condition, rate of bleeding and vital signs of the patient, but is generally set at a haemoglobin level of around 7.0 g/dL. Transfusion should be performed if patients with significant comorbidities (e.g., ischaemic cardiovascular disease) have higher haemoglobin levels (>7.0 g/dL). Red blood cell transfusion was associated with high rates of mortality and rebleeding.

Transfusion is performed using packed red blood cells rather than whole blood. The haematocrit levels should be regularly monitored, because the haematocrit levels, soon after the onset of bleeding, may not accurately reflect the blood loss. The haematocrit value only falls as extravascular fluid enters the vascular space to restore volume, a process that is typically completed after 24–72 hrs. The haematocrit levels should be increased by 30% in elderly patients, and they should be in the range of 20–25% in young individuals. In patients with portal hypertension, haematocrit level should not exceed 27%.

Clinical History

Attention should turn to the clinical history only once the patient’s haemodynamics is stabilized.

1. ***Haematemesis***

n Haematemesis indicates source of bleeding above the ligament of Treitz.

n Fresh blood or altered blood or “coffee-colour” materials.

n Frequency and quantity are most important.

n Haematemesis of more than 500 mL is called severe haematemesis.

2. ***Melena***

n Melena indicates that blood has been present in gastrointestinal tract for 12–14 hrs.

n At least 60 mL of blood is required to produce melena.

n Black, tarry, foul-smelling stool is due to degradation of blood in the gastrointestinal tract.

n Melena can persist for 4–7 days after treating the source of bleeding.

n Melena indicates bleeding source is from proximal intestine.

3. ***Haematochezia***

n Haematochezia usually represents lower GI bleeding.

n Haematochezia also occurs in upper GI lesion when bleeding is very brisk and intestinal transit is fast.

4. ***Abdominal pain***

n Upper abdominal ulcer-like pain indicates peptic ulcer disease as a cause of UGIB.

n Upper abdominal pain also suggests aetiology like mesenteric ischemia.

n There is an increased risk of spontaneous bacterial peritonitis (SBP) in patients with decompensated cirrhosis liver, following an episode of GI bleeding.

5. ***Symptoms of liver decompensation***

n Associated symptoms like ascites, jaundice or hepatic encephalopathy suggest variceal bleeding as a cause of gastrointestinal bleeding.

n Development of symptoms of liver decompensation following bleeding episodes like ascites, jaundice or hepatic encephalopathy strongly favours variceal bleeding due to cirrhosis liver.

n Patient with extrahepatic portal hypertension or non-variceal cause of GI bleeding usually does not show signs of liver decompensation.

6. Recent history of nonsteroidal anti-inflammatory drugs (NSAID), alcohol or corrosive ingestion.

7. History of excess retching indicates Mallory-Weiss tear.

8. Symptoms of volume contraction like dry mouth, dizziness, headache, decreased urine output and postural syncope.

Past History

1. Past history of similar episodes indicates recurrent variceal bleeding, non-healing peptic ulcer disease, bleeding from arteriovenous malformation or diverticular bleeding.

2. History of umbilical vein catheterization or umbilical sepsis in child presenting with haemetemesis indicates possible portal vein thrombosis.

Personal/Social History

1. Chronic alcohol consumption or known liver disease raises the possibility of the varices or portal gastropathy.

2. Smoking impairs the ulcer healing.

General Examination

1. Signs of volume contraction

n Dry mouth

n Pallor

n Cold extremity

n Postural tachycardia: Heart rate increases by 10 beats/min following change in the posture from supine to sitting or standing position.

n Postural hypotension: Drop in the systolic blood pressure by more than 10 mmHg following change in the posture from supine to sitting or standing position.

n Low-volume pulse or shock in case of massive blood loss.

n *Postural hypotension/postural tachycardia indicate 10–20% blood loss, whereas resting hypotension indicates 20–25% blood loss.*

2. Stigmata of cirrhosis liver (Ch. 12).

3. *Acanthosis nigricans* suggests underlying gastrointestinal malignancy.

4. Pigmented lips, palms and soles suggest Peutz-Jeghers syndrome.

5. Purpura suggests vascular disease.

Abdominal Examination

1. Abdominal tenderness presents in peptic ulcer disease, ischaemic bowel disease and pancreatitis.

2. Umbilical nodule suggests intra-abdominal malignancy.

3. Presence of ascites and splenomegaly suggests portal hypertension.

4. Abdominal mass suggests malignancy.

5. Digital rectal examination and proctoscopy for the presence of haemorrhoids, rectal neoplasm or rectal inflammation.

6. Digital rectal and vaginal examination detects pelvic deposits, which indicates gastrointestinal malignancy.

Nasogastric Lavage and UGIB

1. Bloody aspirate confirms the UGIB.

2. It is difficult to judge the severity of bleeding by naso-gastric lavage.

3. Nasogastric lavage has 79% sensitivity and 55% speci-ficity for active bleeding. Thus, nasogastric lavage to assess UGIB is discouraged.

4. Around 25% of the time, nasogastric aspirate is non-bloody in case of active UGIB.

5. Nasogastric lavage does not give any aetiological clue for UGIB. Thus, primary use of the nasogastric lavage to assess bleeding activity is discouraged.

Diagnostic Procedures and Management

of uGiB

Diagnostic Procedures

UGIB is broadly divided into either variceal bleeding (bleeding secondary to portal hypertension) or non-variceal bleeding (bleeding secondary to peptic ulcer disease, neoplasm, angiodysplasia or erosions).

Blood Chemistry

1. Haematocrit should be monitored serially (as mentioned previously).

2. The blood urea nitrogen level may be elevated out of proportion to elevation in the serum creatinine level because of breakdown of blood proteins to urea by intestinal bacteria and its absorption, and from a mild reduction in the glomerular filtration rate.

3. Liver function tests and coagulation parameters

Upper Endoscopy

Endoscopy should be the primary procedure. It not only identifies the source of bleeding **(Fig. 8.1)**, variceal bleeding versus non-variceal bleeding, but is also useful for control of bleeding by various methods. Early endoscopy defined as endoscopy within 24 hrs of patient hospital presentation or admission. Early endoscopy has been shown to reduce resource use, reduce hospital stay and decrease transfusion requirements. Patient with PUD, risk-stratification and evidence-based prediction of rebleeding following endo-therapy is possible using modified Forrest criteria **(Table 8.2)**.

Management of Non-variceal Bleeding

1. **Pharmacotherapy**

n The aim of pharmacotherapy is to stop active bleeding and to prevent rebleeding.

n Pharmacological agents have been used to treat bleeding peptic ulcer: H2-receptor antagonist, proton pump inhibitors (PPIs), somatostatin, octreotide, secretin and prostaglandins.

n According to the available evidence, PPI is the most important pharmacological therapy for bleeding peptic ulcer. If gastric pH is maintained above 6 by PPI infusion, platelet aggregation is optimized and fibrinolysis relatively inhibited, leading to clot stability at an ulcer site.

2. **Endoscopic injection therapy (Table 8.3)**

n Major endoscopic injection therapy in patient with non-variceal upper gastrointestinal bleeding is injection of a vasoconstrictor, sclerosant or other agent **(Fig. 8.2)**. Injection of dilute epinephrine (1:10,000)

at the site of bleeding reduces blood flow by temporary creating local tamponade and vasoconstriction of blood vessels. Injection of large volume of epinephrine (>13 mL) can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcer and is superior to injection of lesser volumes.

n Thrombin-fibrinogen mixture (fibrin-sealant glue) is equally effective as adrenaline injection.

n The use of a novel haemostatic powder spray appears to be effective and safe in controlling UGIB. Hemospray demonstrates adhesive properties and dehydrates tissue through absorption of water molecules. It acts as a physical barrier upon contact with moisture. Hemospray is neither taken up nor broken down by the mucosa and therefore no local or systemic side effects.

n The Endo Clot (Endo Clot Plus, Santa Clara, CA, USA) is a polysaccharide haemostatic powder that can be delivered endoscopically to the site of bleeding in the GI tract without the need for direct mucosal contact.

3. **Endoscopic thermal therapy**

n Haemostasis is achieved by coaptive coagulation by compressing the underlying vessels to achieve thermocoagulation.

n Contact thermal techniques - Heater probe thermo-coagulation and bipolar electrocoagulation use thermal contact to achieve haemostasis by compression of the vessel and cooptation. In addition, a single device system, including bipolar electrocoagulation and injector-irrigator channel (e.g., Gold Probe; Boston Scientific, Boston, MA) is used for adrenaline injection and irrigation of the culprit lesion **(Fig. 8.3)**.

n Noncontact thermal techniques - Laser (neodymium: yttrium-aluminum-garnet) and argon plasma coagulation (APC) are currently available non-contact thermal therapies. High-frequency electrical current through a beam of ionized argon gas results in superficial tissue damage and coagulation.

4. **Mechanical techniques**

n Endoloops and haemoclip are mechanical methods to obtain haemostasis. The difficult-to-reach lesions for haemoclip are high on the gastric lesser curvature or posterior wall of the duodenum **(Fig. 8.4)**. The over-the-scope clip (OTSC) is effective in achieving haemostasis and significantly reduces rebleeding and rebleeding-associated mortality. Dual endoscopic therapy is superior to monotherapy with epinephrine injection in the management of patients with high-risk bleeding peptic ulcer; moreover, dual therapy reduces the risk of recurrence of bleeding and the risk of emergency surgery and mortality.

5. **Endoscopic suturing**

n Endoscopic suturing is used for gastroplication in patients with gastroesophageal reflux. Suturing techniques similar to endoscopic suturing are an attractive prospect in patients with upper gastrointestinal bleeding, but further development of new devices is required.

6. **Cryotherapy**

n Contact thermal techniques for bleeding lesions have drawbacks such as the requirement for contact, expensive, lack of control of depth of injury and difficulty in targeting multiple lesions.

n Cryotherapy involves freezing tissue to achieve a therapeutic response. Endoscopic cryotherapy is possible by delivering liquid nitrogen or nitrous oxide for bleeding lesions.

7. **Video capsule endoscopy**:The use of video capsule endoscopy (VCE) in the emergency department (ED) as a risk stratification tool for identifying high and low-risk patients with UGIB has been evaluated. It has shown potential to identify high and low-risk patients presenting with signs of UGIB, helping to determine the need for intervention with significant reduction in the time to emergent endoscopic therapy. VCE in the ED is safe and effective in identifying UGIB.

Management of Acute Variceal Bleeding

1. **Pharmacotherapy**

n Vasoactive agents like vasopressin, somatostatin, octreotide and terlipressin are used in patients with bleeding related to portal hypertension.

n Vasoactive agents cause splanchnic vasoconstriction. Vasopressin causes systemic vasoconstriction, thus has significant adverse effect.

n Somatostatin, a natural peptide, lacks most of the cardiovascular adverse effects seen with vasopressin. Octreotide, a somatostatin analogue, has similar properties as somatostatin, but with a longer biological half-life.

n Terlipressin is a long-acting derivative of vasopressin. It is transformed slowly to vasopressin by enzymatic cleavage. Terlipressin releases slowly, thus has significantly low side effects. Terlipressin has long half-life, thus can be administered at home or in the emergency room.

n Recently, there has been use of recombinant factor VIIa (rFVIIa) in managing patients with UGIB secondary to cirrhosis liver. However, it did not show advantage over standard therapy with vasoactive agents.

2. **Endotherapy**

n Endoscopic sclerotherapy (EST) and endoscopic band ligation (EBL, **Fig. 8.5**) are two methods to control the acute oesophageal variceal bleeding and prevent rebleeding.

n Haemostasis is achieved in 80–90% of patients using both these methods. Results of recent studies indicate that band ligation is superior to sclerotherapy in terms of decreasing the re-bleeding rates, complications and eradication of the varices. Thus, band ligation should be the first-line endoscopic therapy for acute variceal bleeding. Band ligation is a local therapy that has no effect on portal hypertension; band ligation is performed in patients with recurrence of varices, and patients require indefinite endoscopic monitoring.

n Tissue adhesives like cynoacrylate are not recom-mended in patients with bleeding oesophageal varices.

n Use of vasoactive agents in combination with endoscopic therapy appears to be more efficacious than individual therapies.

n Early TIPS (pre-emptive) may be helpful in selected patients with high risk of failure of endotherpay or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding on endoscopy).

n For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2–5 days and nonselective beta-blockers (NSBBs) should be initiated once vasoactive drugs are discontinued. Rescue TIPS is indicated in these patients if haemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs plus EVL.

n Following successful TIPS, intravenous vasoactive drugs can be discontinued.

3. **Transjugular intrahepatic portosystemic shunt**

n Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in situations when bleeding varices are refractory to medical therapy. Efficacy of TIPS to control the bleeding is 95%.

4. **Surgery**

n Surgery is only indicated when endotherapy fails and TIPS is not available.

n Surgical interventions include devascularization procedures, selective portosystemic shunting and calibrated H grafts (Ch. 26).

5. **BRTO (balloon occluded retrograde transvenous obliteration)**

n Transvenous obliteration by instilment of sclerosants and/or liquid embolic agents into a gastro-/splenorenal collateral through the left renal vein aided by balloon occlusion.

6. **Balloon tamponade**

n Balloon tamponade with a Sengstaken-Blakemore tube successfully achieves haemostasis in 90% of cases of bleeding varices, but it has a high recurrence rate for rebleeding once the balloon is deflated. Thus, balloon should be reserved as a rescue procedure, so that patients are stabilized for a more definitive therapy.

Preventing Recurrent Variceal Bleeding

Variceal bleeding recurs in two thirds of patients within 2

months after initial control. There are various factors

associated with an increased risk of recurrent bleeding include severity of liver disease, large varices, severity of index haemorrhage, renal dysfunction, presence of encephalopathy and severe portal hypertension.

1. **Pharmacotherapy**

n Reduction of portal pressure below 12 mmHg prevents rebleeding. Thus, the main goal of pharmacotherapy is to reduce portal pressure below 12 mmHg. Portal pressure is measured by the hepatic venous pressure gradient (HVPG). The best time to measure portal pressure is within the first month after a bleeding episode. Reduction of portal pressure by more than 20% significantly reduces the rebleeding rate.

n Nonselective beta-blockers (NSBBs; propranolol, nadolol and carvedilol) are the main pharmacological agent used. NSBBs lead to both vasoconstriction of the splanchanic circulation by beta-2 blockade and decrease in the heart rate and cardiac output through beta-1 blockade. Dosage of the NSBB should be adjusted according to the heart rate (target heart rate of 55 beats per minute or a 25% reduction in the heart rate from baseline). The effect of NSBBs in decreasing flow is more related to their -2 blocking effect than to their -1 effect and explains the lack of correlation between decreases in portal pressure and decreases in heart rate. Carvedilol is an NSBB with an additional anti-1 adrenergic (vasodilator) activity. HVPG response is greater with carvedilol than with propranolol or nadolol, but given its vasodilatory properties, carvedilol is associated with a greater decrease in mean arterial pressure (MAP).

n The addition of an exogenous NO donor such as isosorbide 5-mononitrate (ISM) enhances the fall in the portal pressure caused by NSBB by acting on the increased hepatic vascular tone. The combination of NSBB plus ISM has been extensively used in secondary prophylaxis as ISM allows further reducing HVPG in patient haemodynamic non-responders to NSBB. Monotherapy with ISM is not recommended.

2. **Endoscopic therapy**

n Band ligation and sclerotherapy are two modalities to prevent rebleeding. Due to fewer complications band ligation is superior to sclerotherapy.

n Combination of band ligation with pharmacotherapy may be the ideal treatment modality.

3. **Shunt procedures**

n Surgical shunts and TIPS prevent rebleeding. Rebleeding after surgical shunt is caused by shunt thrombosis, which occurs usually within the first year. It is unusual for surgical shunts to thrombose beyond 1 yr.

n Rebleeding rate is significantly lower in TIPS compared to endotherapy (19 vs 47%), but significantly high rate of hepatic encephalopathy (34 vs 19%), with no difference in survival.

Primary Prophylaxis for Variceal Bleeding

1. Nonselective beta-blockers significantly reduce the risk of first variceal bleeding and remain the treatment of choice for patients with high-risk varices. Many patients may not tolerate beta-blockers because of side effects (sexual dysfunction, asthenia or hypotension). Nonselective beta-blocker once tolerated should be administered indefinitely.

2. Band ligation is more effective than nonselective beta-blocker as a prophylaxis, but has no survival advantage. Majority of the studies had modest duration of follow-up, thus the long-term benefits of prophylactic band ligation are unclear.

Portal Hypertensive Gastropathy

1. Portal hypertensive gastropathy (PHG) is the characteristic mosaic-like gastric mucosa with or without red spots. It is seen both in cirrhotic as well as noncirrhoitc portal hypertension.

2. There are two types of PHG according to McCormack and colleagues. PHG is classified into mild (fine pink speckles, superficial reddening or mucosal mosaic pattern) or severe (discrete red spots or diffuse haemorrhagic lesions; **Fig. 8.6)**.

3. Iron-deficiency anaemia or occult blood in stool is more frequent presentation than acute bleeding.

4. The specific treatment options include nonselective beta-blockers, endoscopic cauterization (bipolar probe or argon plasma coagulation), or TIPS or surgical shunts.

Management of Gastric Varices

1. Gastric varices (GV) are not uncommon in patients with portal hypertension. GV can be classified into gastroesophageal varices (GOV) or isolated gastric varices (IGV).

2. GOV are classified into GOV1 (in continuity with oesophageal varices and extend 2–5 cm below the gastroesophageal junction, 75% of GV) or GOV2 (oesophageal varices extending into the fundus). IGV can be located in the fundus (IGV1) or body/antrum (IGV2). GOV2 and IGV1 are commonly referred to as “**Cardiofundal varices**.” They are much more frequent in patients with portal vein and/or splenic vein thrombosis.

3. The main factors associated with a higher risk of bleeding are localization (IGV1>GOV2>GOV1), large size, presence of red spots and severity of liver dysfunction.

4. The specific treatment for gastric variceal bleeding include endoscopic (cynoacrylate or its derivatives or thrombin), radiological (TIPS or balloon-occluded retrograde transvenous obliteration) and surgical shunts.

5. Endoscopic therapy with cynoacrylate is very effective in managing gastric variceal bleeding. Peripheral embolization (to lungs, brain or viscera) is rare complication.

Important Message for Variceal Bleeding

1. Patients with cirrhosis and portal hypertension, but no prior variceal haemorrhage (especially those with platelet counts <140,000/mm3 or Child Class B or C) should undergo screening endoscopy and treatment with beta-blocker if large varices are found.

2. PRBC transfusion should be done conservatively, starting to transfuse when the haemoglobin reaches a threshold of around 7 g/dL with the goal of maintaining it between 7 and 9 g/dL.

3. Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI haemorrhage.

4. Following an episode of bleeding from oesophageal varices, EVL should be performed every 2–4 weeks until the varices are eradicated. Concomitant beta-blocker therapy should be considered.

5. Following variceal eradication, endoscopy should be repeated every 6–12 months and recurrent varices should be treated with EVL.

6. There are not sufficient data to recommend endoscopy for obliteration or as primary or secondary prophylaxis of isolated gastric varices.

Diagnostic Procedures and Management of Lower Gastrointestinal Bleeding

Diagnostic Procedures

1. ***Colonoscopy***

n Colonoscopy is the best test for confirming the source of lower gastrointestinal bleeding **(Fig. 8.7)**.

n Diagnostic yield ranges from 45 to 95%.

n Various therapeutic interventions are possible with colonoscopy; therefore, it is the most cost-effective approach to patients with lower gastrointestinal bleeding.

n Yield of unprepared colonoscopy is less as compared to prepared one.

n Bowel preparation is safe and complication rates are very low in patients with lower gastrointestinal bleeding.

2. ***Radionuclide scintigraphy***

n It is a non-invasive test and can detect the bleeding rate as low as 0.05–0.1 mL/min.

n No bowel preparation is required.

n Two methods exist – One using technetium-99m (Tc-99m) sulfur colloid and other Tc-99m-labeled red blood cells (tagged red blood cell scan).

n Sulfur colloid is simple to prepare and is rapidly cleared from the circulation, whereas radiolabeled red blood cells have a longer half-life, thus repeat scan following single injection is possible.

n It cannot confirm the source of bleeding.

n Radionuclide scan is advocated for two primary purposes – as a guide for surgical resection and as a screening test prior to angiography.

3. ***Angiography***

n Angiography is less sensitive than nuclear scan with the ability to detect bleeding of more than 0.5 mL/min.

n Angiography offers therapeutic possibilities like pharmacologic vasoconstriction or selective microemboli-zation.

n Complications occur in 0–10% of patients undergoing angiography. They are haematoma or bleeding at the catheter site, arterial dissection, catheter site infection and contrast reaction. Localized bowel ischemia and infarction are concern with therapeutic embolization.

Management of Lower Gastrointestinal Bleeding

1. **Endotherapy**

n Endoscopic haemostasis methods include injection therapy (epinephrine or saline), heater probe therapy, monopolar and multi-polar electrocoagulation, argon plasma coagulation, haemoclip and band ligation.

n In contrast to UGIB, there are no data to compare the effectiveness of each modality in different conditions.

2. **Angiography**

n Intra-arterial infusion of vasopressin or super selective embolization with various agents (gelatin sponge, microcolis and polyvinyl alcohol particles).

n Selective embolization initially controls haemorrhage in up to 100% of patients, but rebleeding rates are 15–40%.

3. **Surgery**

n Surgery is indicated in case of massive or recurrent bleeding.

n Around 15–20% patients with diverticular bleeding require surgery.

n It is very important to accurately localize the site of bleeding preoperatively for segmental rather than major resection.

Causes of Angiodysplasia in Renal Failure

1. Fluid overload leads to failure of pre-capillary sphincter.

2. Reactive hyperaemia following dialysis.

3. Hyperkalaemia- and hypergastrinemia-mediated reduction in pre-capillary arterial tone.

4. Dieulafoy’s lesion (exulceratio simplex) is a large “caliber-persistent” vessel within the submucosa.

New Anticoagulant drugs and GI bleeding

The direct oral anticoagulants (DOAC: dabigatran, rivaroxaban, apixaban and edoxaban) decreased the need for regular monitoring of the serum required for patients on warfarin; however, compared to warfarin, DOACs have a 25–30% increased risk of GI bleeding. The risk is mostly relevant in the elderly and those with hepatic disease, renal disease and patients on concomitant antiplatelet agents. In the case of a patient with UGIB, reversal agents can be used; however, different assays are needed to indirectly quantify the levels of DOAC before reversal. These assays include the dilute thrombin time and ecarin clotting time for dabigatran and the drug-specific calibrated anti-Xa factor assay for rivaroxaban, edoxaban and apixaban. In addition, reversal agents such as prothrombin complex concentrate (PCC), activated PCC and idarucizumab are available.

Gastric Antral Vascular Ectasia

Gastric antral vascular ectasia (GAVE) refers to morpho-logical endoscopic appearance of prominent submucosal blood vessels in the antrum of the stomach.

GAVE is characterized by tortuous red vessels along the longitudinal folds of antrum. It is considered traditionally to be limited to the antrum of stomach and can be mistaken for commonly encountered antral gastritis or portal hyper-tensive gastropathy (PHG). GAVE is associated with portal hypertension, and the symptoms of GAVE are similar to those of PHG; however, they are distinctly different conditions. GAVE is predominantly distributed in antrum, whereas PHG causes predominant changes in the fundus and body of the stomach. **(Table 8.4)**

Causes

Gastric antral vascular ectasia is seen in various conditions including cirrhosis of liver. **(Table 8.5)**

n Cirrhosis of liver

n Collagen vascular disorders

- Scleroderma

- Sjogren’s syndrome

- Raynauds disease

n Bone marrow transplantation

n Chronic renal failure

n Ischaemic heart disease

n Hypertension

n Valvular heart disease

n Familial Mediterranean fever

n Acute myeloid leukaemia

n Supportive measures n Medical therapy

a) Iron supplements - Lowering of portal

b) Blood transfusions hypertension

- Corticosteroids

- Oestrogen-

Progesterone

combination

- Tranexamic acid

- Thalidomide

n Endoscopic therapy n Surgery

- Sclerotherapy - Antrectomy

- Heater probe - Portal pressure

- Laser photocoagulation reduction

- Argon-plasma coagulation - Liver transplantation

- Band ligation

Management

No specific treatment is available for GAVE. Various modalities were tried but none is proven in large randomized trial. **(Table 8.6)**

Further Reading

1. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922–38.

2. de Franchis R, Baveno V Faculty. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743–52.

3. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254–61.

4. Garber A, Jang S. Novel therapeutic strategies in the management of non-variceal upper gastrointestinal bleeding. *Clin Endosc* 2016;49:421–4.

5. Mehta G, Abraldes JG, Bosch J. Developments and controversies in the management of oesophageal and gastric varices. *Gut* 2010;59:701–5.

6. Guadalupe Garcia-Tsao, Juan G Abraldes, Annalisa Berzigotti, Jaime Bosch. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2017;65:310–35.

7. Khamaysi I, Gralnek IM. Acute upper gastrointestinal bleeding (UGIB) - initial evaluation and management. *Best Pract Res Clin Gastroenterol* 2013;27:633–8.

8. Feinman M, Haut ER. Upper gastrointestinal bleeding. *Surg Clin North Am* 2014;94:43–53.

9. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21.

10. Abraham NS, Horsley-Silva JL. Gastrointestinal bleeding secondary to the new anticoagulants. *Curr Opin Gastroenterol* 2016;32:474–80.

**Chapter 9.**

**Obstruction or Ileus**

Over past 100 years, the anatomical location of bowel obstruction (BO) has remained unchanged; however, the aetiological factors in small and large BO have changed significantly. BO is one of the most common abdominal emergencies. Peritoneal adhesions and hernia are the most common (42%) causes of BO. Abdominal wall hernia is the cause of BO in about 26% of patients with virgin abdomen. Bowel dilatation occurs proximal to obstruction primarily from swallowed air and secondarily from intra-luminal fluid accumulation. Dilatation increases tension in the bowel wall, decreases mucosal perfusion, causes bacterial proliferation and decreases tensile strength of the vessel wall, thereby increasing the risks of bowel perforation. The classical clinical tetrad of BO is abdominal pain, nausea and emesis, abdominal distention and constipation-to-obstipation. All patients with BO, particularly mechanical obstruction, are potential candidates for major abdominal surgery with long-term morbidity and possible mortality. Thus, the decision and timing of surgery is very vital.

Definitions

1. **Intestinal obstruction** means complete or partial blockage of the gut at one or more levels.

2. **Ileus** is a potentially reversible state of inhibited motor activity in the gastrointestinal tract.

3. **Chronic pseudo-obstruction** is a functional abnormality of longer duration that simulates mechanical obstruction in absence of anatomic cause.

4. **Toxic megacolon** means acute dilatation of colon with loss of haustrations (transverse colon diameter > 6 cm); indicates severe transmural inflammation.

Causes

Intestinal Obstruction (Dynamic Obstruction)

1. **Extrinsic causes**

n Adhesions

n Congenital bands with malrotations (Ladd bands)

n Volvulus

n External, internal, diaphragmatic or pelvic hernias

2. **Intrinsic causes**

n Congenital conditions like intestinal atresia

n Benign and malignant tumours of small and large intestine

n Inflammatory process leading to stricture formation like Crohn’s disease, intestinal tuberculosis, ischemia, radiation and eosinophilic enteritis

n Fecal impaction produces colonic obstruction in immobile patients

Ileus (Adynamic Obstruction)

1. Postoperative

2. Abdominal trauma

3. Biliary or chemical peritonitis

4. Pancreatitis

5. Diverticulitis

6. Cholecystitis

7. Appendicitis

8. Retroperitoneal haemorrhage

9. Mesenteric ischemia

10. Drugs (opiates, antidepressants, anti-cholinergic)

11. Metabolic (hypokalaemia, hypocalcaemia, diabetic ketoacidosis)

Chronic Pseudo-obstruction

1. Endocrine disorders (diabetes, hypothyroidism, Addison disease)

2. Hereditary diseases (familial visceral neuropathy or myopathy)

3. Neuromuscular disease

4. Rhematological disease (scleroderma, SLE, amyloidosis)

Large Bowel Obstruction

1. Sigmoid volvulus

2. Colorectal neoplasm

3. Crohn’s disease

4. Radiation stricture

Clinical History

1. **Age**

nBO is the most common reason for the neonates for admission in the ICU. There are 4 cardinal features of intestinal obstruction in a newborn: (a) Prenatal maternal polyhydramnios; (b) Bilious vomiting; (c) No passage of meconium; and (d) Abdominal distension.

nInternal hernia and Meckel’s diverticulum is important case in children.

nColonic malignancy leading to obstruction is seen in elderly patients.

2. **Abdominal pain**

n Adynamic BO and gastric obstruction cause little abdominal pain, whereas mechanical small and large BO cause moderately severe abdominal pain.

n Pain of mechanical obstruction is dull, ill-defined or squeezing type with intermittent waves of increased pain. Small intestinal obstruction usually causes upper and mid abdominal pain while colonic obstruction causes lower abdominal pain.

3. **Abdominal distension**

n Gastric obstruction causes little abdominal distension, while distal obstruction and ileus lead to pronounced distension.

4. **Vomiting**

n Non-bilious, copious vomiting characterizes obstruction proximal to sphincter of Oddi, whereas bilious vomiting indicates obstruction distal to ampulla of Vater. Distal obstruction and ileus produce mild vomiting.

n Vomiting relieves the pain of proximal intestinal obstruction.

5. **Constipation**

n Adynamic obstruction produces constipation, whereas complete obstruction produces obstipation (inability to expel flatus).

6. **Diarrhoea**

n Diarrhoea presents in partial obstruction and fecal impaction (watery stool passes from the side of impacted stool).

7. **Gastrointestinal bleeding**

n Melena or hematochezia may present in intestinal ischaemia.

n Red currant jelly stool is seen in children with intus-susceptions.

8. Aggravation of pain with menstruation suggests endo-metriosis.

9. Careful history of medications and prior abdominal surgery are very important. BO in a virgin abdomen is non-adhesive and mostly due to congenital bands and internal hernia. Peritoneal adhesions causing SBO is the most common cause contributing 42.3%.

10.Recurrent BO is observed in three clinical situations. The first is on an unscarred abdomen, mostly due to internal

hernia, secondly during an early postoperative period, where there is likely confusion of postoperative ileus/ BO. The third scenario is being adhesive obstruction.

Physical Examination

1. Patient with mechanical obstruction usually appears to be in great distress, whereas patients with adynamic obstruction appear more comfortable despite abdominal distension.

2. Careful assessment of hydration status is very important in patients with obstruction or ileus.

Abdominal Examination

1. Inspect the abdomen for previous operative scar, hernia, distension, visible peristalsis and Cullen or Grey-Turner sign.

2. Signs of peritonitis indicate viscus perforation.

3. Hepatosplenomegaly, lymphadenopathy and masses suggest possibility of malignancy.

4. Tympany indicates both ileus and obstruction, whereas shifting dullness indicates ascites.

5. High-pitched, hyperactive, musical sounds indicate mechanical obstruction while hypo-active or absent bowel sound indicates ileus.

6. Digital and pelvic examinations are very important to detect subtle masses.

Diagnostic Procedures

1. ***Biochemistry***

n Laboratory tests are very important in patients with adynamic obstruction.

n Endocrine and metabolic parameters need to be measured in appropriate cases.

n Anaemia is one of the poor predicator of postoperative recovery.

2. ***Imaging studies***

n Plain radiographs (both supine and erect) are the most important. Left lateral decubitus film if patient cannot assume an upright position. In ileus, luminal dilatation is generalized. In complete mechanical obstruction, dilatation of proximal bowel with collapse distal end of the obstruction with no air seen distal to the obstruction is observed.

n Ultrasound abdomen may not be useful because of the excess bowel gas, which obscures the vision.

n Spiral CT abdomen with contrast has great value in identifying the aetiology of mechanical obstruction, able to differential dynamic versus adynamic obstruction. The radiographic transition zone alone does not increase the likelihood of surgical intervention or identify patients who will fail non-operative management. The four cardinal features - intra-peritoneal free fluid, mesenteric oedema, presence of the “small bowel faeces sign” and history of vomiting - are predictive of requiring operative intervention.

n MR pelvis is better than CT abdomen in sigmoid volvulus.

n Upper endoscopy is useful in suspected gastric or proximal duodenal obstruction.

3. ***Functional studies***

n Gastric emptying study for suspected gastroparesis.

n Antroduodenal manometry for chronic pseudo-obstruction.

Management

1. Correction of dehydration, electrolytes and acid-base imbalance is very crucial in the management of obstruction and ileus.

2. Patient should be nil orally with nasogastric suction. Oral gastrograffin solution may improve obstruction secondary to postoperative adhesion.

3. Discontinuation of the medication, which reduces intestinal motility.

4. Placement of rectal tube or endoscopic colonic decompression in patients with acute colonic pseudo-obstruction.

5. Complete obstruction and viscus perforation needs emergency surgery.

6. Prokinetic therapy and octreotide may be of benefit in patients with chronic pseudo-obstruction.

7. Studies are on to find an anti-adhesive intraperitoneal fluid or surface application like 4DryField PH and Seprafilm. Only the surface application of 4DryField PH and Seprafilm showed significant adhesion prevention capabilities. 4DryField PH achieved the highest adhesion prevention effectiveness without restrictions concerning mode of application and compatibility and, thus, is a promising strategy to prevent abdominal adhesions.

Further Reading

1. Baig MK, Wexner SD. Postoperative ileus: a review. *Dis Colon Rectum* 2004;47:516–26.

2. Saunders MD, Kimmey MB. Systematic review: acute colonic pseudo-obstruction. *Aliment Pharmacol Ther* 2005; 22:917–25.

3. Drozdd W, Budzynski P. Change in mechanical bowel obstruction demographic and aetiological patterns during the past century: observations from one health care institution. *Arch Surg* 2012;147:175–80.

4. Leung AM, Vu H. Factors predicting need for and delay in surgery in small bowel obstruction. *Am Surg* 2012;78:403–07.

5. Rami Reddy SR, Cappell MS. A Systematic review of the clinical presentation, diagnosis, and treatment of small bowel obstruction.*Curr Gastroenterol Rep* 2017;19:28.

**Chapter 10.**

**Gas and Bloating**

The intestine of a normal person typically contains 200 mL of gas and 600 mL of flatus evacuation per day. The principal gases in flatus are nitrogen, oxygen, carbon dioxide, hydrogen and methane. Nitrogen and oxygen content in flatus reflects the contribution from swallowed air, whereas hydrogen is generated by bacterial breakdown of dietary carbohydrates. Methane gas is produced by anaerobic methanogenic bacteria (e.g., *Methanobrevibacter smithii*). Carbon dioxide is produced from bacterial fermentation of dietary carbohydrates, fats and proteins. Flatus odour is related to sulphur-containing compounds in the expelled gas.

Definitions

1. **Eructation or belching** is the retrograde expulsion of oesophageal and gastric gas from the mouth.

2. **Supragastric belching** - Eructated air does not originate from the stomach and is expelled air from the oesophagus.

3. **Gastric belching** - A gastric belch is characterized by the escape of swallowed intragastric air that enters the oesophagus during a transient lower oesophageal sphincter relaxation. Gastric belches occur 25–30 times per day and are usually physiological and involuntary. Individuals with belching disorder usually have habitual air swallowing (aerophagia) and air may transit only to the oesophagus before being vented (supragastric belching).

4. **Magenblase syndrome** is defined as epigastric fullness and bloating relieved by belching.

5. **Flatulence** is the involuntary or volitional release of gas from the anus. The volume of gas passed per rectum varies from about 500–1500 mL per day. The frequency of flatus released varies between 10 and 20 times per day in healthy subjects.

6. **Bloating** is the perception of retained excess gas within the gut lumen.

According to the Rome IV criteria, belching disorder is defined as bothersome (i.e., severe enough to impact usual activities) belching from the oesophagus or stomach more than 3 days a week. These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Causes

Eructation

1. Involuntary postprandial belching

2. Magenblase syndrome

3. Aerophagia (e.g., as from gum chewing, smoking, oral irritation)

4. Gastroesophageal reflux

Bacterial Overgrowth

1. Intestinal or colonic obstruction

2. Diverticula of the small intestine

3. Hypochlorhydria

4. Chronic intestinal pseudo-obstruction

Functional Bowel Disorders

1. Irritable bowel syndrome

2. Non-ulcer dyspepsia

3. Idiopathic constipation

Carbohydrate Malabsorption

1. Lactase deficiency

2. Excess bean and legume ingestion

Gas Bloat Syndrome

1. Post fundoplication

Gas Bloat Syndrome

A consequence of fundoplication for gastroesophageal reflux disease is an inability to belch or vomit secondary to an unyielding wrap of gastric tissue around the distal oesophagus. In the initial months after fundoplication, up to two-third of patients experience bloating, upper abdo-minal cramping and flatulence (gas bloat syndrome).

Clinical History

1. Relief of symptoms with defecation or passage of flatus is consistent with a functional disorder.

2. Presence of associated vomiting, fever, weight loss, nocturnal diarrhoea, steatorrhoea and rectal bleeding indicate probable organic disease.

3. In patients with isolated symptoms of excessive belching, psychological and behavioural factors play an important role. Belches typically increase when patients

are aware they are being observed and are almost absent during sleep.

4. Ingestion of legumes, fruits, unrefined starches, and lactose-containing foodstuffs should be addressed.

5. Gum chewing, smoking and chewing tobacco predispose to aerophagia.

Physical Examination

n Physical findings are usually normal.

n Cachexia, jaundice and palpable masses indicate organic lesions.

n Functional disease patient may exhibit anxiety, hyper-ventilation and air swallowing.

n Peripheral or autonomic neuropathy is usually associated with dysmotility syndromes.

n Visible scars on abdominal inspection may be evidence of prior fundoplication and indicates gas bloat syndrome.

n Abdominal percussion and palpation may reveal tympany and distension in mechanical obstruction or pseudo-obstruction.

Diagnostic procedures

1. ***Blood chemistry***

n Usually normal blood chemistry as majority of the patients exhibit functional bowel disorders.

2. ***Imaging studies***

n Supine and erect plain abdominal radiographs may reveal generalized luminal distention with ileus, diffuse haziness in ascites and air-fluid levels in mechanical obstruction.

n Barium studies mainly for suspected mechanical obstruction.

3. ***Endoscopy study***

n Endoscopy indicated in suspected mechanical obstruction and in patients with alarming symptoms.

4. ***Functional studies***

n Gastric emptying scintigraphy or manometry of the oesophagus, stomach and small intestine can be performed when an underlying motility disorder is considered.

n Hydrogen breath testing to detect carbohydrate mal-absorption and bacterial overgrowth.

Management

1.Management is directed to the cause of gas and bloat. Patients should be advised to avoid gas-producing foods

(e.g., cabbage, onions, broccoli, brussel sprouts, wheat,

and potatoes). In patients without a significant improvement despite exclusion of gas-producing foods, we suggest a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs).

2.Lactase deficiency is controlled by excluding lactose from the diet.

3.Mechanical obstruction is usually managed surgically.

4.Proton pump inhibitors may reduce eructation associated with gastroesophageal reflux disease.

5.Baclofen (10 mg three times daily) by reducing transient lower oesophageal sphincter relaxations and centrally suppressing the swallowing rate may decrease both supragastric and gastric belching. It should be used judiciously in view of side effect profile.

6.Surgeries to vent the gut may help selected individuals with gas-bloat syndrome or intestinal pseudo-obstruction.

7.Aerophagia may be controlled by cessation of gum chewing and smoking and improving oral hygiene.

8.Simethicone alters the elasticity of mucus-covered intraluminal gas bubbles and promotes their coalescence.

9.Activated charcoal reduces symptoms caused by carbo-hydrate malabsorption.

10.Alpha galactosidase hydrolyzed complex carbohydrate in the lumen of the small intestine before they are fermented by colonic bacteria.

11.Prebiotic (fructooligosaccharides) repopulate the gut with nonpathogenic organisms that do not generate gas.

12.The prokinetic drug reduces bloating in patients with irritable bowel syndrome and constipation.

13.In patients with functional abdominal distension, biofeedback may decrease distension. EMG activity of the intercostals and diaphragm significantly decreased after biofeedback, whereas activity of the abdominal muscles, particularly the internal oblique, significantly increased.

Further Reading

1. Salvioli B, Serra J, Azpiroz F, Lorenzo C, Aguade S, Castell J, Malagelada JR. Origin of gas retention and symptoms in patients with bloating. *Gastroenterology* 2005;128:574–9.

2. Jones MP. Bloating and intestinal gas. *Curr Treat Options Gastroenterol* 2005;8:311–8.

3. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480.

4. Schmulson M, Chang L. Review article: the treatment of functional abdominal bloating and distension. *Aliment Pharmacol Ther* 2011;33:1071.

SECTION 2

BASIC SCIENCE

**Chapter 11.**

**Anatomy and Physiology of Gastrointestinal Tract**

oEsophagus

The oesophagus is a hollow muscular tube for carrying food from mouth to stomach. It is collapsed in the resting state but can be distended to 2 cm anteroposteriorly and 3 cm laterally for a food bolus. From inside out it is composed of mucosa, submucosa, muscularis propria and adventitia. It has no serosa.

Upper oesophagus is composed of skeletal muscles, the lower half by smooth muscle and a mix of both in between. The proximal end of oesophagus is made by the **upper esophageal sphincter (UES)** – a merger of inferior pharyngeal constrictor and cricopharyngeus muscles. Below the UES, the oesophagus has outer longitudinal and inner circular muscle layers of the muscularis propria. The thoracic oesophagus lies posterior to the heart and anterior to the aorta and at level of T10 vertebra pierces the right crus of diaphragm to enter the abdomen. The circular muscle of oesophagus in the diaphragmatic hiatus is asymmetrically thickened to create a 2–4 cm high pressure region called **lower esophageal sphincter (LES)**. At rest, the LES is a contracted, high pressure zone maintained by the phrenoesophageal ligament.

The oesophageal wall has both parasympathetic and sympathetic innervations. Peristalsis is regulated via vagus. Nucleus ambiguous controls the skeletal muscle while dorsal motor nucleus manages the smooth muscle. Efferent vagal nerves terminate in the striated muscle of upper oesophagus while those of the smooth muscle end in the myenteric plexus of Auerbach between the two muscle layers.

The upper oesophagus is supplied by branches of superior and inferior thyroid arteries, middle by branches of bronchial and intercostal arteries and distal by branches of left gastric, left inferior phrenic and splenic arteries. The upper oesophagus drains into superior vena cava, middle through azygos veins and distal through portal vein by left and short gastric veins. Submucosal venous network of distal oesophagus contributes to the formation of varices. Lymph from the upper oesophagus drains into deep cervical nodes, from mid-oesophagus to mediastinal nodes and from lower to celiac and gastric nodes.

The mucosa of the oesophagus is smooth and pink and formed by stratified columnar epithelium. The junction with the stomach is marked by irregular white Z-line. There are three layers of the mucosa of which the outer most is basal layer composed of cuboidal cells. Basal cell hypertrophy leading to increase in its thickness to more than 15% indicates reflux disease. Below the mucosa is the lamina propria composed of loose connective tissue with vessels.

Submucosa is dense network of connective tissue with blood vessels, lymphatic channels, Meissner’s plexus and glands. These glands produce mucus, bicarbonate and growth factor, which are delivered to the mucosa. Oesophageal motor function is described in Chapter 1.

The **esophagogastric junction (EGJ)** is a high pressure zone due to the LES and the surrounding crural diaphragm. Resting LES pressure is 10–30 mmHg relative to intragastric pressure. It is a property of the sphincter itself and the nerves supplying it. Other factors that affect LES pressure are intra-abdominal pressure, gastric distension, peptides, hormones, food and medications. The LES has both excitatory and inhibitory neurons and is controlled by the vagus. Adrenergic stimulation increases the LES pressure, whereas nitric oxide reduces LES pressure. The diaphragm is a major additive to the EGJ pressure. On inspiration, there is an increase in the LES pressure due to the diaphragm.

The function of the EGJ is to contain the stomach content but allow venting of gas. This is done by transient relaxations of the LES independent of swallowing or pressure. These **transient LES relaxations (tLESRs)** are different from swallow induced in many ways:

1. More than 10 sec relaxation without pharyngeal swallowing

2. Oesophageal shortening caused by contraction of longitudinal muscle

3. No synchronised peristalsis

4. Inhibition of crural diaphragm

5. They occur in post-prandial state and cause belching

Fatty meal increases tLESRs by CCK and baclofen inhibits tLESRs by acting on receptors of dorsal motor nucleus of vagus and peripheral receptors.

Mechanical, electrical, chemical and thermal stimuli are detectable by the oesophagus. These are felt as chest pressure, warmth or pain with overlap. Sensation is carried by both vagal and spinal afferent nerves.

Stomach

The stomach, a J-shaped dilation of the alimentary canal connects the oesophagus and duodenum and acts mainly to store food, initiate digestion and release it into the duodenum intermittently after grinding. The adult volume of the stomach is 1.5–2 liters. The gastroesophageal (GE) junction lies to the left of tenth thoracic vertebral body and the gastroduodenal junction at L1 to the right of the mid line.

Posterior to the stomach are pancreas, transverse colon, diaphragm, spleen and apex of right kidney and adrenal gland. The posterior wall of the stomach is the anterior wall of the lesser sac.

Peritoneum covers the stomach. Greater sac (peritoneal cavity) and lesser sac are two main regions of the peritoneal cavity, connected by the omental foramen (previously known as the Foramen of Winslow). The lesser omen-tum (or gastrohepatic) is attached to the lesser curvature of the stomach and the liver. The greater omentum (or gastrocolic) hangs from the greater curve of the stomach upwards to the transverse colon. Anterior margin of lesser sac consist of quadrate lobe of the liver, lesser omentum, stomach and gastrocolic ligament. Left kidney, left adrenal gland and pancreas form posterior margin, spleen and gastrosplenic ligament form lateral margin while, greater omentum forms inferior margin.

The part of the stomach immediately inferior to the GE junction is the cardia. Below the fundus is the body and its lower boundary is marked by a sharp indentation in the lesser curvature - incisura angularis. Below the body is the antrum, which meets the pylorus.

The stomach is supplied by the common hepatic, left gastric and splenic branches of the celiac artery forming an arcade along greater and lesser curvatures. The lesser curvature is supplied from above by left gastric artery and below by right gastric artery (branch of common hepatic or gastroduodenal artery). The greater curvature is supplied below fundus by left gastroepiploic artery (branch of splenic artery) above and below by right gastroepiploic artery (branch of gastroduodenal artery). The short gastric branches of the splenic artery supply the fundus and left upper aspect of greater curvature. The venous drainage accompanies the arterial supply. The lymphatic drainage of stomach is ultimately to the celiac nodes. Gastric innervation is carried out by the sympathetic (T6-T8 level) and parasympathetic system (right and left vagus nerves).

The wall is made up of mucosa, submucosa, muscularis propria and serosa. The mucosa of the stomach forms thick longitudinal folds called rugae, which flatten on distension. The stomach mucosa’s epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. The submucosa is composed of dense

connective tissue of collagen and elastin. The muscularis propria has three layers: inner oblique, middle circular and outer longitudinal. The inner oblique fibres course over the fundus. Middle circular fibres encircle the body of the stomach and thicken to form the pyloric sphincters. The outer longitudinal fibres are mainly seen in greater and lesser curvature of the stomach. The outermost layer or serosa is basically visceral peritoneum.

The main function of the stomach is production of hydrochloric acid (HCL). Acid converts pepsinogen into pepsin helping in protein digestion. It facilitates absorption of iron, calcium, vitamin B12, drugs like thyroxin and prevents bacterial overgrowth, enteric infections and perhaps community-acquired pneumonia.

The stomach also secretes lipase, intrinsic factor, electrolytes and mucins. Neurocrine agents like acetylcholine (ACh), gastrin-releasing peptide (GIP) and vasoactive intestinal peptide (VIP) are released from nerve terminals. Histamine and somatostatin are released by paracrine methods.

The functional areas of the stomach are oxyntic and pyloric gland areas. The parietal cell or oxyntic cell area (oxys = acid) occupies the fundus and body (80% of stomach). The pyloric gland area occupies the antrum and is marked by gastrin or G-cells.

The glandular area is formed by tubular pits (gastric pits) composed of apical pit region, isthmus and the actual gland, which is the lower part of the unit. These glands are made up of a variety of secretory cells. These include parietal cells (produce **hydrochloric acid** and **intrinsic factor**), chief cells (secrete **pepsinogen**), mucous neck cells and entero-endocrine cells (G-cells secrets gastrin, enterochromaffin-like cells release histamine, etc).

Parietal cells secrete acid. The stimulants of acid secretion are: (a) ACh released by enteric neurons (neural), (b) Gastrin secreted by antral G-cells (hormonal) and (c) Histamine released by ‘ECL’ cells. The main inhibitor is somatostatin released from oxyntic and D-cells.

In the basal or resting stage, acid secretion is maintained at a lower level by somatostatin. During ingestion of meal, the inhibition is removed. The thought, sight, smell and taste of food acts by the vagus to raise gastric secretion. The parietal cell is stimulated directly by ACh, and ACh also inhibits somatostatin secretion. In the antrum, cholinergic neurons act on G-cells to stimulate gastrin secretion. Gastrin stimulates parietal cells to secrets acid. As meal empties, the inhibitory effect of somatostatin is restored.

The motor functions of the stomach are: (a) Relaxation of the fundus on receipt of food, (b) Peristaltic waves of fundus and antrum, (c) Peristaltic waves of antrum in coordination with antropyloroduodenal activity. These results

in proper reception of food, grinding of the food into suspension called chyme.

The myoelectrical activity of the stomach is called slow waves. These waves originate from the pacemaker region of the greater curvature sited between fundus and proximal corpus and propagate both distally and circumferentially at a rate of 3 cycles per second. The **interstitial cells of Cajal (ICCs)** are the pacemaker located in the myenteric plexus (MY-ICCs). MY-ICCs are responsible for the slow waves. Loss of ICCs of the antrum leads to gastroparesis in diabetes mellitus.

**Enteric nervous system (ENS)** of the stomach receives signals from CNS via the sympathetic and para-sympathetic systems. The ENS provides local reflex circuits, which cause secretion and contraction. ACh leads to contraction and nitric oxide (NO) leads to relaxation.

Gastric neuromuscular activity during fasting is characterized by the highly regular pattern called **migrating motor complex (MMC)**. These migrate from antrum to ileum. They are responsible for clearance of non-digestible, fibrous foodstuff of stomach after meal. MMCs are independent of vagus and are caused by motilin released from duodenum.

The work of the stomach to mix, grind and empty food depends on physical characteristics and volume of food. The work begins with relaxation of the fundus during a meal to accommodate it without any change in the intragastric pressure. Solid food is stored in the fundus while liquids are distributed to corpus and antrum. Food is transferred to corpus and antrum for trituration. Accommodation and trituration constitute the lag phase, which may last up to 60 min for a solid meal. Once the food is grinded to 1–2 mm particles, peristalsis mixes the acid, saliva, pepsin and food to produce chyme; a process called milling. The pylorus is closed during the trituration stage but opens up regularly during the linear emptying phase.

The gastric neuromuscular response to liquids is totally different to that for solids. Liquids are emptied faster than solids as no trituration is required. Non-caloric liquids empty without lag phase but caloric liquids require time. The rate of gastric emptying is influenced by volume, nutrient content, viscosity and osmolarity of the liquids.

Fat delays gastric emptying. Monosaccharides in the duodenum stimulate release of incretin such as **glucagon-like polypetride-1 (GLP-1)**, which promote insulin secretion and delays gastric emptying. Hyperglycaemia decreases the fundic tone, decreases antral contractions and induces gastric dysrhythmias. Hypoglycaemia increases contractility and emptying.

Fatty acids in ileum lead to decreased gastric emptying by a reflex called the “**ileal brake**.” Women have slower gastric emptying and emptying increases as BMI increases.

Hunger is a basic human instinct that is suppressed by eating. **Motilin** is increased in the fasting state but its role in hunger is not clear. **Ghrelin** (secreted by oxyntic glands of fundus) stimulates food intake. Orexins synthesized by hypothalamus stimulate appetite. Food in stomach leads to decrease in ghrelin levels. Bariatric surgery leads to great drop in ghrelin levels. CCK, leptin, GLP-1, apolipoprotein A-IV and polypeptide YY (PYY), lead to satiety by enhancing fullness and decreasing antral contractions.

Pancreas

The pancreas is a small, soft flattened gland with a length of around 12–20 cm and weighs around 70 and 110 g. The head on the right side lies within the duodenal curve. The neck, body and tail lie obliquely in the posterior abdomen with the tail reaching to the gastric surface of the spleen. The head is surrounded by the second and third parts of duodenum. Its anterior surface is adjacent to pylorus, D1 and transverse colon. The posterior surface touches the hilus and medial border of right kidney, the IVC and right renal vessels, the gonadal vein and right crus of diaphragm. The uncinate process, an extension of the lower part of the head, lies anterior to aorta and IVC and is covered by superior mesenteric vessels. The neck is the constricted part of gland and is at the confluence of superior mesenteric vein and portal vein. Anteriorly it is covered in part by pylorus and lesser sac. The body of pancreas is retroperitoneal and runs towards the left side with the aorta behind it. Also posterior are origin of SMA. The midline part of the body overlies the lumbar vertebrae making it vulnerable to abdominal trauma. The tail reaches the hilus of the spleen. It is in the two layers of splenorenal ligament with splenic artery and vein. The splenic flexure of the colon is close to the tip of the tail.

The pancreas develops from two outgrowths of the foregut distal to the stomach. The ventral outgrowth gives rise to the common bile duct, gallbladder, liver and the ventral pancreatic anlage that becomes a portion of the head of the pancreas with its duct system including the uncinate portion of the pancreas. The dorsal pancreatic anlage gives rise to a portion of the head, the body and tail of the pancreas. Fusion of the duct systems results in the formation of the main pancreatic duct from the ducts of both dorsal and ventral anlagen. The caudal portion of the head of the pancreas (uncinate) and the major papilla (ampulla of Vater) are derived from the ventral anlage. The minor papilla that drains the duct of Santorini is derived from the dorsal anlage.

The **main pancreatic duct (MPD) of Wirsung** begins near the tail consequent to anastomosing ductules and lies between the upper and lower borders. The MPD turns caudally and posteriorly on reaching the head of the pancreas and then horizontally to join with CBD at the major papilla. The MPD and CBD may open separately; have a common channel or have an interposing septum. Around 75% of patients have the common channel, 20% have separate openings and the rest have a septum. The MPD is 3.1–4.8 mm in the head and tapers off to 0.92–2.4 mm in the tail.

The pancreas has a good supply from branches of celiac and superior mesenteric arteries. The head of the pancreas is supplied by two pancreaticoduodenal arterial arcades. They are formed by anterior and posterior-superior pancreaticoduodenal arteries from hepatic branch of celiac artery joining second pair of anterior and posterior inferior pancreaticoduodenal arteries. Other arteries supplying the body and tail are dorsal pancreatic artery and caudal pancreatic artery. The lymphatic drainage of head flows into celiac and superior mesenteric groups of pancreatic nodes and in to cisterna chyli. The visceral afferent fibres of the vagi and splanchanic nerves supply the pancreas.

Exocrine pancreas, the portion of the pancreas that makes and secretes digestive enzymes into the duodenum. This includes acinar and duct cells with associated connective tissue, vessels and nerves. The exocrine components comprise more than 95% of the pancreatic mass.

Endocrine pancreas, the portions of the pancreas (the islets) that make and secrete insulin, glucagon, somatostatin and pancreatic polypeptide into the blood. Islets comprise 1–2% of pancreatic mass.

The pancreas is a compound gland that does not have a fibrous capsule. The lobules are visible on gross examina-tion and are connected by septa that carry blood vessels, nerves, lymphatics and excretory ducts. Two percent of the gland is endocrine as represented by the islets of Langarhans, which are clusters scattered throughout the gland. The exocrine cells are dark staining acini made of tubular and spherical masses of cells.

The acinus is the basic unit of pancreas. Its lumen is the beginning of the ductal system. Next are the intralobular and interlobular ducts, which open into the MPD. Acinar cells are tall, pyramidal columnar epithelial cells with zymogen granules, which are the enzymes contained within a capsule. The islets of Langarhans are 1 million in number and are composed of polygonal endocrine cells. The blood from islet cells goes to the capillaries of the acinar cells forming a portal system. Insulin is secreted by B (beta) cells, which are in majority (50–80%). A or alpha cells secrete glucagon, PP cells secrete pancreatic polypeptide and D cells secretes somatostatin. The main inorganic constituents of pancreatic

secretion are water, sodium, potassium, chloride and bicarbonate. These neutralize gastric acid and deliver the enzymes to the lumen. Organic constituents are the proteolytic, amylolytic, lipolytic and nuclease digestive enzymes. Enzymes are stored and secreted in precursor forms. Trypsinogen is activated to trypsin by enterokinase of small bowel, which then activates other enzymes.

Amylase is secreted by pancreas as well as salivary glands. It digests the starch of food into maltose, maltotriose and alphadextrins. Final digestion is done by intestinal enzymes of the brush border. Pancreas is the most important source of the lipase. There are three lipases: triglycerides lipase, phospholipase A2 and carboxyelasterase. Salivary and gastric lipases act in a minor manner. Triglyceride is hydrolyzed to two fatty acid molecules and one mono-glyceride molecule. Bile acids and colipase are important for digestion of fat. The two major pancreatic proteases are trypsin and chymotrypsin, which are synthesized and packaged into secretory vesicles as the inactive proenzymes trypsinogen and chymotrypsinogen. Once trypsinogen and chymotrypsinogen are released into the lumen of the small intestine, they must be converted into their active forms in order to digest proteins. Trypsinogen is activated by the enzyme enterokinase, which is embedded in the intestinal mucosa.

During interdigestive periods, very little pancreatic secretion takes place. But once food enters the stomach and, a little later, chyme flows into the small intestine, pancreatic secretion is stimulated. Like gastrin, pancreatic secretion has three phases: cephalic, gastric and intestinal. The cephalic phase secretion is carried out by the vagal nerves. The gastric phase occurs due to distension caused by a meal. As chyme enters into the small intestine, cholecystokinin (secreted by enteric endocrine cells located in the duodenum) is released into blood and binds to receptors on pancreatic acinar cells lead to secrete large quantities of pancreatic enzymes. Secretin (secreted by enteric endocrine cells located in the proximal small intestine) stimulates duct cells to secrete water and bicarbonate to neutralize acidic chyme. Pancreatic juice secretion is principally regulated by the hormones secretin and cholecystokinin, which are produced by the walls of the duodenum, and by the action of autonomic innervation.

Liver

The liver is the largest organ, accounting for approximately 2–3% of average body weight (approximately 1400 g in females and 1800 g in males) occupy in right upper quadrant of abdomen with brown colour and smooth surface. It has unique dual blood supply: 80% is delivered by the portal vein (deoxygenated blood, from the spleen and intestines); the remaining 20% (the oxygenated blood), is delivered by

the hepatic artery. The portal vein is formed by the union of the splenic and the superior mesenteric veins with the inferior mesenteric vein draining into the splenic vein. In the majority of cases, the common hepatic artery is a branch of the celiac artery along with the splenic and left gastric arteries. Externally, the liver is divided by the falciform ligament into a larger right lobe and a smaller left lobe. The falciform ligament attaches the liver to the anterior abdominal wall. Its base contains the ligamentum teres, which has a remnant of the vestigial umbilical vein. In cirrhosis, this vein recanalizes as a result of portal hypertension. It is covered by Glisson’s capsule, a visceral continuation of the peritoneum. Cantlie’s line, joining the gallbladder fossa to the inferior vena cava, separates the liver into the true right and left lobes.

Based on **Couinaud’s classification**, the liver is divided into eight independent functional segments **(Figs 11.1 and 11.2)**. Each segment has its own portal pedicle consisting of the hepatic arterial branch, portal branch and the bile duct with a separate hepatic venous branch that provides outflow. The numbering of segments is in a clockwise manner. Segments II and III, are known as the anterior and posterior segments of the left lobe, respectively, are also known collectively as the left lateral segment of the liver. Segment IV is the medial segment of the left lobe. Segments II, III and IV collectively make up the functional left lobe of the liver. The functional right lobe of the liver is made up of segments V and VIII, the anterior segments, and segments VI and VII, the posterior segments. Segment I, the caudate lobe, is located post-eriorly. Nomenclature of hepatic resection is described below **(Table 11.1)**.

The outflow of the liver is provided by the three hepatic veins. The right hepatic vein divides the right lobe of the liver into anterior and posterior segments. The middle hepatic vein divides the liver into the right and left lobes and runs in the same plane with the inferior vena cava and the gallbladder fossa. The left hepatic vein divides the left liver into medial and lateral segments. The portal vein divides the liver into the upper and lower segments **(Fig. 11.2)**.

It is important to know the segmental anatomy on the CT scan or ultrasound abdomen. Transverse anatomy at the level of right and left hepatic vein **(Fig. 11.3)**, at the level of left portal vein **(Fig. 11.4)** and at the level of splenic vein **(Fig. 11.5)**.

Microscopically, each liver lobe is seen to be made up of hepatic lobules **(Fig. 11.6)**. The lobules are roughly hexagonal and consist of plates of hepatocytes radiating from a central vein. The central vein joins to the hepatic vein to carry blood out from the liver. Portal triad, running along each of the lobule’s corners, consists of five structures: a branch of the hepatic artery, a branch of the portal vein, a bile duct, lymphatic vessels and a branch of the vagus nerve.

Between the hepatocyte plates are liver sinusoids, which are enlarged capillaries through which blood from the portal vein and hepatic artery enters via the portal triads and then drains to the central vein. Hepatic acinus (metabolic zone), a diamond-shaped structure is formed by two hepatic lobules **(Fig. 11.7)**. Zone I hepatocytes are specialized for oxidative liver functions such as gluconeogenesis, beta oxidation of fatty acids and cholesterol synthesis. Zone III cells are more important for glycolysis, lipogenesis and cytochrome P-450-based drug detoxification.

**Anatomical resection Liver segments**

Left lateral segmentectomy II, III

Left medial segmentectomy IV

Right anterior segmentectomy V, VIII

Right posterior segmentectomy VI, VII

Left hepatectomy II, III, IV

Right hepatectomy V, VI, VII, VIII

Extended left hepatectomy II, III, IV, V, VIII

Extended right hepatectomy IV, V, VI, VII, VIII

There are two major types of liver cells: parenchymal cells and nonparencyamal cells. About 70–85% of the liver volume is occupied by parenchymal hepatocytes and rest are non-parenchymal cells. The liver sinusoids are lined with two types of cells, sinusoidal endothelia cells and phagocytic Kupffer cells. Hepatic stellate cells are non-parencyamal cells found in the perisinusoidal space between sinusoids and hepatocytes.

Gallbladder and Biliary System

Biliary System

The adult human liver has an extensive network of bile ductules and ducts. The portal blood vessels, lymphatics and bile ductules are in close proximity near hepatic hilum allowing exchange of materials between each other. Although ultrastructurally similar, large ducts have different functions vis-a-vis small ducts. For example, large ducts respond to secretin to change bile secretion. The common hepatic duct (CHD) arises from the union of right and left hepatic ducts and emerges from the porta hepatis. In 95% of the cases, the right and left hepatic ducts fuse outside the liver. The hepatoduodenal ligament envelops the hepatic duct and binds it to the blood vessels. The CHD is 3 cm long and is joined by cystic duct on the right side to form the common bile duct (CBD). This happens in 70% of the cases. The CBD is 7 cm long and is anterior to portal vein, lateral to hepatic artery and runs in the lesser momentum. It has a diameter of 0.5–1.5 cm. The CBD passes behind the first part of duodenum and pancreas and enters the second part of duodenum. Then it passes obliquely through the posteromedial aspect of duodenal wall and joins the MPD to form the ampulla of Vater. The bile duct tapers to a diameter of 0.6 cm before uniting with the MPD.

The sphincter of Oddi **(Fig. 11.8)** is the thickening of smooth muscle that happens to pancreatic and biliary ducts traversing the duodenal wall. It is composed of: (a) sphincter choledochus – muscle surrounding intramural portion of CBD before its junction with MPD, (b) sphincter pancreaticus – muscle investing intraduodenal portion of MPD before its union with CBD, (c) fasciculi longitudinales – longitudinal fibres between CBD and MPD and (d) sphincter ampullae – longitudinal muscle layers surrounding scanty circular muscle fibres around ampulla of Vater. Contraction of fasciculi longitudinales shortens length of CBD and speeds up bile flow into duodenum. Contraction of sphincter ampullae shortens ampulla and prevents of reflex of intestinal contents into the ducts.

The bile ducts are supplied by right hepatic artery. The lymphatic vessels of the hepatic, cystic and proximal portions of bile duct empty into nodes at the hilum of liver. Lymphatics draining from lower portion of the bile duct drain into nodes near the head of pancreas. All the structures of the liver are innervated by both limbs of the autonomic nervous system. Multiple neurotransmitters are involved in the regulation of bile flow.

Bile secretion begins at the level of bile canaliculus, which is the smallest branch of the biliary tree. The canaliculi form a network of channels between hepatocytes. Next bile passes through the canals of Hering having basement membrane lined by hepatocytes and cholangiocytes. Bile goes to large perilobular or intralobular ducts via the canals of Hering. Initially lumen is bounded by cholangiocyte and hepatocyte but later ducts are lined by 2–4 cuboidal cells. Bile flows from central lobular cells to portal triads (zone 3 to zone 1).

The network of lobular ducts surrounds the branches of the portal vein. This helps to participate in the exchange of substances with bile and plasma. As calibre of ducts increases, there are smooth muscle fibres in the wall and the epithelium becomes thick with increased surrounding connective tissues, which contains elastin fibre. The cystic, common hepatic and bile ducts have mucosa, submucosa and muscularis. The lining is by columnar epithelium. Tubular glands secreting mucus are found in submucosa and open into the mucosal surface.

Gall Bladder

The gall bladder is the storage for the bile secreted by the liver and delivers it in a concentrated form to the duodenum as required. It is located in its fossa on the under surface of the right lobe of liver. It has a capacity of 30–50 mL.

The mucosal surface is thrown into many folds. The gall bladder is divided into fundus, body, infundibulum and neck. The anterior portion of the fundus is located at the level of right border of rectus abdominis and ninth coastal cartilage. The posterior aspect is in contact with transverse colon and duodenum. Bulging of the infundibulum on the inferior

surface lying close to the neck is Hartman’s pouch. Impac-tion of stones in Hartman’s pouch and lead to cholecystitis and inflammation can lead to extrinsic biliary duct comp-ression (Mirizzi’s syndrome).

The gall bladder is connected to the cystic duct at the neck and is 4 cm long. The mucosa of the neck forms the spiral valves of Heister, which regulates bile flow.

The cystic artery, a branch right hepatic artery, supplies the gall bladder. Ischaemic injury and necrosis of the gall bladder are possible because the cystic artery is an end artery. The cystic vein drains into the portal vein and occasionally into hepatic sinusoids. The subserosal and submucosal lymphatics empty into a lymph node near the neck of gall bladder. The sympathetic nerves of gall bladder are from the celiac axis and travels with branches of hepatic artery and portal vein. Gall bladder motility is likely regulated by branches of the vagi.

The lining of the gall bladder is columnar epithelium. The wall has a mucosa, lamina propria, tunica muscularis and serosa. **Mucus** is produced by the tubuloalveolar glands of the neck region. Invaginations of the surface epithelium that may extend through the muscularis are called Rokitansky– Aschoff sinuses. Hepatic surface of the gall bladder may show ducts of Luschka, which open into the intrahepatic bile ducts instead of the gall bladder cavity. They may cause bile leak after cholecystectomy.

Bile Acid

**Bile** is a lipid-rich micellar solution made up of water, inorganic electrolytes, organic solutes like bile acids, phospholipids (mainly phosphatidylcholine), cholesterol and bile pigments. The amount of bile formed is 500–600 mL/day. Bile is required for lipid digestion and absorption, cholesterol balance and hepatic excretion of xenobiotics, drug metabolites and heavy metals. The process of bile formation is dependent on bile acids synthesized by hepato-cytes and secreted by canaliculi. Bile is stored in the gall bladder. After meal, it is emptied into the duodenum. Bile acids are absorbed by ileum and returned to liver and absorbed by hepatocytes across the sinusoidal membrane (enterohepatic circulation).

**Bile acids** are essential for the absorption of dietary fats, fat-soluble vitamin and cholesterol. They also accelerate protein hydrolysis by pancreatic enzymes. Bile acids are important for cholesterol homeostasis.

They facilitate cholesterol absorption in the intestine. They are also a major route of cholesterol elimination by fecal expiration. Bile acid form a part of antimicrobial defense mechanism of the intestine by bacteriostatic action of mixed micelles. Bile acids prevent the formation of calcium gallstones and oxalate kidney stones.

Bile Acid Synthesis and Metabolism

Bile acids are derived from cholesterol in pericentral hepatocytes. The primary bile acids are **cholic acid (CA)** and **chenodeoxycholic acid (CDCA)**. Before secretion into the bile canaliculus, both CA and CDCA are conjugated with glycine or taurine. The utility of conjugation is to prevent diffusion across cells in the small intestine as they are absorbed in the ileum. Most of the conjugated bile acids are absorbed intact. Around 15% of bile acids are deconjugated by bacterial flora in distal small bowel; the unconjugated bile acids are absorbed passively and returned to the liver. Bacteria convert CDCA into **ursodeoxycholic acid (UDCA)**. UDCA is conjugated in the liver and forms 5% of the bile acid pool. A small portion of bile acids reaches colon where bacterial action converts CA into **deoxycholic acid (DCA)** and CDCA into **lithocholic acid (LCA)**. These are the secondary bile acids and are absorbed by the colon into the liver.

The Enterohepatic Circulation

The participants in the enterohepatic circulations are liver, biliary tract, gall bladder, small intestine, portal venous circulation and to a minor extent, colon, systemic circulation and kidneys. In fasting, bile moves to the gall bladder and gets concentrated there. After meal, the bile acids are emptied into the small bowel and carry out digestion of fat. The gall bladder being empty, hepatic bile also enters the small bowel. In the interdigestive period, the sphincter of Oddi contracts and bile collects in the gall bladder. After cholecystectomy, bile acids are stored in the upper small bowel.

Less than 10% of the intestinal bile acids escape into the feces. Bile acids are absorbed by active transport system in the terminal ileum. Around 2–4 g of bile acids forms the pool and it is recycled 2–3 times per meal. Only 0.2–0.6 g of bile acids is excreted in the stool. A portion of the bile acids (10–50%) returning via the portal circulation escapes hepatic extraction and spills into systemic circulation. Herein they bind with plasma proteins and are reabsorbed by the renal tubules. Only 1% of the bile acids in the glomerular filtrate is detectable in the urine.

Small and Large Intestine

Small Intestine

It is a specialized tubular structure contiguous with the stomach proximally and the large intestine distally. In an adult, it measures 600–800 cm (20–26 feet).

The duodenum, most proximal part of the small bowel, lies retroperitoneally from bulb to the junction with the jejunum where it becomes intraperitoneal. The jejunum and ileum are suspended in the peritoneal cavity by mesentery

attached to posterior wall, which facility allows for mobility.

The jejunum and ileum form 40 and 60% of the small bowel, respectively. The jejunum is in the left upper abdomen and the ileum occupies the right part of abdomen and pelvis.

The mucosal surface of the small bowel is thrown into folds, the **plicae circularis**. They are more numerous in the jejunum and progressively decrease distally and are absent in the terminal ileum. **Peyer’s patches** are clusters of lymphoid follicles in the small bowel with the highest number in the ileum.

Colon and Rectum

The colon joins the small bowel at the ileocecal valve, which has two semilunar lips protruding into the cecum. The valve acts as a barrier to colonic contents and is maintained by superior and inferior ileocecal ligaments. The colon is a tube of length 150 cm with a diameter of 7.5 cm at the cecum and 2.5 cm at the sigmoid. The longitudinal muscle fibres of the colon unite to form 3 bands called taeniae located at 120o intervals around the colonic circumference. The taeniae stretch from the appendix to proximal rectum. Between the taeniae are out pouching of the colon called the haustra. The external surface of the colon shows small sacs of peritoneum filled with adipose tissue called appendices epiploicae.

The beginning of the colon is the cecum, which lies in the right iliac fossa and projects as the blind pouch below ileum. It is a sacccular structure 6–8 cm in length as well as breadth. On account of its large diameter and thin wall, it is likely to rupture due to distal obstruction and can harbour tumors without symptoms. The vermiform appendix is a blind out pouching beginning below the ileocecal valve. The ascending colon stretches from cecum to hepatic flexure. Its length is 12–20 cm and it lies retroperitoneally.

The colon turns anteriorly and medially into the peritoneal cavity at the hepatic flexure to form the transverse colon. It is longest part (40–50 cm) of the colon and the most mobile. In the upright position, it may dip into the pelvis where it may become fixed by adhesions as after hysterectomy, making colonoscopy difficult. The descending colon, about 30 cm in length, travels posteriorly and then inferiorly and retroperitoneally to the pelvic brim where it emerges peritoneally as the sigmoid colon. This S-shaped

segment is variable in length, tortuosity and mobility and challenges colonoscopists and radiologists.

The rectum is 10–12 cm and beginning at the peritoneal reflection follows the sacral curve and ends at the anal canal.

Anal Canal

The anal canal is approximately 5 cm in length and has well-defined upper and lower boundaries. The anorectal ring is the proximal boundary and is composed of upper portion of

the internal anal sphincter, rectal longitudinal muscle, deep

portion of the external anal sphincter and puborectalis of the levator ani muscle. The distal boundary is the transition of anoderm to true skin. The anal canal and distal 3 cm of rectum contains 6–12 longitudinal folds called **columns of Morgagni**, which culminate in the anal papillae. These columns are joined by folds called anal valves situated at the dentate line. The muscularis mucosa is absent in the anorectal canal. The inner circular muscular layer thickens to form the internal anal sphincter. The external anal sphincter surrounds the anal canal and its fibres blend with those of levator ani to attach posteriorly to coccyx and anteriorly to perineal body.

Vascular Supply

The superior mesenteric artery supplies to distal duodenum, jejunum and ileum, ascending colon and proximal two thirds of transverse colon. The rest of the colon is supplied by branches of inferior mesenteric artery. The anal canal is supplied by superior, middle and inferior haemorrhoidal arteries being the branches of inferior mesenteric, hypo-gastric and internal pudendal arteries, respectively. Venous drainage is by both portal and systemic circulations. The internal haemorrhoidal plexus drains into portal circulation and the distal anus drains into the internal iliac vein.

Lymphatic Drainage

The lymphatic drainage is along the blood supply to lymph nodes in celiac, superior preaortic and inferior preaortic regions. From there lymph goes to cisterna chyli to thoracic ducts and then to left subclavian vein. Anal drainage proximal to dendrite region is to inferior mesenteric and periaortic nodes while distally it is to inguinal lymph nodes. The lymphatics of the small intestine are called lacteals due to milky lymph called chyle generated after eating.

Innervation

The parasympathetic and sympathetic nervous system supply the intestine and connect with the **enteric nervous system (ENS)**. The **myenteric plexus of Auerbach** is located between two layers of muscle.

The submucosal plexus of Meissner’s has ganglia and nerve bundles. The nerve fibres from the plexus supply the muscularis mucosa and smooth muscle of the villi.

Histology

Mucosa

The inner most layer of the intestine is formed by glands, lamina propria and muscularis mucosa. The glands form crypts. The lamina propria is connective tissue with lymphocytes, plasma cells, eosinophils, lymphatics and capillaries. The muscularis mucosa is the layer of smooth

muscle. The glandular epithelium is made of variety of cells:

stem cells, undifferentiated crypts cells, absorptive cells, secretory cells (goblet, Paneth and enteroendocrine cells) and M cells.

Submucosa

The submucosa lying below the mucosa is fibrous connective tissue containing fibroblasts, mast cells blood and lymph vessels and a plexus of nerve fibres - **Meissner’s plexus** - made of unmyelinated, post ganglionic sympathetic fibres and parasympathetic ganglion cells.

Muscularis Propria

It is responsible for contraction and is made of two layers: inner circular and outer longitudinal arranged in helicoidal pattern. Between the two layers is a nerve fibre plexus called myenteric plexus or Auerbach’s plexus. Parasympathetic and post-ganglionic sympathetic fibres end in parasympathetic ganglion cells and postganglionic para-sympathetic fibres terminate in smooth muscle.

Adventitia or Serosa

It is the outer most layer of connective tissue. When covered by a single layer of mesothelial cells it is called the serosa.

Specific Characteristics of Small Intestine

The distinguishing feature of the small intestine is the presence of folds (called plicae circularis or valves of Kerckring) composed of mucosa, submucosa and villi. Villi are only mucosal and of different shapes in different parts of intestine: leaf like in duodenum, tongue-like in jejunum and finger-like further distally. Villus pattern varies according to ethnicity. Villi in specimens from Indians and Africans are shorter and thicker and have more mononuclear cells in comparison with specimens from North Americans. Height of normal villus is 0.5–1 mm; it should be more than half the thickness of mucosa and 3–5 times length of crypts. Villi are lined by enterocytes, goblet cells and neuroendocrine cells.

**Brunner’s glands** found in the submucosa are seen in the first part of duodenum and decrease in number distally. They secrete bicarbonate-rich alkaline juice to neutralize acid. The other type is the crypts of Lieberkuhn that extend into muscularis mucosa. Cells are generated in the base and as they migrate upwards they differentiate into goblet cells, enteroendocrine cells, Paneth cells and enterocytes.

Paneth and columnar cells dominate the base. Above are absorptive cells and oligomucin (goblet cells). Goblet cells are predominant in upper half of the crypt. Lymphoid tissue is present as solitary nodules and Peyer’s patches along the

antimesenteric border. Most enteroendocrine cells are

present in the duodenum. These produce ghrelin, gastrin, CCK, motilin, neurotensin, GIP and secretin.

Specific Characteristics of Colon

The mucosa is characterized by crypts of Lieberkuhn with predominant goblet cells and few absorptive and entero-endocrine cells. Glucagon-like immuno reactant (GLI), pancreatic polypeptide like polypeptide (PYY) and tyrosine amide (L) cells predominate. EC, ECL and PP cells are also found. Paneth cells are very few. Lymphoid follicles are developed in rectum and decrease with age. Confluent lymphoid tissue is present in the appendix.

Specific Characteristics of Anal Canal

There are three microscopic zones of the anal canal: proxi-mal, intermediate or pectinate and distal or anal skin. Proximal zone is lined by stratified cuboidal epithelium. The intermediate zone is made of stratified squamous epithelium but without hair or sebaceous glands. It begins with dentate lines proximally. The anal skin is similar to skin elsewhere.

Interstitial Cells of Cajal

These are specialized cells of the muscle layer that form an interconnecting network via gap junctions. They act as intermediaries between nerves and myocytes. There are three groups: myenteric ICCs, intramuscular ICCs and ICCs in deep muscular plexus. Myenteric ICCs are responsible for initiating the slow wave potentials. Other two groups transduce nerve signals to the muscles. ICCs are the pacemakers and regulators of the smooth muscle of the intestine. Excitatory motor neurons release acetylcholine while inhibitory motor neurons release NO, ATP, VIP, etc. Actions of both are mediated by ICC. Inhibitory motor neurons relax sphincteric muscles at the ileocecal junction and the internal anal sphincter.

Gastrointestinal Hormones

Hormones relevant to small intestine act in humoral and paracrine pathway to stimulate enteric neurons and myocytes. Food is the main stimulus for their release. The important ones are CCK, somatostatin, VIP, glucagon-like peptide (GLP-1), gastric inhibitory peptide (GIP), ghrelin and motilin. Most hormones lead to slowing of small intestinal transit, satiety and increased mixing or segmenting contractions.

Peristalsis

Peristalsis is the characteristic fundamental motility pattern of the small bowel and can be regulated entirely by the ENS

and musculature. It is initiated by mechanical and chemical

stimuli and results in progressive contractile activity usually in aboral direction. This is in the form of contraction proximal to the bolus and relaxation distal to the bolus with the sequence progressing aborally.

Interdigestive Motor Cycle (IDMC)

The IDMC is a series of periods of variable activity occurring in phases during fasting and with regularity. It propagates aborally and demonstrates the integrative capacity of the ENS. It is believed that vagal reflexes act on motility, secretion, blood flow and control of food and water intake. Sympathetic reflexes are concerned with inhibition of motility and response to noxious stimuli.

Fed Motor Pattern

In the fed state, rhythmic segmentation is observed. These are contractions that divide and form columns of chyme over distances of less than 2 cm. Peristalsis is also observed. One type is slow advance of chyme over short distances and the other is fast peristalsis over longer distances.

Colonic Motor and Sensory Function

Around 1200–1500 mL of ileal effluent enters the colon daily of which 200–400 mL is excreted as stool. Colon primarily stores stools but also participates in the exchange of water, electrolytes and short-chain fatty acids by mixing of contents. This is done by to-and-fro movement and forward movements of contents with a flow rate of 1 cm/hr. In times of dehydration, the colon can increase water absorption by 5-fold.

Propagating Motor Patterns in Large Bowel

Strong contractions, which can occlude the lumen and travel longer are called propagating sequences are high amplitude propagating contractions (HAPCs). They can be antegrade or retrograde, increase after meal and decrease during sleep. They originate more commonly in the proximal than distal colon.

Colonic Filling and Transit

Colon acts as storage for stool till appropriate time for emptying. It is not settled as to which part of colon is responsible for storage. In a mixed diet of liquids and solids,

both ascending and transverse colon store the stools. Proximal colon empties in response to distension leading to propagating contractions or to chemical stimulations. Most motility events are to-and-fro motions of the contents of the colon, which maximizes absorption, retards colonic transit and reduces stool frequency.

Defecation

It is the end result of integration of colonic and anorectal motility. There is a pre-defecation phase of 1 hr in which there is increase in the frequency of propagating pressure sequences starting in the proximal colon but not inducing any sensation. In the 15 min prior to defecation, there is a big increase in the frequency of contractions leading to defecatory urge. In this phase, propagating pressure waves begin in distal colon and successively have greater amplitude and distance. These lead to filling of rectum and defecatory urge.

Low-volume distension of the rectum by gas or stool causes a reflex inhibition of internal anal sphincter and contraction of external anal sphincter. In contrast, a large-volume distension of rectum causes longer duration relaxation of internal anal sphincter and requires extra voluntary and conscious effort of the external anal sphincter. Suppression of urge leads to storage of stools in rectum or transport to sigmoid. This is an adaptive increase in compliance. By feedback, it also slows gastric emptying and slows small bowel and colonic transit. If urge to defecate is satisfied, the full process is initiated. The pelvic reflexes involves are coordinated in medulla and pons. The internal anal sphincter relaxes fully. Sitting or squatting causes descent of ano-rectal junction and increase of the anorectal angle. The external anal sphincter is relaxed. The levator ani muscle contracts, the puborectalis relaxes and stool is guided into anal canal from where straining and colonic contractions lead to its expulsion.

Colonic Motility Modulation

Myoelectrical activity recordings show that there is an increase in the colonic phasic and tonic activity in colon after food, which is known as gastrocolonic response or gastrocolic reflex. This response is seen in the entire colon with all the motility patterns showing an increase. An optimal caloric amount and an optimal fat content of food is required to trigger this response. Colonic activity stops during sleep with the exception of antipropulsive rectal motor complexes, which protect the internal anal sphincter from challenges.

Any arousal leads to increase in pressure waves. This explains the morning urge to defecate that we have. Stress leads to increase in propagatory waves while exercise leads to decrease in motility via sympathetic discharge.

Colonic Motility Modulation by Laxatives

Laxatives act by increasing mucosal secretion or stimulating propulsive activity. Bisacodyl causes diarrhoea by direct effect on mucosal afferent nerves. Lubiprostone activates the chloride channels to increase the chloride and fluid secretion and thereby colonic transit. 5HT4 agonists like

prucalopride act on presynaptic receptors to increase Ach and CGRP leading to induction of colonic propagating contractions. Morphine decreases the rectal tone and blunts the gastrocolic reflex leading to constipation.

Non-pharmacologic Methods of Colonic Modulation

Probiotics have shown some evidence of ability to influence colonic motility but definitive data are awaited. Nerve stimulation of S3 root increases the external sphincter tone and propulsive motor activity of the entire colon. Acupunc-ture by virtue of acting on multiple pathways was shown to increase stool frequency in children. Biofeedback has proved useful in pelvic floor dyssynergia and relief of constipation.

Digestion and Absorption of Nutrients

Nutrients are absorbed with good efficiency in the adult. Only 5% or less of consumed carbohydrates, proteins and fat are excreted in stool. Even indigestible fibre is absorbed by colon as short chain fatty acids. Absorptive mechanisms adapt to quantity and nature of nutrients as also specific states like pregnancy. Digestion and absorption of various nutrients are described below.

**Carbohydrate** is the main source of energy in almost all societies. They can contribute around 50–60% of calories in the daily diet. Most carbohydrate is derived from cereals and plants where it is present as starch. Starch is composed of amylase and amylopectin and made up of long chain of glucose molecules. Other sources of carbohydrates are in milk (lactose), fruits and vegetables (fructose and sucrose) or purified from cane or beet (sucrose). Sorbitol and corn syrup are found in processed foods. Dietary fibre contains unavailable carbohydrates, i.e., those that cannot be absorbed. These are celluloses and hemi-celluloses. Both are resistant to amylase. They are partially digested by colonic bacteria to produce short-chain fatty acids. Other carbohydrates in this category are pectins, gums and alginates.

Digestion and absorption of carbohydrate includes breakdown by salivary and pancreatic amylase to poly-

saccharide chain. The products of digestion are maltose and maltotriose, which are oligosaccharides. The end products of amylopectin digestion are short-branched oligosaccharides called -limit dextrins. Action of salivary amylase is unreliable as it is dependent of chewing of the food in the mouth and it is inactivated by gastric acid.

**Pancreatic amylase** is the major enzyme involved. The products of starch digestion and sucrose or lactose cannot be absorbed and are hydrolysed by brush border enzymes mainly found in the villi of duodenum and jejunum.

The three major monosaccharides glucose, galactose and fructose are absorbed by carrier-mediated transport systems located on the brush border of the enterocytes. The

transporter is glucose–sodium co-transporter. Water enters the cell behind sodium to maintain osmolarity. This simultaneous absorption of glucose, water and sodium is the basis of oral rehydration therapy. Fructose is absorbed by facilitated diffusion that is by a carrier protein. This protein is GLUT5. Most absorbed fructose enters circulation and reaches liver. Fructose is not as well absorbed as glucose and high intake can lead to diarrhoea. Around 20% of starch enters the colon and is acted upon by bacteria to produce short-chain fatty acid, hydrogen and methane.

**Fat** is absorbed in upper two-thirds of jejunum. Fat is water insoluble. In the human, it has to be released from food and broken down into emulsion droplets. Then it has to be transported from the water phase of lumen to the epithelium where it is reconstituted into larger molecules (mainly triglycerides). This has to be exported from the cell to lymph or blood stream. Despite these interfaces, 95% of fat is absorbed. Gastric lipase starts the process but most work is done by pancreatic lipase. An unstable emulsion of fat is created by chewing and gastric milling. For stabilization, droplets have to be coated. Phospholipids of diet and bile coat the droplets. This is strengthened by fatty acids liberated by lipolysis in stomach and bile salts. In the small bowel, phospholipase A2 degrade to phospholipid coat, whereas lipase breaks down the fats into free fatty acids and monoglycerides (lipolysis). Lipase requires an alkaline pH of 8. This is made possible by carbonate secretion of pancreas. The products of lipolysis have to be transported to the brush order of the intestine. This is done by formation of mixed micelles with bile salts and fatty acid lamellae on the mixed micelles. The epithelial surface has an unstirred water layer, which can decrease absorption of long-chain fatty acids but not short- or medium-chain fatty acids. Fatty acids dissociate from the micelles because of the slightly acidic pH and become protonated. They then diffuse into the cell where they are trapped, due to a neutral pH, in ionized form.

Phosphatidylcholine is hydrolysed by pancreatic phospholipase A2 into fatty acid and lysophosphatidyl-choline. Cholesterol is hydrolysed by pancreatic cholesterol esterase to liberate sterol, which is absorbed. Unabsorbed long-chain fatty acids that enter colon are not absorbed. Fecal fat excretion of seven grams per day originates from bacteria and membrane phospholipids.

Most transfer of end products of lipid digestion is by passive. Uptake of linoleic, oleic and arachidonic acids is by active transport. The transporter proteins are called fatty acid transporter proteins (FATPs). Short-chain fatty acids do not

require FATPs. Cholesterol transport is also mediated by transport proteins. Various diseases are caused by genetic lack of transporter proteins. Niemann-Pick C1-like protein deficiency leads to Niemann-Pick disease type C.

Inside the enterocytes, fatty acids bind to **fatty acid binding protein (FABPs)**. There are three types: liver-type FABP (L-FABP), intestinal FABP (I-FABP) and ileal lipid binding protein (ILBP). All have greater attraction to unsaturated fatty acids. I-FABP is involved in intracellular transport of fatty acids while L-FABP is involved in the transport of monoglycerides and lysophosphatidylcholine.

Subsequently, triglyceride is synthesized in the endoplasmic reticulum. Fatty acid is converted to acylCoA and combined with monoglyceride to form diglyceride. Subsequently triglyceride is formed. This pathway is seen during feeding. After synthesis all lipids are packaged for export as chylomicrons and very-low-density lipoproteins (VLDLs). In feeding stage, chylomicrons predominate while VLDLs are seen in fasting. Fatty acids of dietary triglycerides form chylomicrons while those of phospholipids form VLDL. Chylomicrons comprise of core of triglycerides with a coat of cholesterol ester and phospholipids. A small part of the coat is apolipoprotein A and B. Apo B is important in the intracellular transport of chylomicrons. One way the body stores fat involves the body transforms carbohydrates into glycogen that is in turn stored in the muscles for energy. When the muscles reach their capacity for glycogen storage, the excess is returned to the liver, where it is converted into triacylglycerols and then stored as fat. The chylomicrons are responsible for shuttling the triacylglycerols to various locations such as the muscles, breasts, external layers under the skin, and internal fat layers of the abdomen, thighs and buttocks where they are stored by the body in adipose tissue for future use. The chylomicrons are large lipoprotein that contains triglycerides and fatty acid. Lipoprotein lipase of capillary wall degrades triglycerides into fatty acid and glycerol, which enters into adipose cells. In adipose cells, fatty acid and glycerol are reassembled as triglyceride and stored for future use.

**Proteins** are the major source of amino acids and provide almost 10–15% of energy intake. Western countries have per capita protein consumption of 70–100 g/day while low affluent people in Asia and Africa may be consuming 50 g/day or less. Plant proteins are less digestible than animal proteins but keratin and collagen of animal sources are also indigestible. Protein rich in essential amino acids are considered high quality; animal proteins belong to this class. Western countries consume 70% of animal protein as total protein intake while in developing nations it can be as low as 20%. There are 20 amino acids in plant and animal proteins of which 8 cannot be synthesized by animals and are labelled essential. These are lysine, leucine, iso-leucine, methionine, phenylalanine, valine, threonine and tryptophan. Half of all protein entering the intestine is from endogenous

sources. 20–30 g/day are derived from salivary, gastric, biliary, pancreatic and mucosal secretions. Desquamated epithelial cells from villi provide another 30 g/day and 2 g

of plasma proteins are delivered daily.

**Pepsinogen** is released by the chief cells of the stomach mucosa on stimulation by gastrin, histamine and ACh and is activated to pepsin by acid. Pepsins can be active only in acidic milieu of stomach. Proteases secreted by pancreas are proenzymes activated by trypsin. Endopeptidases act on the internal bonds and include trypsin, chymotrypsin and elastase. Amino acids can be absorbed as monomers or di-or tripeptides and absorption of peptides is more efficient. Digestion of larger peptides (4 or more amino acids) is done by brush border enzymes, whereas smaller peptides are digested in the cytoplasm. Absorption peptides are done by a peptide transporter. Peptide transporter systems also exist to allow peptides to enter the portal circulation.

**Ascorbic acid (Vitamin C)** is available in abundance in fresh fruit and juices. The daily requirement is 40 mg. Absorption is inversely proportional to intake and around 80–90% of ingested vitamin C is absorbed.

**Folic acid** is available in abundance in spinach, liver, peanut and beans. Recommended daily intake is 200 mcg for adults and 400–800 mcg during pregnancy. Body does not store folate.

**Cobalamin (Vitamin B12)** exists largely as hydroxy-cobalamin, methylcobalamin and adenosyl-cobalamin and is found in liver, kidney, beef, fish, eggs and milk. Vegetables are lacking in vitamin B12. The daily requirement is 1–2 µg, which is 10% of the daily intake. In the first step, R-protein of saliva or gastric juice combines with the vitamin strongly. This complex is broken down in the duodenum by pancreatic proteases and the released vitamin is bound with intrinsic factor IF released by the parietal cells.

IF has strong affinity for cobalamin. This complex resists digestion and binds to ileal enterocytes. Inside the entero-cytes, free cobalamin is released. At the basolateral mem-brane, cobalamin is bound to transcobalamin II and reaches all cells of the body.

**Vitamin A** is available in abundance in milk and milk products, egg yolk and fish oils. Among vegetables, it is found as carotenoids. Retinal (vitamin A aldehyde) esters are broken down to retinol before absorption. Carotenes are converted to retinol in enterocytes

by two cytosolic enzymes. Carotenes enter enterocytes by diffusion. Free retinol inside the cell is esterified with palmitic acid and incorporated into chylomicrons before export.

**Vitamin D** has two derivatives - vitamin D2 (ergo-calciferol) and D3 (cholecalciferol). Both are produced by

ultraviolet radiation of ergosterol and 7-dehydro cholesterol, respectively. Major dietary form is D3 found in fish oil. Most supply for any person is by endogenous synthesis in skin during exposure to sunlight. Vitamin D is absorbed by passive diffusion and passes unchanged in chylomicrons in the lymphatics. Liver converts D2 and D3 to 25-hydroxy-cholecalciferol and kidneys convert this into 1,25 dihydro-xycholecalciferol.

**Vitamin E** comprises a group of 8 tocopherols of which -tocopherol is an effective member. Dietary sources are vegetables, oils, cereals, eggs and fruit. It is absorbed passively as micelles and then incorporated into chylomicrons to be passed on to the lymphatics.

**Vitamin K** is a major dietary form obtained from plants and beef liver. K2 is produced by colonic bacteria and is absorbed but is inadequate for the body. Uptake of K1 from small intestine is a carrier-mediated process requiring bile salts.

**Iron** is the major source required for haemoglobin synthesis. Non-vegetarians consume around 20–30 mg of iron daily as myoglobin or haemoglobin. Vegetarians ingest much less and iron is less readily absorbed. Daily require-ment is 8 mg. The requirements are higher for children, adolescents, menstruating women and women in pregnancy. Only 10% (1–2 mg) of iron ingested is absorbed. The site of absorption is proximal small bowel and ferrous form is better absorbed than ferric form. Dietary iron is found as ferric form and is reduced to ferrous form by reductase at the apical cellular membrane. Iron uptake occurs at apical and basolateral plasma membranes. At the apical membrane level at the villus tips, three pathways are involved. The first is by the transport protein divalent metal transporter (DMT). It can also transport other metal ions like zinc, manganese and cobalt.

Iron is also absorbed as haeme from haemoglobin and myoglobin and globin acts as an enhancer. The third pathway is by action of intestinal mucins, mobiliferin, integrin and ferric reductases. Across the basolateral membrane, two proteins ferroprotein 1 (FPN1) and hephestin are involved in the uptake of iron. Regulation of iron absorption takes place in three ways. Mucosal block is the inability of the mucosa to absorb iron after a large oral iron dose. The stores regulator leads to slow accumulation of non-haeme iron. The third is erythropoietin regulator that adjusts absorption according to demands of erythropoiesis. The stores and the

erythropoietin regulators are circulating factors acting on the entire body. Additionally, cells in the crypt of Lieberkuhn respond to plasma transferrin saturation, in unknown ways to alter iron absorption as they migrate to the villus.

Further Reading

1. Gastrointestinal Anatomy and Physiology. *https://online library.wiley.com.*

2. Gastrointestinal Anatomy and Physiology: the Essentials. *https://www.wiley.com.*

3. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. *https://www.elsevier.com›books›Feldman.*

4. Yamad’s Textbook of Gastroenterology. *https://online library.wiley.com.*

SECTION 3

PHYSICAL EXAMINATION

**Chapter 12.**

**General and Abdominal Examinations**

Clinical examination is very much vital for accurate diagnosis and concise management. In the present chapter, we will discuss first on general examination followed by abdominal examination.

**GENERAL EXAMINATION**

**Format of General Examination**

1. Build and nutrition including body mass index (BMI)

2. Vital signs

n Temperature

n Pulse

n Respiration

n Blood pressure

3. Pallor

4. Icterus

5. Clubbing, cyanosis

6. Koilonychia

7. Jugular venous pressure

8. Pedal oedema

9. Lymphadenopathy

10. Signs of cholestasis (in case of obstructive jaundice)

11. Signs of malabsorption (in case of chronic diarrhoea and malabsorption syndrome)

12. Stigmata of chronic liver disease (in patients of ascites, hepatocellular carcinoma and obstructive jaundice)

13. Kayser-Fleischer ring

14. Cutaneous markers of gastrointestinal malignancy

15. Eyes and joints examination (in case of inflammatory bowel disease)

16. Cutaneous markers for colorectal neoplasm

**Temperature**

1. A normal body temperature is maintained by thermoregulatory centre in the hypothalamus.

2. Normal body temperature is 36.8°±0.4°C (98.2°±0.7°F). Temperature is lowest at 6 am and highest between 4 and 6 pm. Normal body temperature variation is less than 0.5°C (0.9°F).

3. Fever is an elevation of body temperature that exceeds the normal daily variation and more than 37°C (99°F).

4. Fever more than 41.5°C (106.7°F) is called hyperpyrexia.

5. Exogenous pyrogens (substances that cause fever) like microorganisms produce pyrogenic cytokines like IL-2, IL-4 and IL-6. These cytokines trigger the hypothalamus to raise the set point to febrile levels. The temperature is elevated by increasing heat production and reducing heat loss. Heat production is by increasing the metabolic rate and muscle contraction, whereas heat loss is by peripheral vasoconstriction.

**Pattern of Fever**

1. ***Continuous fever***: The temperature is elevated all the time, but the difference between the maximum and minimum does not exceed 1°C.

2. ***Remittent fever***: Diurnal fluctuations exceed more than 1°C.

3. ***Intermittent fever***: A fever that touches normal for a few hours during the day is called intermittent.

*Intermittent fever that occurs daily* is called quotidian; occurs on alternate days is called tertian, and every fourth day is called quartan.

4. ***Irregular fever***: A fever that does not conform to any of these three types.

**Pulse**

1. Detailed discussion of pulse is out of scope for the present chapter.

2. Normal pulse rate is between 60 and 100 beats/min.

3. Pulse more than 100 beats/min is called tachycardia and less than 50 beats/min is called bradycardia.

4. Examination of pulse includes rate, rhythm, force, volume, tension, condition of arterial wall, radio-femoral delay, radio-radial delay and equal peripheral pulsation.

**Respiration**

1. A normal rate of respiration in healthy adults is 12–20 per minute. Respiratory rate is higher in childhood and infancy.

2. Normal inspiration is an active process, whereas normal expiration is a passive process.

3. In women, the intercostal muscles play a dominant role in respiration; thus, breathing is thoracoabdominal. Whe, in male respiration is mainly abdominal, called abdo-minothoracic breathing.

4. Respiratory rate more than 25 per minute is called tachypnea.

5. Abdominal movements are very much diminished in patients with generalized peritonitis.

**Blood Pressure**

1. Blood pressure should be measured both in supine as well as in standing position, using standard sphygmomanometer with Riva-Rocci cuff.

2. Systolic blood pressure reflects stroke volume of the heart, whereas diastolic blood pressure reflects total peripheral resistance.

3. Systolic blood pressure between 100 and 130 mmHg and diastolic blood pressure between 60 and 85 mmHg is considered normal.

4. Postural hypotension is defined as fall in systolic blood pressure more than 10 mmHg after changing posture from supine to standing position. This is a very important clinical sign in patients with acute diarrhoeal disease and gastrointestinal bleeding.

5. Postural hypotension indicates 10–20% blood loss, whereas resting hypotension indicates more than 20% blood loss.

**Pallor**

1. Normal colour of the skin depends on the degree of pigmentation and the vascularity of the part.

2. Pink colour of the mucus membranes and nails depends on the amount of haemoglobin in the circulating blood.

3. Pallor is paleness of the skin and mucus membrane. Pallor is due to either reduced circulating red blood cells or reduced blood supply.

4. Anaemia is the most common cause of pallor.

5. Causes of anaemia are either blood loss, nutrition or haemolysis.

6. Sites where pallor is detected:

n Tongue

n Lower palpebral conjunctiva

n Soft palate

n Palms and nails

7. Overt gastrointestinal bleeding is one of the most common causes of anaemia in gastroenterology practice (Ch. 8).

8. Easy fatigability, generalized weakness, shortness of breath are the usual complaints of patients with anaemia.

**Icterus (Ch. 13)**

1. This is yellow pigmentation of the sclera, skin, mucus membrane and other tissues caused by excess of circulating bilirubin.

2. Bilirubin has high affinity to collagenous tissue, thus tissues rich in collagen are stained most.

3. Sites where icterus is detected:

n Sclera

n Undersurface of the tongue

n Palms

n Nails

n Skin

4. Excess bilirubin may accumulate in the blood due to:

n Excess production of bilirubin secondary to exaggerated haemolysis (haemolytic jaundice).

n Impaired handling of the bilirubin by the liver in the form of defective conjugation or defective excretion (hepatocellular jaundice).

n Impaired excretion of bilirubin secondary to extrahepatic biliary excretion (obstructive jaundice).

***Causes of Jaundice***

1. Haemolytic jaundice

n Intravascular haemolysis

- Hereditary spherocytosis

- Haemoglobinopathies like sickle cell anaemia, beta thalassemia major

- Paroxysmal nocturnal haemoglobinuria (PNH)

n Extravascular haemolysis

2. Hepatocellular jaundice

n Viral hepatitis

n Autoimmune hepatitis

n Drug-induced hepatitis

n Wilson’s disease

3. Obstructive jaundice (Ch. 13)

**Clubbing**

1. Clubbing is the hypertrophy of the nail bed and finger pulp giving rise to convexity of the nails.

2. Normal nail bed angle with respect to the phalanx is 160°. Nail bed angle is increased in clubbing, which is demonstrated by viewing the side of the flexed distal index finger (profile sign).

***Grades of Clubbing***

1. Grade I: Softening of nail bed.

2. Grade II: Obliteration of the angle of the nail bed.

3. Grade III: Bulbous swelling of the finger ends with both transverse and longitudinal curving of the nail (drum stick or parrot beak appearance or Hippocratic fingers).

4. Grade IV: Swelling of the finger with hypertrophic pulmonary osteoarthropathy.

***Mechanism of Clubbing***

The postulated mechanism of clubbing is opening up of deep arteriovenous fistulas secondary to hypoxia, which increases the blood supply of the fingers and toes leading to hypertrophy.

***Causes of Clubbing***

1. Cardiopulmonary causes:

n Subacute bacterial endocarditis

n Congenital cyanotic heart diseases

n Bronchogenic carcinoma

n Bronchiectasis

n Lung abscess

2. Gastrointestinal causes:

n Hepatopulmonary syndrome

n Inflammatory bowel disease like ulcerative colitis and Crohn’s disease

n IPSID (immunoproliferative small intestinal disease)

n Familial polyposis syndrome

3. Endocrine causes:

n Myxedema

n Acromegaly

**Koilonychia**

1. Spoon-shaped deformity of the nails is called koilonychia.

2. Toe nails are affected earlier than finger nails.

3. Koilonychia is suggestive of iron-deficiency state.

4. Plummer-Vinson syndrome is a triad of iron-deficiency anaemia, glossitis and post cricoid web.

***Other Nail Changes***

1. ***Leuconychia***: It is the whitish discolouration of the nail. It can be seen in normal persons. But, usually, it indicates low serum albumin level (<2.29 g/dL).

2. ***Splinter haemorrhages*** are seen in bacterial endocarditis and certain forms of vasculitis.

3. ***Beau’s lines***: Transverse ridges on the nails are called Beau’s lines. It indicates serious systemic illness.

4. ***Onycholysis*** is separation of the nail from the nail bed.

**Cyanosis**

1. Cyanosis is bluish or dark purple colouration of the skin and mucus membranes due to the presence of excessive amounts of reduced haemoglobin in arterial blood.

2. The amount of reduced haemoglobin should be more than 5 g/dL for cyanosis to become evident.

3. Cyanosis may be due to central or peripheral causes.

4. Central cyanosis is due to either mixing of arteriovenous blood in the heart or defective oxygenation in the lungs. While peripheral cyanosis is due to reduced circulatory

state either by reduction in cardiac output or peripheral vasospasm.

*Sites where cyanosis is detected*:

1. Central cyanosis – Tongue, mucus membrane, finger tips and nail beds.

2. Peripheral cyanosis – Finger tips and nail beds.

3. Most important gastrointestinal cause of cyanosis is hepatopulmonary syndrome.

**Jugular Venous Pressure**

1. The jugular veins are in direct continuity with the superior vena cava. Thus, jugular venous pressure reflects pressure changes in the right atrium.

2. Elevated jugular venous pressure is seen in right ventricular failure, cor pulmonale, cardiac tamponade and superior vena cava obstruction.

3. Jugular venous pressure is very important in gastroenterology general examination, particularly, in patient with sudden onset of ascites. If the cause of ascites is right ventricular failure, JVP is elevated; whereas, in acute Budd-Chiari syndrome, JVP is normal.

**Pedal Oedema**

1. Oedema is an excessive accumulation of fluid in the tissue space.

2. Oedema could be generalized or localized. Pedal oedema can be unilateral or bilateral:

n *Unilateral*

- Inflammatory

- Lymphatic oedema

- Venous thrombosis

- Varicose veins

n *Bilateral*

- Cirrhosis liver

- Congestive cardiac failure

- Hypoalbuminemia

- Pericarditis

- Chronic renal failure

- Myxedema

- Inferior vena cava obstruction.

3. Skin overlying the oedema is shiny, stretched with loss of wrinkles.

4. Confirmatory sign of pedal oedema is pitting on pressure.

5. Chronic lymphedema and myxedema are non-pitting oedema.

6. Pitting test for pedal oedema: Pressure on the oedematous part leads to displacement of the fluid and

formation of the dimple. The test is performed by exerting gentle pressure with the flat of the thumb for at least 10 sec over bony area like shin of tibia and looking as well as feeling for pitting.

**Lymphadenopathy**

1. Lymphadenopathy is inflammatory or non-inflammatory enlargement of lymph nodes.

2. Lymph node enlargement may be primary or secondary. Primary, which tends to generalize, is due to lymphoma, lymphatic leukaemia or tuberculosis; whereas secondary enlargement is usually localized due to disease in the areas of drainage.

3. Lymph node in the left supraclavicular fossa (Virchow’s node) is the most important alimentary examination. Virchow’s node is palpable between the two heads of sternomastoids. It indicates intra-abdominal malignancy, particularly in upper gastrointestinal tract.

4. Following points to be noted while examining lymph nodes:

n Size

n Site

n Localized or generalized

n Number

n Consistency

n Mobility

n Tenderness

n Matted or discrete

n Overlying skin

**Stigmata of Chronic Liver Disease**

It is very important to look for the presence of stigma of chronic liver disease in hepatobiliary cases **(Fig. 12.1)**:

1. Diminished body hair

2. Jaundice

3. Parotid enlargement

4. Spider nevi

5. Gynecomastia

6. Palmar erythema

7. Dupuytren’s contracture

8. Ascites

9. Testicular atrophy

10. Flapping tremors

11.Fetor hepaticus

***Diminished Body Hair***

1. Diminished body hair is mainly seen in the male.

2. Hair loss mainly affects the face, axilla and chest.

3. Hair loss is due to increased circulating oestrogen secondary to impaired liver function.

***Parotid Enlargement***

1. Bilateral parotid enlargement is more seen in alcoholic cirrhosis.

2. The parotid gland is situated below, behind and slightly in front of the lobules of the ear. A swelling of the parotid gland obliterates the normal hollow just below the lobule of the ear and ear lobule pushes forward.

3. The cause of parotid enlargement is not known.

***Spider Nevi***

1. It is also called spider angioma, vascular spider or arterial spider.

2. A spider nevus consists of a central arteriole with radiating thin-walled vessels.

3. Compression of the central vessel leads to blanching and temporarily obliterates the lesion. When released, the vessels quickly refill with blood from the central arteriole.

4. The size can vary from a pinhead to 1 cm in diameter.

5. Spider nevi usually are bright red with a small (1 mm), central, red papule surrounded by several distinct radiating vessels. They are usually seen over the vascular territory of the superior vena cava (face, neck and upper part of the trunk and arms).

6. It is seen in alcoholic liver disease, pregnancy, thyrotoxicosis and in women who are on oral contraceptive pills.

7. The pathogenesis of spider nevi is still unclear. Their occurrence is due to dilatation of pre-existent blood vessels rather than true vascular proliferation.

8. Increased plasma levels of estrogen, vascular dilation and neovascularization are possible aetiologies for spider nevi. Generalized hyperdynamic circulation in patients with cirrhosis liver leads to the development of angioma.

9. Multiple spider angiomata are more frequent in patients with alcoholic cirrhosis than in those with cirrhosis due to other causes.

10. Recent study showed that spider nevi and thrombocytopenia, with either splenomegaly or hypoalbuminemia, were useful predictors of hepatic fibrosis in patients with hepatitis C infection.

***Gynecomastia***

1. Gynecomastia is more common in alcoholic cirrhosis.

2. This is due to increased blood estrogen level

3. The fate of testosterone is by three ways: peripheral conversion to dehydroxy testosterone, peripheral conversion to oestrogen and hepatic degradation. Liver is responsible for around 50% clearance of testosterone.

4. In cirrhosis, peripheral conversion of androgens to estrogen increases.

5. Cirrhotic patients have increased SHBG (sex hormone binding globulin), which leads to reduced circulating testosterone.

*Why gynecomastia is more common in alcoholic cirrhosis?*

1. In alcoholics, there is increased 5--reductase activity leading to increased conversion of testosterone; alcoholics have more aromatase, which also increases estrogen level.

2. Alcoholics have more estrogen receptors in the breast tissues, which enhances the effect of circulating estrogen.

***Palmar Erythema***

1. Palmar erythema is secondary to increased blood flow.

2. This is seen as erythema of thenar and hypothenar eminences. It may be seen on the sole.

3. Palmar erythema is seen in other hyperdynamic states.

***Dupuytren’s Contracture***

1. This condition mainly affects the palm and rarely plantar fascia.

2. There is localized thickening of palmar facia, mainly in the medial part, which leads to flexion of ring finger and to some extent little finger.

3. The exact cause of this condition is not known.

***Testicular Atrophy***

1. Testis diameter less than 3 cm and loss of normal sickening sensation while palpating the testis is called testicular atrophy.

2. It is a consequence of increased circulating estrogen.

***Flapping Tremor (Asterixis)***

1. It is a disorder of motor control characterized by brief, arrhythmic interruptions of sustained voluntary muscle contraction.

2. Multiple brainstem-spinal pathways such as the vestibulospinal, reticulospinal or rubrospinal tracts, which in turn, are regulated by supratentorial structures, maintain the postural stability.

3. Diffuse, widespread derangement of CNS function in patients with hepatic encephalopathy leads to asterixis.

4. Electrophysiological evaluation showed that asterixis is due to abnormal activity in the motor field in the cerebral cortex.

5. Mini-asterixis, which is a part of the spectrum of the gross flapping tremor seen in hepatic encephalopathy was

proposed as being due to the involvement of motor cortex causing a pathologically slowed and synchronized motor cortical wave.

6. Toxic-metabolic encephalopathies, especially hepatic, renal, electrolytes imbalances and hypercapnia are the most common causes of bilateral asterixis. The flapping tremor (liver flap) is characteristically seen in hepatic encephalopathy.

7. Unilateral asterixis is due to focal structural brain lesions in the genu and the anterior portion of the internal capsule or ventrolateral thalamus.

8. Pseudoasterixis is due to a primary disorder of muscle tone, mimicking asterixis.

9. Methods to demonstrate asterixis:

n The examiner applies his index finger over the dorsum of the patient wrist while asking the patient to dorsiflex the wrist. Asterixis is the downward drift and abnormal recovery motion of the hand with the fingers either together or outstretched.

n The examiner asks the patient to clench his fingers. Asterixis is elicited with subtle movements of the examiner’s wrist.

***Fetor Hepaticus***

Fetor hepaticus is slightly sweet, ammoniacal odour that is common in patients with liver failure, mainly due to portal venous shunting of blood.

**Nail Changes in Cirrhosis**

1. Muehrcke’s line: White transverse line, indicates <2.2 g% serum albumin, but also seen in nephrotic syndrome.

2. Blue lunulas (azure half moon sign): Seen in Wilson’s disease.

3. Terry nail: 1–2 mm white end seen in chronic liver disease, rheumatoid arthritis, diabetes mellitus, congestive cardiac failure and multiple sclerosis.

**Skin**

1. Examination of the skin is performed by inspection and palpation. It is very important to make quick, but careful visual examination of the entire body. This “quick-look”

gives an idea about the distribution and extent of any lesions **(Table 12.1)**.

2. The colour of normal skin ranges from deep to light brown or black, or whitish pink to ruddy with yellow overtones. Skin colour depends on the pigmentation and vascularity underneath.

***Variations in Skin Colour in Healthy Adults***

1. Non-pigmented striae: Silver or pink stretch markers occur after parturition or weight gain.

2. Melasma: Hyperpigmentation in face and neck seen in adult women during pregnancy or the use of hormones.

3. Some birth marks like flat or raised nevi of various sizes and colour.

***Definitions of Various Skin Lesions***

1. **Macule**: It is flat, non-palpable, circumscribed, <1 cm in diameter; brown, red or tan in colour.

2. **Patch**: Flat, non-palpable, irregular in shape, macule that is >1 cm in diameter.

3. **Papule**: It is an elevated, palpable, firm, circumscribed, <1 cm in diameter; brown, red or tan in colour.

4. **Plaque**: Elevated, flat, firm, papule >1 cm in diameter.

5. **Nodule**: Elevated, firm, circumscribed palpable, deeper in dermis than papule, 1–2 cm in diameter.

6. **Tumour**: Elevated, solid; may or may not be clearly demarcated; >2 cm in diameter.

7. **Vesicle**: Elevated, circumscribed, superficial; filled with serous fluid, <1 cm in diameter.

8. **Bulla**: Vesicle >1 cm in diameter is called bulla.

9. **Pustule**: Vesicle filled with purulent fluid is called pustule.

10.**Petechiae**: Red-purple discolouration <0.5 cm in diameter.

11.**Purpura**: Red-purple discolouration, >0.5 cm in diameter.

12.**Ecchymoses**: Red-purple discolouration of variable size.

13.**Spider angioma**: Red central body with radiating spider-like legs that blanch with pressure to the central body.

14.**Telangiectasia**: Fine, irregular red line produced by dilatation of capillary.

**Physical Examination in Malabsorption Syndrome**

Physical examination is very important in patient with malabsorption syndrome as it gives idea about the nutrient deficiency as well as probable site of involvement **(Table 12.2)**.

***Cutaneous Manifestations of Inflammatory Bowel Disease***

1. Oral manifestations occur in 4–15% patients with Crohn’s disease and include aphthous ulcer, lip fissures, cobblestone plaques and perioral erythema.

2. Pyostomatitis vegetans

n Cutaneous counterpart of pyoderma vegetans

n Pustules, erosions involving the labial mucosa and skin of the axilla, genitalia and trunk

n Specific markers of IBD

n May precede the symptoms by months to years

n Biopsy shows intraepithelial or subepithelial miliary eosinophilic abscess

n Treatment by topical/systemic steroids

3. Erythema nodosum

n Multiple tender and inflamed nodules on anterior aspect of leg.

4. Pyoderma gangrenosum

n Multiple pustules on the legs and trunk, which break down, ulcerate and coalesce with considerable necrosis.

***Cutaneous Markers of Internal Malignancy***

1. Dermatomyositis

n Violaceous colour of the eyelids with oedema; keratotic papules over the knuckles (Gottron’s papules) associated with photosensitivity

n Seen in gastric cancer

2. Keratosis palmaris et plantaris (Howel-Evans syndrome)

n Diffuse keratosis of palm and sole (tylosis)

n Seen in oesophageal carcinoma

3. Tripe palms (*Acanthosis palmaris*)

n Gastric and pulmonary malignancy

4. *Acanthosis nigricans*

n Gastric cancer

5. Bazex’s syndrome (*Acrokeratosis paraneoplastica*)

n Periungual skin thickening with nail atrophy and rash

n Seen in oesophageal cancer

6. Hypertrichosis lanuginosa

n Colorectal cancer

7. Flushing

n Carcinoid tumour

8. Necrolytic migratory erythema

n Glucagonoma

9. Venous thrombosis

10. Subcutaneous fat necrosis

n Pancreatic carcinoma

11. Skin tags

n Colorectal cancer

12. Sign of Leser Tre’lat

n Multiple seborrheic keratosis

13. Sweet syndrome

n Acute febrile neutrophilic dermatosis

***Skin Changes in Chronic Diarrhea***

1. Carcinoid syndrome – Flushing

2. Celiac sprue – Dermatitis herpetiformis

3. Mastocytosis – Urticaria pigmentosa

4. Addison’s disease – Hyperpigmentation

5. Amyloidosis – Waxy papule

6. Glucagonoma – Migratory necrolytic erythema

**Eyes**

1. Quick, but thorough examination of both the eyes is mandatory.

2. Examination can be done in daylight as well as with the help of ophthalmoscope.

3. Look for pallor, icterus.

4. KF ring, sunflower cataract (deposition of copper in the lens) seen in patients with Wilson’s disease.

5. Episcleritis: It is an inflammation of the superficial layers of the sclera anterior to the insertion of rectus muscles. It is seen in patients with inflammatory bowel disease (IBD).

6. Uveitis is seen in patients with IBD.

7. Xanthelasmas are bright yellow plaques on eyelids seen in patients with hyperlipidemia and cholestatic jaundice.

***Kayser-Fleischer Ring***

1. Golden brown pigmented ring at the periphery of the cornea.

2. It is seen in Wilson’s disease due to deposition of copper in the Descemet’s membrane of the cornea.

3. KF ring is present in around 50–62% of patients with Wilson’s disease. It is invariably present in patients with neurological manifestation.

***Xanthomas***

1. Xanthomas are due to abnormal accumulations of cholesterol, triglycerides and phospholipids in the skin, fascia and periosteum.

2. Xanthomas are seen in patients with obstructive jaundice.

n *Tendon xanthomas*: Nodules over the Achilles tendon due to increased cholesterol.

n *Tuberous xanthomas*: Bright yellow nodules over knee, elbow, etc due to increased triglycerides.

n *Plane xanthomas*: Flat, narrow to broad yellow patches in the palmar creases.

n *Xanthelasmas* are bright yellow plaques on eyelids seen in patients with hyperlipidemia and cholestatic jaundice.

**Lips**

1. Lips may be abnormally thick or swollen in oedema as in nephrotic syndrome, acromegaly, cretins, gigantism and cellulitis of the lips.

2. Cheilosis and angular stomatitis is seen in riboflavin and nicotinic acid deficiency.

3. Pale lips in severe anaemia, bluish in cyanosis, darkly pigmented in excessive smoking or in melanosis, red or brown in cutaneous haemorrhages.

4. Lips are also to be looked at for ulcers and fissures.

5. Cleft lip (harelip) may be associated with a cleft palate.

6. An area of small vesicles on the lip may occur in herpes simplex; these may rupture and form a crust.

**Teeth**

1. Congenital syphilis may cause characteristic appearance of a peg-top of the central incisors with notching of incisor edges (Hutchinson’s teeth); in this condition, milk molars may be affected, which develop rough, pitted occlusal surfaces (mulberry molars).

2. A yellowish brown discolouration of teeth may occur after administration of tetracyclines to infants or to women in the last trimester of pregnancy.

3. A reddish brown discolouration of the teeth may be found due to deposition of porphyrins in the developing teeth in congenital porphyria.

4. Presence of dental caries and gingivitis is noted.

**Gums, Oral Mucosa and Tongue**

1. Gingival hyperplasia is seen in myelomonocytic leukaemia and with drugs like phenytoin and cyclosporine.

2. The presence of gingival inflammation, ulceration and bleeding is also noted.

3. Gingival hypertrophy, ulceration, bleeding and petechiae are found in leukaemias.

4. Extensive ulceration of lips, gums, buccal mucosa, soft palate, pharynx and tonsil may be found in agranulocytosis.

5. Petechiae, ecchymosis and bleeding gums are found in thrombocytopenia.

6. Deficiency of vitamin C may cause petechiae in buccal mucosa, swollen, spongy and bleeding gums and loosening of teeth.

7. Bluish-black or dark brown pigmentation in irregular spots throughout buccal mucosa may be seen in Addison’s disease.

8. Dark brown spots of pigmentation of oral mucosa, lips, eyes, nostrils and limbs are found in Peutz-Jeghers syndrome.

9. Ulcers in oral mucosa may be seen in uraemia, syphilis, tuberculosis, histoplasmosis, squamous cell carcinoma, leukaemia, lymphosarcoma and autoimmune disorders.

10. Single or multiple painful ulcers surrounded by erythematous border in oral mucosa are found in recurrent aphthous ulcers.

11. A dark line along the gingival margin may be observed in lead, mercury and bismuth poisoning.

12. Raised, painless brown-black spots with or without ulceration may be seen in oral mucosa in malignant melanoma.

13. Pale tongue is seen anaemia, yellow in jaundice, blue in cyanosis, brownish in uraemia, dark or black in melanosis, patchy red or reddish brown in haemorrhages.

14. Black hairy tongue due to elongated filiform papillae over the dorsum of tongue is due to failure of keratin layer of papillae to desquamate normally.

15. Brownish black colouration of the tongue is due to staining by tobacco.

16. A large tongue (macroglossia) may be found in acromegaly, cretinism, haemangioma of tongue, lymphangioma, primary amyloidosis, Down’s syndrome (caused by

trisomy of chromosome 21); whereas, a small tongue (microglossia) is seen in scleroderma.

17. A magenta-coloured tongue may be present in riboflavin deficiency.

18. The tongue is red, atrophic, smooth and inflamed in pernicious anaemia.

19. A red, swollen and painful tongue, soreness of the mouth along with cheilosis and angular stomatitis may be present in niacin deficiency (deficiency of B group of vitamins).

20. A **geographical tongue** is an asymptomatic inflammatory condition of the tongue where there is an appearance of denuded red patches, which wander over the surface of the tongue due to rapid loss and re-growth of filiform papillae.

21. A **bald tongue** or **smooth tongue** is due to severe atrophy of tongue papillae and is found in iron-deficiency anaemia, pernicious anaemia, pellagra, etc.

22. **Fissured tongue or scrotal tongue** is due to the presence of fissures over the dorsal surface and sides of tongue, which are painless.

23. **Median rhomboid glossitis** is an ovoid area of denuded surface of tongue, which is situated in posterior part of the tongue in the middle line and is present congenitally.

24. **Strawberry tongue** occurs in scarlet fever due to hypertrophy of fungiform papillae along with changes in the filiform papillae.

**Abdominal Examination**

**Format of abdominal examination**

**Inspection**

1. Contour or shape of abdomen

2. Flanks

3. Umbilicus

4. Abdominal movement

5. Skin over the abdomen

6. Dilated veins

7. Visible pulsation

8. Visible mass

9. Visible peristalsis

10.Scars and sinuses

11.Hernial orifices

12.External genitalia

**Palpation**

1. Tenderness, guarding and rigidity

2. Palpation of liver, spleen, kidney and gallbladder

3. Palpation of a mass

4. Fluid thrill

**Percussion**

1. Horse-shoe dullness

2. Shifting dullness

3. Dullness over the lump

**Auscultation**

1. Bowel sounds

2. Arterial bruit

3. Venous hum

**Digital Rectal Examination**

**Abdominal Quadrants**

n The abdomen is divided into nine regions **(Fig. 12.2)** by

four imaginary planes (two horizontal and two vertical).

n Two horizontal planes are transpyloric and trans-tubercular planes.

n Transpyloric plane: It passes through the tips of the ninth costal cartilage; and posteriorly through the body of L1 vertebra near its lower border.

n Transtubercular plane: It passes through the tubercles of the iliac crest and the body of vertebra L5 near its upper border.

n Two vertical lines are right and left lateral planes. Both these lines correspond to the midclavicular line.

n Renal angle: The angle between the 12th rib and outer border of erector spinae.

**Inspection**

1. **Contour or shape**

n There are three main types of abdominal contour:

- *Flat type* of abdomen: common in young adults; the rib margins and anterior abdominal wall are more or less on the same level.

- *Globular or round type* of abdomen: The anterior abdominal wall presents a forward convexity, usually through obesity or lack of muscle tone.

- *Scaphoid or “boat”* *type* of abdomen: It is common in thin subjects and those suffering from wasting diseases.

n A symmetrical distension or bulging of the abdomen may be due to obesity, gaseous distension, pregnancy or ascites.

n Asymmetry of the abdomen may be due to local bulging or retraction of the abdominal wall.

n A localized swelling, bulging or protrusion of the abdominal wall may be due to enlargement of a solid organ such as the liver or spleen.

2. **Flanks**

n Bulging flanks indicates ascites.

n Bluish discolouration near the flanks suggests intra-abdominal haemorrhage or severe pancreatitis (Grey Turner’s sign).

3. **Umbilicus**

n Normally, the umbilicus is centrally placed, slightly retracted and inverted.

n In the presence of ascites, umbilicus is transversely stretched (smiling umbilicus), everted or ballooned out (umbilical hernia).

n In ovarian cyst, it tends to be vertically stretched.

n Normally, distance from xiphisternum to umbilicus is equal to distance from umbilicus to pubic symphysis.

n In case of ascites, distance from xiphisternum to umbilicus is more than the distance from umbilicus to pubic symphysis. Reverse is seen in case of ovarian cyst.

n A bluish discolouration of the umbilical area is suggestive of intra-abdominal haemorrhage (Cullen’s sign).

n Sister Mary Joseph nodule suggests intra-abdominal malignancy.

n An umbilical discharge may be due to bacterial or fungal infection of the umbilicus.

n Omphalolith is a common finding in the umbilicus of elderly obese women due to concentration of inspissated desquamated epithelium and debris.

4. **Abdominal movements**

n Normally, the abdominal wall moves freely with respiration in males (predominant abdominal breathing), but not in female, in whom breathing is predominantly a costal type.

n Restriction of the respiratory movement of the abdominal wall in a male may be due to:

- Peritonitis

- A tense ascites

- A massive intra-abdominal cyst or tumour

- Referred pain from an inflammatory lesion of the diaphragmatic pleura or an abdominal muscle

n Diminution of respiratory movement of the abdominal wall in a restricted area suggests inflammation of an underlying viscus.

5. **Skin over the abdomen**

n Tense, shiny and transparent abdominal skin suggests chronic distension of the abdomen, mainly in patients with ascites.

n White lines over the lower part of the abdomen, the so-called linea albicantes with an associated loss or rupture of elastic fibres are evidence of previous stretching of the skin, through pregnancy.

n Purplish stria over the abdomen is suggestive of Cushing’s syndrome and in those receiving long-term glucocorticoids therapy.

6. **Dilated veins**

n The normal flow of blood in the superficial veins of the abdomen is from the umbilicus upwards to the thorax and from the umbilicus down to the groin **(Fig. 12.3)**.

n The veins may remain collapsed in the supine position; they should be examined in sitting or standing position.

n There is no effective functional communication between the abdominal veins and the portal venous system in health.

n To determine the direction of blood flow in a dilated vein, the examiner’s two fingers are pressed close

together over the mid-section of the vein and then drawn apart to empty a part of the vein, the pressure with the fingers being maintained. One finger is then lifted at a time and the direction of filling up of the emptied section of vein is observed **(Fig. 12.4)**.

n In portal hypertension, large and tortuous veins radiating from the umbilicus may be seen; the blood flow in these veins is directed radially away from the umbilicus (caput medusae). This occurs due to opening up of the collaterals near the umbilicus between the falciform ligament of the liver and to the systemic veins.

n In inferior vena cava obstruction, blood flow on either side of the umbilicus is below upwards. These dilated veins represent dilated anastomotic channels between the superficial epigastric and circumflex iliac veins below, and the lateral thoracic veins above, conveying the diverted blood from long saphenous vein to axillary vein.

n In superior vena cava obstruction, the blood flow is downwards.

7. **Visible pulsation**

n Abdominal aortic pulsations are visible on the abdominal wall in thin, healthy subjects.

n Expansile liver pulsation is seen in right hypochondrium in tricuspid regurgitation.

n Pulsation in epigastric region may be due to right ventricular enlargement, whereas in epigastrium and umbilical area it may be due to abdominal aortic aneurysm.

8. **Visible masses**

n Visible mass due to either enlargement of solid organs like liver, spleen, kidneys or mass arising from bowel can be visible in their anatomical position.

n It is always ideal to examine the patients in tangential direction to inspect the mass.

9. **Visible peristalsis**

n Visible peristalsis is always indicative of bowel obstruction.

n To look for peristalsis, the abdomen must be carefully observed for several minutes with a gentle flicking of the abdominal wall.

n The site, direction and nature of the peristalsis are helpful in determining the site of obstruction.

n In pyloric obstruction, peristalsis will be seen as a slow wave either passing across the upper abdomen from left to right or, gross dilatation of stomach passing down to the suprapubic region.

n In distal small bowel obstruction, visible peristalsis is seen near the center of the abdomen in a “ladder pattern.”

n In transverse colon obstruction, peristaltic waves, traveling from right to left are seen either in the epigastric region or below the umbilicus.

10. **Scar**

n Inspect the abdomen for the presence of any scar and its site.

n Look whether scar is old (dark) or recent (red or pink).

n Look for any presence of incisional hernia.

11.**Hernial sites and external genitalia**

n Examination of the groins and external genitalia is a part of general examination.

Remember that the patient should be examined not only lying down, but also standing up.

n Detailed examination of hernia and hydrocele is mandatory.

**Palpation**

***Superficial Palpation***

1. Superficial palpation is especially helpful in identifying abdominal tenderness, muscular resistance (guarding and rigidity) and some superficial organs and masses. Its gentleness helps also to reassure and relax the patient.

2. Keeping your hand and forearm on a horizontal plane, with fingers together and flat on the abdominal surface, palpate the abdomen with a light, gentle, dipping motion. It is very important to move smoothly, and feel in all quadrants in a systematic way. Identify any superficial organs or masses, any area of tenderness or increased resistance to palpation. If resistance is present, try to determine whether it is voluntary resistance or involuntary muscular spasm.

3. Normal structures felt during abdominal palpation:

n Abdominal aorta

n Bodies of the lower lumbar vertebrae

n Border of the liver

n Right kidney

n Sigmoid colon

n Transverse colon

*Abnormal findings*:

1. Increased resistance or rigidity

2. Generalized rigidity

3. Localized or unilateral rigidity

4. Transient or momentary rigidity

5. *Tenderness* means pain during palpation.

6. *Guarding*: Voluntary resistance during palpation.

7. *Rigidity*: Involuntary resistance during palpation is usually secondary to peritoneal irritation. Classical “board-like rigidity” is present in peritonitis.

8. *Rebound tenderness*: Rebound tenderness also indicates peritoneal irritation. Press fingers in firmly and slowly, and then quickly withdraw them. Watch the patient for signs of pain. Pain induced or increased by quick withdrawal constitutes rebound tenderness. It results from the rapid movement of inflamed peritoneum.

9. Rigidity and rebound tenderness are the signs of peritoneal irritation.

***Deep Palpation***

1. Deep palpation is usually required to delineate abdominal masses. Again using the palmar surfaces of your fingers, feel in all quadrants. Identify any masses and note their location, size, shape, consistency, tenderness, pulsations and mobility (e.g., with respiration or with the examining hand).

2. When deep palpation is difficult due to either obesity or tense ascites, use two hands, one on top of the other. Exert pressure with the outside hand while concentrating on feeling with the inside hand. It is also called “dipping method” of palpation.

**Palpation of Specific Structures**

***Liver Palpation***

1. Place the left hand under the patient at the eleventh and twelfth ribs, pressing upward to elevate the liver toward

the abdominal wall. Place your right hand on the abdomen, fingers pointing toward the left axilla and extended so the tips rest on the right midclavicular line below the level of liver dullness.

2. Alternatively, you can place your right hand parallel to the right costal margin. In either case, press your right hand gently but deeply in and up. Have the patient breathe normally a few times and then take a deep breath. Try to feel the liver edge as the diaphragm pushes it down to meet your fingertips.

3. Ordinarily, the liver is not palpable although it may be felt in some thin persons even when no pathologic condition exists.

4. An alternative technique is to hook the fingers over the right costal margin below the border of the liver dullness.

5. Stand on the patient’s right side facing his or her feet.

6. Press in and up toward the costal margin with the fingers and ask the patient to take a deep breath. Try to feel the liver edge as it descends to meet the fingers.

*In case of palpable liver, following features must be examined systematically*:

1. Size: This is expressed as either “inches” or “centimeters” below the right costal margin.

2. Edge or margin: The liver edge must be carefully palpated to determine if edge is regular or irregular, rounded or sharp.

3. Surface: The anterior surface of the liver must be examined, for smoothness, irregularity, nodularity and umbilication.

4. Tenderness.

5. Consistency: Normal liver is soft, whereas firm liver indicates the diagnosis of cirrhosis or extrahepatic malignant biliary obstruction.

6. Movement with respiration

7. Pulsation

*Causes of Hepatomegaly*

1. Infective

n Viral hepatitis

n Amebiasis

n Typhoid

n Malaria

n Kala azar

n Echinococcus infection

n Tuberculosis

2. Congestive

n Congestive cardiac failure

n Constrictive pericarditis

n Budd-Chiari syndrome

3. Infiltrative

n Fatty infiltration

n Hodgkin’s disease

n Amyloidosis

n Leukaemia

n Gaucher’s disease

4. Neoplastic

n Hepatocellular carcinoma

n Cholangiocellular carcinoma

n Metastasis

*Tender Hepatomegaly*

1. Viral hepatitis

2. Amoebic liver abscess

3. Pyogenic liver abscess

4. Congestive cardiac failure

5. Hepatocellular carcinoma

*Pulsatile Liver*

n Tricuspid regurgitation

*Massive Hepatomegaly (edge >10 cm below the costal margin)*

1. Hepatocellular carcinoma

2. Metastatic liver disease

3. Polycystic liver disease

4. Infiltrative disease like amyloidosis

5. Congestive cardiac failure

6. Amoebic liver abscess

*Cirrhosis with Enlarged Liver*

1. Alcoholic hepatitis

2. Hepatocellular carcinoma

3. Budd-Chiari syndrome

4. Haemochromatosis

5. Secondary biliary cirrhosis

6. Autoimmune liver disease

7. Wilson’s disease

8. Glycogen storage disease

*Soft Hepatomegaly*

1. Acute viral hepatitis

2. Fatty liver

3. Congestive cardiac failure

4. Acute Budd-Chiari syndrome

5. Malaria

*Firm Hepatomegaly*

1. Extrahepatic malignant biliary obstruction

2. Cirrhosis liver

3. Infiltrative disorders

*Hard Hepatomegaly*

1. Malignancy (primary or secondary)

*Massive Hepatosplenomegaly*

1. Myeloproliferative disorders like chronic myeloid leukaemia

2. Lymphoma

3. Polycystic disease

4. Glycogen or lysosomal storage disease

5. Thalassaemia major

*Mild Hepatosplenomegaly*

1. Malaria

2. Infective endocarditis

3. Viral hepatitis

4. Infectious mononucleosis

5. Early cirrhosis with portal hypertension

6. Tuberculosis

*Hepatosplenomegaly with Ascites*

1. Cirrhosis with portal hypertension

2. Budd-Chiari syndrome

3. Constrictive pericarditis

4. Lymphoma

*Left Lobe Enlargement*

1. Left lobe abscess

2. Left lobe hepatocellular carcinoma

3. Budd-Chiari syndrome

4. Cholangiocarcinoma with right portal vein thrombosis (atrophy-hypertrophy complex)

5. Cirrohosis liver

A decrease in the size of the liver despite persistent heart failure or a fixed enlargement of the liver despite clearing up of heart failure suggests the development of cardiac cirrhosis.

**Spleen**

1. While still standing on the patient’s right side, reach across with your left hand and place it beneath the patient over the left costovertebral angle. Press upward with that hand to lift the spleen anteriorly towards the abdominal wall. Place the palmar surface of the right hand with fingers extended on the patient’s abdomen below the left costal margin. Press the fingertips inward towards the spleen as the patient is asked to take a deep breath.

2. Try to feel the edge of the spleen as it moves downward toward the fingers. The spleen is not usually palpable in

an adult. Spleen should enlarge twice the normal size before it can be palpated.

*In case of palpable spleen, following features must be examined systematically*:

1. Size

2. Shape: The normal triangular shape of the spleen is usually maintained in disease

3. Consistency: Normal consistency of spleen is soft

4. Palpable notch

5. Movement with respiration

6. Tenderness

7. Finger cannot be introduced between the mass and the left costal margin (unlike in enlarged kidney)

Sometimes, splenomegaly may mimic enlarged left kidney. Enlarged spleen may be distinguished from an enlarged kidney by the following points.

***Kidney***

1. Notch is not palpable

2. Less movement with respiration

3. Resonance on percussion

4. Bimanually palpable

5. Enlargement usually downward

***Spleen***

1. Notch is palpable

2. Superficial

3. Moves freely with respiration

4. Fingers cannot be introduced beneath the costal margin

5. Dull on percussion

6. Bimanually not palpable

7. Enlargement usually towards umbilicus

*Mild Splenomegaly (<5 cm enlargement)*

1. Infections

n Malaria, acute viral hepatitis, typhoid, bacterial endocarditis

2. Haemolytic anaemia

3. Lymphoma

4. Splenic vein thrombosis

5. Connective tissue disorder

6. Tumours or cysts from the spleen

7. Cirrhosis liver with portal hypertension

*Moderate Splenomegaly (5–10 cm enlargement)*

1. Malaria, kala azar

2. Myeloproliferative disorder

3. Lymphomas

4. Leukaemia

5. Haemolytic anaemia

6. Extrahepatic portal hypertension

*Massive Splenomegaly (>10 cm enlargement, crossing the midline)*

1. Chronic malaria

2. Chronic myeloid leukaemia

3. Myelofibrosis

4. Extrahepatic portal hypertension

*Soft Splenomegaly*

1. Acute viral hepatitis

2. Septicaemia

3. Bacterial endocarditis

4. Typhoid fever

*Firm Splenomegaly*

1. Myeloproliferative disease

2. Lymphoma

3. Cirrhosis liver

*Hard Splenomegaly*

1. Tropical splenomegaly syndrome

2. Chronic myeloid leukaemia

**Gallbladder**

1. Palpate below the liver margin at the lateral border of the rectus muscle for the gallbladder.

2. A healthy gallbladder will not be palpable.

3. A palpable, tender gallbladder indicates cholecystitis.

4. Murphy’s sign: As the inflamed gallbladder comes in contact with the examining fingers, the patient will experience pain and abruptly halt inspiration.

*Causes of Enlarged Gallbladder*

1. Periampullary carcinoma

2. Gallbladder cancer

3. Mucocele of gallbladder

4. Pyocele of gallbladder

5. Xanthogranulomatous cholecystitis

***Left Kidney***

1. Ask the patient to lie supine. Standing on the patient’s right side, reach across with your left hand as in palpation of spleen and place it over the left flank. Place your right hand at the patient’s left costal margin.

2. Have the patient take a deep breath, elevate the left flank with your left hand and palpate deeply (because of the retroperitoneal position of the kidney) with the right hand. Try to feel the lower pole of the kidney with the fingertips

as the patient inhales. The left kidney is ordinarily not palpable.

***Right Kidney***

Stand on the patient’s right side, placing the left hand under the patient’s right flank and the right hand at the right costal margin. Perform the same maneuvers as was done for the left kidney.

**Percussion**

1. Percussion is used to assess the size and density of the organs in the abdomen and to detect the presence of fluid (ascites) or solid masses (tumour).

2. First percuss all quadrants or regions of the abdomen for a sense of overall tympany and dullness. Tympany is the sound due to the presence of air in the stomach and intestines. Dullness is heard over organs and solid masses.

***Liver Percussion***

1. *Upper border of the liver*: Percussion should begin on the right midclavicular line at an area of lung resonance. Continue downward until the percussion tone changes to dull note, which marks the upper border of the liver. Mark the upper border of the liver. Usually upper border of liver is situated in the fifth or sixth intercostal space inside the midclavicular line. Dullness extending above that suggests upward displacement due to abdominal fluid or masses. An upper border below this may indicate downward displacement or liver atrophy.

2. *Lower border of liver*: Liver percussion at the right midclavicular line below the level of the umbilicus over an area of tympany to determine the lower border of liver. It is advisable to start with an area of tympany and proceed to an area of dullness. Percuss upward along the midclavicular line to determine the lower border of the liver. The area of liver dullness is usually at the costal margin or slightly below it. A lower liver border that is more than 2–3 cm below the costal margin suggests either liver is enlarged or downwardly displaced.

3. Liver span is calculated by measuring the upper border and lower border. The usual span is approximately 6–12 cm. Greater liver span indicates liver enlargement, whereas a lesser span suggests liver atrophy secondary to cirrhosis.

*Sudden Decrease in Liver Dullness*

1. Massive or submassive liver cell necrosis

2. Localized dilatation of transverse colon (as in toxic megacolon)

3. Fulminant colitis

4. Peritonitis

***Spleen Percussion***

There are various methods for percussion of the spleen.

1. ***Nixon’s method***: The spleen is percussed just posterior to the midaxillary line on the left side. Percuss in several directions beginning at areas of lung resonance. A small area of splenic dullness may be heard from the sixth to the tenth rib. A large area (>8 cm) of dullness suggests spleen enlargement.

2. ***Castell’s method***: Percuss the lowest intercostal space in the left anterior axillary line before and after the patient takes a deep breath. The area should remain tympanic. Dull note in this area suggests splenomegaly.

3. ***Dullness in Traube’s area***: Traube’s area is bounded by sixth rib, left mid axillary line laterally and left costal margin inferiorly. Dullness in the Traube’s area suggests splenomegaly.

**Auscultation**

1. Auscultation is used to assess bowel movements and to discover arterial bruit or venous hum.

2. Place the diaphragm of a warmed stethoscope on the abdomen and hold it in place with only very light pressure.

***Bowel Sounds***

1. Note the pitch, intensity and frequency of the bowel sounds.

n Site for auscultation of bowel sounds is 1 inch above and lateral to umbilicus in all four quadrants.

n The auscultatory examination usually takes place before percussion and palpation, and may last several minutes.

2. Bowel sounds are usually heard as clicks and gurgles that occur irregularly and range from 5 to 35 per minute.

3. Borborygmi are loud, rumbling and gurgling sounds resulting from a rush of gas or fluid through the lumen of bowel.

4. High pitch, louder and hyperactive bowel sounds are heard in intestinal obstruction; as gas and fluid squeezed through a narrowed passage produces louder sounds.

5. Decreased bowel sounds occur with peritonitis and paralytic ileus.

6. The absence of bowel sounds is established only after 5 min of continuous listening.

***Arterial Bruit and Friction Rubs***

1. Listen with the diaphragm of the stethoscope in the epigastric region and each of the four quadrants for bruits in the aortic, renal, iliac and femoral arteries.

2. A murmur over the liver may suggest tumour, arteriovenous malformation or alcoholic hepatitis.

3. Listen for friction rubs over the liver and spleen. Friction rub indicates inflammation of the peritoneal surface due to infection or tumour. A friction rub over the liver has been noted in patients with carcinoma and perihepatic inflammation and after percutaneous liver biopsy.

***Venous Hum***

1. Venous hum is soft, low-pitched and continuous sound.

2. Auscultation with the bell of the stethoscope should be performed around the umbilicus for a venous hum in case of suspected portal hypertension.

3. Cruveilhier-Baumgarten syndrome is an audible venous hum over the dilated periumbilical circulation in patients with portal hypertension.

***Succussion Splash***

1. Succussion splash can be elicited by either palpation or auscultation.

2. It is classically mentioned in patients with gastric outlet

obstruction. However, it may be heard in advanced intestinal obstruction with grossly distended bowel loops and in paralytic ileus.

3. Patient lies in supine position. The palm of the right hand or stethoscope should be placed on the epigastrium.

4. Then roll the patient from side to side to agitate any fluid and gas in the stomach. If stomach contains fluid and gas, a splashing sound occurs.

5. Since sucussion splash may be heard just after taking food, this test is to be done after 4–6 hrs of taking food.

**Assessment of Ascites**

***Inspection***

1. Fullness of flanks

2. Abdominal distension

3. Shiny skin over abdomen

4. Umbilical hernia

***Palpation***

***Fluid thrill***: This procedure requires three hands, so we will need assistance from the patient or another examiner. With the patient supine, ask him or her or another person to press the edge of the hand and forearm firmly along the vertical midline of the abdomen. This positioning helps stop the transmission of a wave through adipose tissue.

Place the hands on each side of the abdomen and tap one side sharply with the fingertips. Feel for the impulse of a fluid wave with the fingertips of the other hand. An easily detected fluid wave suggests ascites.

***Percussion***

1. ***Shifting dullness***: Patient should be made to lie on one side and again percuss for tympany and dullness and mark the borders. In a patient without ascites, the borders will remain relatively constant. In ascites, the border of dullness shifts to the dependent side (approaches the midline) as the fluid resettles through gravity.

2. ***Horse-shoe dullness***: Percuss for areas of dullness and resonance with the patient supine. As fluid settles with gravity, dullness is heard in the dependent parts of the abdomen and tympany in the upper parts (epigastrium) due to intestines.

3. ***Puddle sign***: This is to detect minimal fluid (120 mL). The patient is asked to assume the knee-elbow position and maintain that position for several minutes to allow any fluid to pool by gravity. Percuss the umbilical area for dullness to determine the presence of fluid. The area will remain tympanic if there is no fluid.

**The Anus and Rectum**

The left lateral position is the best position for routine examination of the rectum. Make sure that the buttocks project over the side of the couch with the knees drawn well up near the chest. Explain the procedure to the patient in detail to reduce apprehension.

***Inspection***

1. Separate the buttocks carefully and inspect the perianal area and anus.

2. Note the presence of any abnormality of the perianal skin such as erythema and anal skin tags. Anal skin tags indicate long-standing prolapsing piles.

3. Anal warts (condylomata acuminata) are sessile or pedunculated papillomata with a red base and a white surface.

4. External opening of a fistula in-ano is seen as a ‘hole’ or dimple near the anus with a telltale bead of pus or granulation tissue surrounding it.

5. Pilonidal sinus is the opening that lies in the midline of the natal cleft but well posterior to the anus.

6. Anal fissure usually lies directly posterior in the midline. The outward pathognomonic sign of a chronic fissure is a tag of skin at the base (sentinel pile). The fissure can easily be demonstrated by gently drawing apart the anus to reveal the tear in the lining of the anal canal.

7. Thrombosed external pile occurs as a result of rupture of a vein of the external hemorrhoidal plexus. It is seen as a small (1 cm), tense, bluish swelling on one aspect of the anal margin and is exquisitely tender to touch. In prolapsed strangulated piles, there is gross swelling of the anal and perianal skin.

8. Perianal abscess is an acutely tender, visible red fluctuant swelling, which deforms the outline of the anus. It is usually easy to distinguish this from an ischiorectal abscess where the anal verge is not deformed.

9. Look for the presence of any ulceration.

10. When rectal prolapse is suspected, ask the patient to bear down and note whether any pink rectal mucosa or bowel appears through the anus, or whether the peri-neum itself bulges downwards. Downward bulging of the perineum during straining at bending down, or in response to a sudden cough, indicates weakness of the pelvic floor support musculature.

***Digital Examination (Palpation)***

1. Put a generous amount of lubricant (2% lignocaine jelly) on the gloved index finger of the right hand; place the pulp of the finger (not the tip) flat on the anus. Press firmly and slowly in a slightly backwards direction. After initial resistance, the anal sphincter relaxes and the finger can be passed into the anal canal. Severe pain during digital examination suggests anal fissure, and palpation should not be performed.

2. Rotate the finger through 360 degrees in the canal and feel for any thickening or irregularity of the wall of the

canal. Assess the tone of the anal musculature; it should normally grip the finger firmly. The anorectal ring may be felt as a stout band of muscle surrounding the junction between the anal canal and rectum.

3. Now pass the finger into the anorectum. The rectal wall should be assessed with sweeping movements of the finger through 360 degrees, 2, 5 and 8 cm inwards or until the finger cannot be pushed any higher into the rectum.

4. Repeat these movements as the finger is being withdrawn. In this way, it is possible to detect malignant ulcers, proliferative and stenosing carcinomas, polyps and villous adenomas. The hollow of the sacrum and coccyx can be felt posteriorly.

5. In men, one should feel anteriorly for the rectovesical pouch, seminal vesicles and the prostate.

6. A boggy, tender swelling lying above the prostate indicates pelvic abscess.

7. In men, the assessment of the prostate gland is important. It forms a rubbery, firm swelling about the size of a large chestnut. Run the finger over each lateral lobe, which should be smooth and regular. Between the two lobes lies the median sulcus, which is palpable as a faint depression running vertically between each lateral lobe. In carcinoma of the prostate, the gland loses its rubbery consistency and becomes hard, whereas the lateral lobes tend to be

irregular and nodular and there is distortion or loss of the median sulcus.

8. In women, the cervix is felt as a firm, rounded mass projecting back into the anterior wall of the rectum. The body of a retroverted uterus, fibroid mass, ovarian cyst, malignant nodule or a pelvic abscess may all be palpated in the pouch of Douglas (rectouterine pouch).

**s**

***Liver***

The upper border of the right lobe is on a level with the fifth rib at a point 2 cm medial to right midclavicular line. The upper border of the left lobe corresponds to the upper border of the sixth rib at a point in the left midclavicular line. The lower border passes obliquely from the 9th right to the 8th left costal cartilage. It crosses the midline about midway between the base of the xipohoid and the umbilicus.

***Gallbladder***

The fundus of gallbladder lies at the outer border of rectus abdominis where it intersects the ninth costal cartilage.

***Spleen***

The spleen occupies the position of the ninth, tenth and eleventh ribs on the left side. Posteriorly, the upper pole is 2–3 cm lateral to the midline and the anterior border comes up to the midaxillary line in front.

***Kidneys***

The kidneys are placed posteriorly in close apposition to the abdominal wall and their position can be indicated by the Morris quadrilateral on either side. Two parallel hori-zontal lines are drawn on the back at the levels of the eleventh dorsal and third lumbar spines. They are intercepted by two vertical lines drawn 3.75 and 8.75 cm, respectively from the midline.

SECTION 4

CASE DISCUSSION

**Chapter 13.**

**Jaundice**

**Introduction**

Jaundice is not a disease, but it is a sign of different underlying diseases. Jaundice refers to the yellowish staining of the skin and sclera (the whites of the eyes) caused by high levels of bilirubin in the blood. Specific treatment is required to treat the cause of jaundice. In this section, the discussion is more focused on the approach to patient with jaundice with more emphasis on cholestatic jaundice either due to extrahepatic bile duct obstruction or intrahepatic cholestasis. Details of each cholestatic disorder are mentioned in the subsequent sections.

**Definition of Cholestasis**

n Condition that affects the production, delivery and recycling of bile at any stage is called cholestasis.

n Pruritus is an unpleasant sensation that triggers the need to scratch.

n The stimulus associated with the sensation of pruritus is transmitted by unmyelinated C-fibres, which also transmit pain.

**Clinical History**

1. Duration

n Acute presentation of jaundice seen in viral or toxin/drug-induced hepatitis, acute Budd-Chiari syndrome, biliary obstruction and ischaemic liver injury

2. Progress

n Progressively worsening jaundice - consider:

- Malignant obstruction

- Primary biliary cirrhosis

- Familial cholestasis

- Primary sclerosing cholangitis

- Advanced end stage liver disease

n Intermittent jaundice - consider:

- Choledocholithiasis

- Ampullary carcinoma

- Biliary ascariasis

- Relapsing viral hepatitis A

3. Prodromal symptoms at or before onset

n Suggestive of viral hepatitis/drug-induced hepatitis

n Due to release of endogenous interferon

4. Fever

n Fever at onset – Viral hepatitis

n Fever with rigors – Cholangitis, liver abscess

n Low-grade fever – Neoplasm

5. Abdominal pain – Suggests extrahepatic cause of cholestasis **(Table 13.1)**

n Biliary colic – It is a visceral pain, which is steady rather than intermittent, usually in the epigastrium and right upper quadrant, increases over a period of 15 min to 1 hr and then remains at plateau for 1 hr or more, and then slowly resolving within 6 hrs.

n Pancreatic pain – Dull, continuous pain mainly in epigastrium lasting for several hours, radiating to back, aggravated by food and relieved by sitting up or leaning forward.

n Dull, continuous, dragging type of pain in right hypochondrium due to stretching of Glisson capsule due to hepatomegaly.

6. Other clinical manifestations:

n Generalized pruritus

n Clay colour stool and tea coloured urine

7. Drug ingestion history

n Bland cholestasis (prodrome followed by pruritus, SAP > 3 x ULN times, mildly elevated AST/ALT, ALT/SAP ratio <2, serum bilirubin <12 mg%)

- Estrogen

- Tamoxifen

- Anabolic steroid

- Azathioprine

n Cholestasis with hepatitis (pain in right hypochondrium with jaundice; SAP > 3 x ULN, ALT > 2–3 x ULN, ALT/SAP ratio between 2–5 times)

- Phenothiazines

- Tricyclic antidepressant

- Macrolide antibiotics

- Amoxicillin-clavulanate

- Azathioprine

n Cholestasis with bile duct injury

- Dextropropoxyphene

- Flucloxacillin

n Vanishing bile duct (cholestasis-like primary biliary cirrhosis, but AMA negative)

- Chlorpromazine

- Flucloxacillin

- Amoxicillin-clavulanate

- Carbamazepine

- Phenytoin

- Phenobarbital

- Azathioprine

n Large duct stricture (like primary sclerosing cholangitis)

- Floxuridine

- Intralesional scolicidal agent (formalin, silver nitrate, hypertonic saline, absolute alcohol, iodine solution)

8. Manifestations that indicate fat soluble vitamin deficiency:

n Vitamin A – Night blindness

n Vitamin D – Bone pain & muscle weakness

n Vitamin E – Leg cramps

n Vitamin K – Easy bruising

9. History of gastrointestinal bleeding – Indicates ampullary malignancy or development of portal hypertension

**Extrahepatic Intrahepatic**

Abdominal pain + –

Fever + –

Prodrome – +

Drugs – +

Previous hepato-

bilary surgery + –

Risk factors like – +

transfusion

Family history – +

Stigma of cirrhosis – +

Encephalopathy – +

PT normalizing + –

with vit K

**Past History**

1. Recurrent jaundice – Relapsing viral hepatitis A

2. Right upper quadrant surgery

n Post cholecystectomy biliary stricture

n Post surgical stricture

3. Recurrent biliary colic – Suggestive of cholelithiasis

n Cholelithiasis

n Asymptomatic - 75%

n Biliary colic - 20%

n Cholecystitis - 10%

n Complications - <5%

n 15% of gallstones have CBD stone

n 95% of CBD stones have gallstone

n Normal CBD pressure – 10–15 cm H2O

n Bile flow stops at 30 cm H2O

*Natural history of asymptomatic cholelithiasis*

n Development of biliary colic – 2% per year

n Complication – 0.2% per year

n Carcinoma – <0.02% per year

*Natural history of patients with biliary colic*

n Recurrent colic – 20–40% per year

n Complication – 1–2% per year

*Natural history of patients with choledocholithiasis with complications*

n 30% recurrence of complications in 3 months

4. Past history of hepatotoxic drugs

5. Past history of contact with jaundiced patient

6. History of cholestasis during pregnancy

**Family History**

1. Family history of cholestasis

n Progressive familial intrahepatic cholestasis (PFIC) syndrome

n 1-Antitrypsin deficiency

2. Family history of jaundice

n Wilson’s disease

n Progressive familial intrahepatic cholestasis syndrome

n 1-Antitrypsin deficiency

**Personal/Social History**

1. Alcohol – Alcoholic hepatitis can lead to cholestasis

**General Examination**

1. Body mass index

2. Vital signs

3. Pallor

n GI bleeding

n Haemolysis

4. Icterus – Mild/moderate/severe

n Lemon yellow – Haemolytic

n Greenish yellow – Obstructive

n Orange yellow – Hepatocellular

5. Pedal oedema

n Hypoproteinemia

n Development of cirrhosis

6. Shiny nails and scratch marks (due to pruritus)

7. Xanthoma/Xanthelasmas

8. Clinical findings associated with fat-soluble vitamin deficiency

n Bitot spot, hyperpigmentation: Vitamin A

n Ecchymosis: Vitamin K

9. Stigmata of chronic liver disease (Ch. 12)

**Abdominal Examination**

**Inspection**

1. Abdominal distension and dilated abdominal veins indicate cirrhosis

2. Operative scar

**Palpation**

1. Hepatomegaly

2. Splenomegaly

n Secondary biliary cirrhosis

n Intrahepatic cholestasis with portal hypertension

n Associated splenic vein thrombosis

3. Palpable gallbladder (see Courvoisier law)

4. Mass palpable

n Epigastric

- Hepatocellular carcinoma (HCC)

- Pancreas

- Stomach cancer with nodes at porta

n Right hypochondrium

- Gallbladder malignancy

- HCC

- Hepatic flexure cancer

- Duodenal carcinoma

- Choledochal cyst

5. Free fluid

n Malignant ascites

n Non-malignant ascites

***Courvoisier Law***

In the jaundice patient, obstruction of the common bile duct due to stone, distension of the gallbladder seldom occurs; the organ is usually shriveled.

n Most patients with jaundice due to stone have a fibrotic, non-distensible gallbladder.

n Malignant obstruction is complete, whereas stone obstruction is usually incomplete to cause distension.

n Double impaction of stone, oriental cholangiopathy and mucocele to the gallbladder are the exceptions the Courvoisier’s law.

**Investigations**

**Biochemical Test**

n Leucocytosis indicates cholangitis.

n Elevated alkaline phosphatase/direct hyperbilirubinemia

n Mild increase in AST/ALT except in case of cholangitis.

n Raised GGT – To confirm SAP of liver origin.

n Prothrombin time – May be prolonged, can be corrected by administration of vitamin K (usually three doses are sufficient; more doses run the risk of precipitating hemolysis in G6PD deficiency states).

**Abdominal Sonography**

n Bedside test, easily available, cheap and no radiation is involved.

n Hypoechoic liver with oedema of the gallbladder wall seen in acute viral hepatitis, dilated inferior vena cava (IVC) and hepatic veins are cardinal features of right sided heart failure. Hepatic vein and IVC Doppler are useful for the diagnosis of hepatic venous outflow tract obstruction (Budd–Chiari syndrome).

n Enables differentiation between extrahepatic/intrahepatic biliary obstruction on the basis of dilatation of common bile duct and intrahepatic biliary radical dilatation.

n Enables localization of the site of obstruction and extent of disease and identified the lesion mass (benign or malignant).

n Features of portal hypertension like portal vein Doppler, splenomeglay, collaterals at splenic hilum.

n Sensitivity (>2 mm) and specificity (shadow) to diagnose gallstone is 95%.

n Sensitivity to diagnose common bile duct (CBD) stone is 50% in patients with non-dilated CBD and 75% in those with dilated CBD.

**Spiral CT Abdomen**

n MDCT scan with intravenous contrast is most important investigations in patients with jaundice.

n Can identify nature of liver lesion, PV thrombus, patency of HV and IVC, level of biliary obstruction.

**MRCP**

n Relies on T2-weighted sequences to visualize static fluid structure.

n Stationary fluid in the pancreatic duct and biliary ducts acts as a contrast medium.

n Ductal system appears as white against a dark background as in ERCP.

n No contrast is required.

n Accuracy is more in dilated system than in non-dilated system.

n Locate the site of biliary obstruction.

n Sensitivity and specificity to diagnose CBD stone is 81% and 85–98%, respectively.

n Acts as a road map for further interventions.

**EUS**

n Staging of periampullary malignancy, identification of small pancreatic tumour, small CBD stone, which was missed on USG abdomen.

n Sensitivity and specificity to detect CBD stone is 93% and 97%, respectively.

**ERCP**

n Mainly for therapeutic purpose rather than diagnosis.

n Gold standard to diagnose choledocholithiasis.

n Sensitivity and specificity to diagnose CBD stone is 95%.

n Used for CBD stone removal, palliative biliary decompression in case of advanced malignant biliary obstruction.

Approach to various cholestatic disorders is illustrated in **Flow chart 13.1**.

**Causes of Cholestasis**

**Neonates**

1. Idiopathic neonatal hepatitis

2. Extrahepatic biliary atresia (EHBA)

3. 1-Antitrypsin deficiency

4. Progressive familial intrahepatic cholestasis syndrome

5. Choledochal cyst

6. Sepsis

7. Galactosemia

**Children/Infants**

1. Choledochal cyst

2. EHBA

3. Mucus plug syndrome

4. Paucity of bile duct

5. Caroli disease

6. Cystic fibrosis

7. Congenital bile duct stricture

8. PFIC

9. Choledocholithiasis

**Adults**

***Extrahepatic Biliary Obstruction***

1. Benign

n Choledocholithiasis

n Mirizzi syndrome

n Postoperative stricture

n Benign stricture in chronic pancreatitis

n Pancreatic pseudocyst causing distal CBD obstruction

n Biliary ascariasis

2. Malignant

n Periampullary carcinoma

n Hilar cholangiocarcinoma

n Gallbladder malignancy

n HCC with metastasis

n Lymph node metastasis at porta

***Intrahepatic Cholestasis***

n Drugs/alcoholic hepatitis

n Post viral infection

n PFIC

n BRIC (benign recurrent intrahepatic cholestasis)

n Pregnancy-induced cholestasis

n TPN-induced cholestasis

n Primary sclerosing cholangitis (PSC)

n Primary biliary cirrhosis (PBC)

**Management of Acute Hepatitis**

Acute viral hepatitis A and E are self-limiting disease. Drug-induced liver injury (DLI) needs specialized management as some cases become fatal. Restoration of blood circu-lation is the treatment for ischaemic liver injury. Budd-Chiari syndrome is managed with either anti-coagulant or venous stenting.

**Management of Cholestatic Jaundice**

Management of patients with cholestasis includes establishing the diagnosis of the condition and determining an effective therapeutic strategy to treat the primary liver pathology and to relieve the pruritus.

Some causes of cholestasis are reversible, such as CBD stone, cholestasis after viral hepatitis, drug-induced cholestasis and extrinsic bile duct compression secondary to pseudocyst of the pancreas. Cholestasis secondary to extrahepatic biliary obstruction can be relieved by either endoscopic or surgical biliary drainage. Resection can be performed to manage malignant biliary obstruction in patients in whom surgery is feasible, whereas those with inoperable malignant biliary obstruction can be managed either by palliative surgical or endoscopic biliary decomp-ression. Many diseases associated with cholestasis are incurable [like primary biliary cirrhosis, sclerosing cholangitis, progressive familial intrahepatic cholestasis (PFIC), etc]. In these conditions, the administration of treatments for the disease may not be able to relieve pruritus. Thus, specific management of pruritus is necessary.

**Extrahepatic Manifestation of Cholestasis**

Three cardinal extrahepatic manifestations of cholestasis are:

1. Pruritus

2. Fatigue

3. Metabolic bone disease

**Pathogenesis of Pruritus in Cholestasis**

There is no correlation between intensity of pruritus and severity of cholestasis. Exact pathogenesis of pruritus is not known. Central and peripheral mechanisms are postulated for pruritus in cholestasis:

1. **Central mechanism** – Increase central opioidergic tone in patients with cholestasis.

2. **Peripheral mechanisms** – Accumulation of numerous substances in the systemic circulation as they cannot be eliminated via bile excretion. They are bile acids, histamine, serotonin and endogenous opiods.

**Treatment of Pruritus in Cholestasis**

There are various modalities to treat pruritus in cholestasis, which is listed below:

1. Opiod antagonist like naloxone, naltrexone or nalmefene as endogenous opioids contributes to pruritus.

2. Cholestyramine

3. Rifampicin – Induce CP450 which inactivates pruritogen.

4. Phenobarbital

5. Oral guar gum – Increase fecal elimination of bile.

6. 5-HT3 antagonist – As serotonin system participates in the mediation of nociception, 5-HT3 antagonist theoretically relieves pruritus.

7. Ursodeoxycholic acid (UDCA) – High-dose ursodeoxy-cholic acid (UDCA) is useful in patients with PBC and PSC.

8. Propofol – Modulate endogenous opioid ligand.

9. Lidocaine – Reduce perception of nociceptive stimuli.

10.Dronabinol – A sesame oil preparation increases the threshold for noxious stimuli, helps in pruritus.

11.Gabapentin – Improves sensitization.

12.Phototherapy to the skin with ultraviolet (UV) light B is useful in some individuals.

13.Charcoal haemofilteration and plasmapheresis.

14.Ileal diversion.

15.Albumin dialysis (MARS) removes pruritogen, but is rarely indicated and very expensive.

**Pathogenesis of Fatigue in Cholestasis**

Fatigue is one of the most debilitating symptoms in patients with primary biliary cirrhosis (86%). Pathogenesis is multifactorial.

1. Neuroendocrine cause – Alteration in hypothalamo-pituitary axis leads to impaired release of CRH (corticotrophin-releasing hormone) following stress.

2. Cytokines-mediated (IL-1b, IL-6, TNF-, INF-) fatigue.

3. Reduced central serotonergic neurotransmitters.

**Treatment of Fatigue in Cholestasis**

1. Healthy lifestyle, regular sleep and exercise and avoidance of stress

2. Cognitive behaviour therapy

3. 5-HT3 antagonist

4. Antioxidant

5. Antidepressant

**Pathogenesis of Metabolic Bone Disease in Cholestasis**

n Metabolic bone disease in the form of either osteoporosis (defective bone mineralization) or osteopenia (defective bone formation), is seen in 40% of patients with cholestasis.

n Osteomalacia is very rare in cholestasis.

n Diagnosed by DEXA scan.

n In DEXA scan if T score is more than –2.5, it is suggestive of osteoporosis while score between –1 and –2.5 suggests osteopenia.

n Causative factors of metabolic bone disease:

- Fat-soluble vitamin D and calcium deficiency

- Deficiency of vitamin K and magnesium

- Reduced IGF-1 production from liver, which leads to reduced osteoblast proliferation

- Cytokine-mediated increase in bone resorption

**Treatment of Metabolic Bone Disease in Cholestasis**

1. Calcium intake at least 1.2–1.5 g/day

2. Bisphosphonate

3. Hormone replacement therapy

4. Reloxifen

5. Role of calcitonin nasal spray is not proved

**Vitamin Replacement Therapy in Patients with Cholestasis**

1. Vitamin A: 25–50,000 U 2–3 times per week

2. Vitamin D: 25–50,000 U 2–3 times per week

3. Vitamin K: 5 mg/day

4. Vitamin E: 100 U twice daily

**Bilirubin Metabolism**

The human body produces approximately 4 mg/kg body weight of bilirubin daily from haeme-containing proteins from erythroid and non-erythroid sources. Bilirubin derives

from two main sources: Senescent red blood cells (80%) and various haeme containing proteins like myoglobin, and various P450 enzymes. Bilirubin is insoluble in water because of the internal hydrogen bonding and is excreted in the bile via enzyme-mediated glucuronidation. Plasma bilirubin typically exists in its unconjugated form (around 98%) and is tightly bound to circulating albumin. Plasma bilirubin is taken up by the hepatocytes via facilitated diffusion and is bound to glutathione-*S*-transferases and is conjugated to glucuronides by microsomal UDP-glucuronosyl transferase 1 (UGT1A1). Then, the ATP-utilizing pump MRP2 actively transports the bilirubin glucuronides into the bile canaliculi. The intestinal bacteria degrade bilirubin into urobilinogens, which are partly excreted in the urine. The plasma levels of unconjugated bilirubin increase in patients with increased production, reduced uptake and low capacity of glucuronidation. Patients with inherited or acquired deficiencies of bilirubin storage or excretion show

accumulation of conjugated and unconjugated bilirubin in the plasma. Conjugated bilirubin is less tightly bound to

albumin and is excreted in the urine.

Bilirubin production is regulated by different genes, and nuclear receptors play an important role in regulating the expression of these genes.

**Further Reading**

1. Bergas NV. An approach to the management of pruritus of cholestasis. *Clin Liver Dis* 2004;8:55–66.

2. Elferink RO. Cholestasis. *Gut* 2003;52:42–8.

3. Greaves MW, Wall PD. Pathophysiology of itching. *Lancet* 1996;348:938–40.

4. Trauner M, Meier PJ, Boyer LN. Mechanisms of disease: molecular pathogenesis of cholestasis. *N Engl J Med* 1998; 339:1217–27.

5. Jones EA, Bergasa NV. The pruritus of cholestasis: from bile acids to opiate antagonists. *Hepatology* 1990;11:884–87.

**Chapter 14.**

**Pancreatic Cancer**

**Introduction**

Pancreatic cancer is an important health problem. The incidence of pancreatic cancer has steadily increased in many countries. The incidence of pancreatic cancer is higher in developed countries in general. Pancreatic cancer rarely occurs before the age of 45 years and more than two-third of patients with pancreatic cancer is in the 60–80-year age group. Around 60–70% of the tumours are located in the head of the pancreas, 5–10% in the body and 10–15% in the tail region of the gland. A simple screening test is not available to date for the general population. Cigarette smoking is thought to be the strongest risk factor associated with pancreatic cancer.

**Clinical History**

1. Jaundice with or without cholangitis – Encasement of lower end of bile duct due to cancer arising from head of the pancreas. In fact, painless progressive jaundice without cholangitis is the chief pathognomonic symptom complex of pancreatic head cancer. Jaundice in patients with pancreatic body or tail region is usually caused by hepatic or hilar metastasis and therefore indicates inoperability.

2. Unexplained anorexia and weight loss.

3. Endoscopy (upper GI endoscopy)-negative persistent dyspepsia.

4. Abdominal pain – Variable intensity, dull, vaguely localized in the upper abdomen, aggravated by food, radiation to back and relieved by leaning forward position. (Leaning forward position reduces compression on celiac ganglion). Abdominal pain although present in nearly all cases is the chief presenting symptom in less than a third of patients.

5. New onset of diabetes (polyuria, polyphagia and polydypsia)

- 6–68% has diabetes.

- Due to reduced beta-cell function and increased amyloid polypeptide, which lead to decrease insulin sensitivity.

6. Clay-coloured stools with pruritus.

7. Haemetemesis or melena – Suggestive of splenic vein thrombosis

8. Persistent back pain is associated with retro-peritioneal infiltration and usually incurability.

9. History of lump or swelling in the abdomen – rare. A lump, which is palpable in pancreatic cancer may often be distended stomach lying over the pancreatic mass than the mass itself.

10. Acute or chronic pancreatitis are possible presentations of pancreatic cancer in 5% of patients.

**Past History**

1. Recurrent pancreatic type of pain in the past indicates chronic pancreatitis

- Chronic pancreatitis is associated with an increased risk of cancer 5–15 folds. Risk of pancreatic cancer in chronic pancreatitis is 2% per decade.

2. Past history of gastric surgery

- Surgery of peptic ulcer disease increases the risk of pancreatic cancer by 2–5 folds after 15–20 yrs.

- Possible cause is due to increased N-nitroso compounds.

**Family History**

1. Hereditary pancreatitis

- Autosomal dominant disease

- Estimated risk of developing pancreatic cancer is 50–70 fold and a cumulative lifetime risk to the age of 75 yrs of 40%.

- Pancreatic cancer can occur maximum in the 4th decade.

2. Pancreatic cancer

- Around 7–8% of patients with pancreatic cancer have similar cancer in first-degree relatives.

**Personal History**

1. Smoking

- 30% of pancreatic cancer is related to smoking

- Relative risk is 1.5

- Associated with amount of smoking

- Due to increased N-nitroso compounds

2. High intake of fat/meat and low intake of fresh vegetables

**General Examination**

1. Build and nutrition

2. Icterus

3. Evidence of fat-soluble vitamins deficiency (may only be present in long-standing jaundice).

4. Supraclavicular lymph node (indicates incurable disease).

5. Thrombophlebitis migrans (migratory thrombophlebitis, an observation made by Trousseau in himself before he was diagnosed with pancreatic cancer).

**Abdominal Examination**

n Ascites (could indicate disseminated disease, hypoalbu-minaemia or biliary cirrhosis due to long-standing obstruction).

n Visible and palpable mass.

n Hepatomegaly invariably present – Does not indicate metastases as a rule. Hepatomegaly is due to obstructive jaundice.

n Splenomegaly – Due to splenic vein thrombosis or cholangitis.

n Palpable gallbladder (Courvoisier’s law) – 25–30% of patients.

n Per-rectal examination – Mandatory and the presence of a pelvic deposit (Blumer’s shelf) indicates peritoneal spread and incurable disease.

n A palpable and fixed epigastric mass, ascites or an enlarged supraclavicular lymph node (Virchow’s node) are signs of inoperability.

**Investigations**

1. ***Biochemical test***

n Leukocytosis indicates cholangitis

n Elevated alkaline phosphatase/direct hyperbilirubinemia

n Mild increase in AST/ALT except in the case of cholangitis

n Raised GGT: To confirm SAP of liver origin.

n Prothrombin time: May be prolonged, can be corrected by administration of vitamin K (usually three doses are sufficient; more dose runs the risk of precipitating haemolysis in G6PD-deficiency states).

2. ***USG abdomen***

n Bedside test, easily available, cheap and no radiation is involved. The sensitivity of this technique is higher for detecting head lesions than body and tail neoplasms.

n Diagnosis of biliary obstruction–intrahepatic biliary dilatation in 100%, the site of the obstruction in 60% and the cause of obstruction only in 50% of the patients is feasible.

n The presence of double duct obstruction (dilatation of biliary and pancreatic ducts) on the US is pathognomonic of pancreatic cancer.

n Identification of a mass on an US is possible only if the echogenicity of the mass is different from that of the surrounding parenchyma. Splenic vein thrombosis can be detected using an US.

n Sensitivity to detect the locoregional spread is poor.

n Poor yield in terms of identifying liver metastases.

n Liver metastases are generally hypoechoic and they can be confused with the end-on view of biliary radicles in patients with biliary obstruction and intrahepatic biliary radicle dilatation.

n Pancreatic visualization is difficult in the case of 20–25% of patients because of bowel gas.

3. ***Spiral CT scan abdomen with contrast***

n Specificity and sensitivity are more than 95%; however, it is much less accurate in identifying potentially resectable small tumours.

n Excellent tool to evaluate resectability by detecting vascular and adjacent organ invasion as well as distant metastasis.

n With vascular reconstruction (now available on modern CT scanners), an accurate assessment of local vascular involvement can be made.

n The main area of weakness is in determining the presence of small liver metastases or peritoneal metastases.

4. ***Endoscopic ultrasonography***

n A very sensitive test too, but poor specificity without biopsy.

n Most accurate test for local staging and best for small tumour detection and invasion of major vascular structures. EUS-FNAC is one of the very easy procedure to obtain tissue from pancreatic neoplasm.

n Cannot replace spiral CT scan for detecting distant metastasis.

5. ***MRI***

n As good as CT scan but additional advantage is MR angiography, which may obviate the need for arteriography.

n MRCP can evaluate pancreatic and biliary ductal anatomy. In patients with biliary obstruction, a combination of CT and MRCP can provide complete information about the location of the tumour, the extent of spread and the ductal involvement. It avoids injection of contrast and radiation. MR, MRCP and MRA could be “one stop” salutation of diagnosis and staging for pancreatic head cancer.

6. ***ERCP***

n “Double duct sign” is classic for pancreatic head malignancy.

n Not used for diagnostic purpose.

n Can be used only for palliative biliary decompression in inoperable patients or patients with cholangitis.

n No role of preoperative biliary decompression in pancreatic head cancer.

7. ***Tissue diagnosis***

n Either CT scan or EUS guided.

n Sensitivity and specificity is around 60–90%.

n Failure to obtain histological confirmation of suspected diagnosis of malignancy does not exclude the presence of a tumour and should not delay appropriate surgical treatment.

n Transperitoneal techniques to obtain a tissue diagnosis have limited sensitivity in patients with potentially resectable tumours and should be avoided in such patients.

n Effort should be made to obtain a tissue diagnosis (EUS-guided FNAC is far superior than transperito-neal FNAC) in patients selected for palliative forms of therapy.

8. ***PET***

n Non-invasive technique using 18-*fluoro-deoxyglucose* (FDG).

n Used to differentiate between benign and malignant lesions if the results of other tests are equivocal.

n Expensive and not widely available.

n The normal pancreas is not usually visualized using FDG-PET. Pancreatic carcinoma, however, appears as a focal area of increased uptake in the pancreatic bed.

n PET identifies metastatic disease better than any other technique. CT scans only show enlarged lymph nodes but do not show their involvement. It is unclear that PET/CT identify pancreatic neoplasm, therefore, PET cannot be used as an alternative to high-quality CT of the abdomen.

9. ***Tumour markers***

n Role is not proved for screening.

n Using cutoff of 37 U/mL CA-19–9 has 86% sensitivity and 87% specificity.

10. ***Laparoscopy***

n Diagnostic laparoscopy, including laparoscopic ultrasound, can detect occult metastasis in the liver and peritoneal cavity not identified by other imaging modalities.

n Staging laparoscopy is indicated in resectable lesion with high-risk features like large tumour, very high

CA 19-9, large locoregional lymph nodes, marked weight loss and severe pain.

**Staging of Cancer**

1. Stage I: Malignancy confined to gland

2. Stage II: Regional lymph node involvement

3. Stage III: Distant metastasis

**TNM Staging System**

TIS Carcinoma in situ

T1 Tumour limited to the pancreas, 2 cm in

greatest dimension

T2 Tumour limited to the pancreas, >2 cm

in dimension

T3 Tumour extends into any of the following:

duodenum, bile ducts and peripancreatic tissues

T4 Tumour extends into any of the following: stomach,

spleen, colon and adjacent large vessels

N0 No lymph node involvement

N1 Regional lymph node

M0 No distant metastasis

M1 Distant metastasis

Stage I: T1-2 N0 M0

Stage II: T3 N0 M0

Stage III: T3 N0 M0 – T3 N1 M0

Stage IVA; Any T Any N M0

Stage IVB: Any T Any N M1

***Different Situations in Patients with Carcinoma Pancreas following CT Scan***

1. Resectable disease (20–25%)

2. Locally advanced tumour without metastasis

3. Distant metastasis

**Pathology**

1. The average size of tumour in the head of the pancreas is 2.5–3.5 cm and 5–7 cm in the body and tail of the pancreas.

2. More than 95% of the pancreatic cancer arises from the exocrine pancreas (ductal and acinar cells).

3. Ductal cell adenocarcinoma is the most common (85%). They are usually locally advanced, exhibit vascular invasion and lymph node metastases. Perineural and vascular invasion is extremely common in ductal adenocarcinoma.

4. Variants of ductal carcinoma and other malignant tumours of the pancreas are rare.

n Adenosquamous carcinoma

n Giant cell carcinoma

n Neuroendocrine tumour

n Mucinous carcinoma

n Acinar cell carcinoma

**Management of Pancreatic Cancer**

1. Surgery is currently the only modality with the potential to cure pancreatic cancer. It provides the best palliation and recurrences following surgery are usually pain free and jaundice free. However, surgical mortality levels must be low. Currently mortality level in units around the world is 0–4%. There are four acceptable type of surgical approach: Proximal pancreaticoduodenectomy with pylorus preservation; proximal pancreaticoduodenec-tomy with antrectomy (Whipple procedure); total pan-creaticoduodenectomy; and distal pancreatectomy.

2. In recent years, there is an increasing use of chemotherapy and radiotherapy, both as palliative treatment and adjuvant therapy, but much of this practice is not evidence based.

**Resectional Surgery**

***Pancreaticoduodenectomy (Kausch-Whipple’s Resection)***

1. En-block resection of pancreatic head, duodenum, distal common bile duct, proximal jejunum, cholecystectomy, partial gastrectomy and regional lymph nodes **(Fig. 14.1a)**

2. Morbidity 30–60% while mortality less than 5%

3. Pancreaticojejunostomy leak in around 10%

4. Wider resection margin along the duodenum

5. 5-year survival after curative resection is 5–20%

***Pylorus-preserving Whipple’s Resection (PPPD)***

1. Helps to preserve more gastrointestinal function and improve postoperative nutritional status **(Fig. 14.1b)**.

2. Leads to transient gastric stasis.

3. Does not allow adequate resection of periampullary tumour and incomplete removal of regional lymph nodes.

4. Pylorus-preserving operation is avoided in patients with proximal duodenal involvement or the tumour close to pylorus.

**Comparison of Different Modalities of Management**

1. **Standard Whipple’s surgery vs pylorus preserving surgery**

n Surgical mortality, morbidity and blood loss are similar.

n Delayed gastric emptying, reduction in enterogastric reflux and improved postoperative nutritional status is more common in PPPD.

n Operative time is slightly more in standard surgery.

2. **Standard vs extended lymphadenectomy**

n Extended lymphadenectomy is not associated with improved survival.

n More postoperative morbidity in extended lymphadenectomy.

3. **Drainage vs no drainage of the pancreatic resection bed**

n Although reports of safe outcome after no drainage are available in literature, all surgeons generally adopt intraperitoneal drainage.

4. **Pancreatic enteric anastomosis**

n Pancreaticojejunostomy (PJ) and pancreatico-gastrostomy (PG) have similar results.

5. **Adjuvant chemoradiation vs no therapy**

n No survival advantage of adjuvant chemoradiation.

n However, the latest European multi-centre trials have

shown benefit with 5-fluorouracil or gemcitabine chemotherapy.

6. **Role of postoperative octreotide to prevent postoperative pancreatic fistula**

n Two large prospective randomized trials on either side of the Atlantic – European trial showed benefit, whereas American one showed no benefit.

**Total Pancreaticoduodenectomy**

This procedure is typically performed for the resection of tumours localized in the major area of the pancreas. Long-term survival of patients with a pancreatic head lesion undergoing this procedure is not significantly different than that of patients undergoing Whipple procedure.

**Left Pancreatectomy (with Splenectomy)**

This procedure is performed for the resection of tumours in the body and tail of the pancreas. Ductal carcinoma is seldom resectable in this location, except in the tail region, but this procedure may be performed for the other slow-growing malignant tumours like mucinous tumour, solid-pseudopapillary tumour (SPT) and neuroendocrine tumour (NET). Involvement of the splenic vein or artery is not a contraindication to such resection.

**Venous Involvement**

The presence of vascular encasement by the tumour is a contraindication for the curative surgery. Resection of the mesenteric veins should only be explored when tumour invasion is identified during curative resection.

*Predictors of successful outcome following curative resection*:

1. Tumour size

2. Tumour grade

3. Lack of jaundice at presentation

4. Negative nodal disease

5. Low tumour stage

6. R0 resection (resection with tumour-free resection margins)

***Palliative Surgery***

1. In younger patients with inoperable malignancy, a palliative choledochoduodenostomy/hepaticojejunostomy and gastrojejunostomy is the preferred approach.

2. Duodenal obstruction occurs in 15% of patients. Surgical bypass by gastrojejunostomy is appropriate in surgically fit patients. Endoscopic placement of metal stents is more appropriate in elderly patient with multiple comorbid illness.

3. Biliary bypass should be constructed with the bile duct in preference to the gallbladder.

***Stent Insertion***

1. Relief of jaundice can be achieved by placing endoscopic or percutaneous stents.

2. Results of endoscopic stenting are similar to palliative surgery.

3. Endoscopic stent placement is preferred to transhepatic stenting.

4. Plastic stents may necessitate frequent hospitalization for stent exchange or cholangitis.

5. Self-expanding metal stents are expensive, but provide more long-term patency. Currently, the choice between plastic and metal stents depends on the local availability, clinical factors and local expertise. In case of life expectancy of more than 6 months, metal biliary stent is preferred.

6. If a stent is placed prior to surgery, this should be of the plastic type and stenting should be done endoscopically. Self-expanding metal stents should not be inserted in patients who are likely to undergone curative resection.

**Role of Palliative Care**

1. Celiac plexus neurolysis using 5% phenol or 50% ethanol is effective for the treatment and prevention of pain. It can be performed at the time of palliative surgery or by percutaneous or endoscopic approach in non-surgical patients.

2. Chemoradiation should be considered for severe pain.

3. Good nutrition and pancreatic enzyme supplements should be used to maintain weight and increase the quality of life.

4. Pancreatic pain may be palliated by external beam radiotherapy, particularly when pain recurs after celiac plexus blockade.

**Adjuvant Chemoradiation for Pancreatic Cancer**

Therapeutic approaches for locally advanced pancreatic cancer include a combination of surgery, chemotherapy (CT) and radiotherapy (RT; **Fig. 14.2**). Previous studies have shown that compared to RT or CT alone, a combination of RT and CT (gemcitabine with or without 5-FU) showed an improved survival in patients with locally advanced unresectable pancreatic carcinoma.

Early recurrence in 10–20% of pancreatic carcinoma patients after curative resection, indicates the need for adjuvant interventions. The bed of the resected pancreas, the peritoneal cavity and the liver are the sites of recurrence following curative resection. Therefore, tumour grade and resection margin status are the predictors of survival after surgery.

The gastrointestinal tumour study group (GISTG) showed that compared to surgery alone, adjuvant CRT showed improved survival. In addition, the results of the study by the European Organization for Research and Treatment of Cancer (EORTC) were similar to those by the GISTG in that adjuvant CRT showed improved overall survival (17 mo vs 13 mo) compared to surgery alone. The impact of chemoradiation on the overall survival after pancreatico-duodenectomy was evaluated in 955 patients in a multi-centre retrospective study. Results of this study showed that the median overall survival in patients treated with chemoradiation and those treated with adjuvant chemotherapy alone was 40 months and 29 months, respectively (*p*<0.001).

**Neoadjuvant Chemoradiation for Pancreatic Cancer**

The high frequency of disease recurrences and low survival

rates are attributed to residual tumour cells left at the surgical margins and lymph node involvement. Postoperative adjuvant therapy could not be performed in 24–56% of the patients because of delayed recovery after major surgery, medical comorbidities and disease prog-ression. Thus, recent studies have focused on preoperative neoadjuvant strategies. Chemoradiation before surgery may provide theoretical advantages. Neoadjuvant therapy could be more effective in patients with normal vascular blood flow; it decreases the risk of peritoneal seeding with surgery, response to chemoradiation can be demonstrated in vivo, and unnecessary surgery could be avoided for rapidly progressing biological tumours. Recent data on neoadjuvant therapy has focused on borderline resectable tumours to achieve a higher probability of margin-negative resection. MD Anderson Cancer Center reported results from a trial with gemcitabine (400 mg/m2/wk) administered concurrently with neoadjuvant RT (30Gy/10 fractions). Out of 86 patients, 64 (74%) patients underwent resection, and had a 5-year overall survival rate of 36%. FOLFIRINOX with or without subsequent chemoradiation or gemcitabine plus albumin bound-paclitaxel with or without subsequent chemoradiation were the preferred regime. Gemcitabine plus capecitabine can also be used, but this combination is mainly used for adjuvant chemotherapy.

**Chemoradiation for Locally Advanced Pancreatic**

**Cancer**

Approximately 30–40% of patients with newly diagnosed pancreatic carcinoma are classified as locally advanced (non-

resectable, non-metastatic, involvement of major blood vessels and regional lymph nodes). Although a consensus has not been reached to date, concurrent chemoradiation has recently been suggested as the standard first-line treat-ment option for advanced pancreatic cancer. Despite its potent radiosensitizing effects similar to those observed with neoadjuvant strategies, the combination of gemcitabine with RT has been suggested as an optimal treatment for locally advanced pancreatic carcinoma with efficient loco-regional control and substantial systemic effects. The effects of various other chemotherapeutic agents such as oxaliplatin, capecitabine, irinotecan and taxol derivatives have been examined in different trials.

**RT with Targeted Therapeutic Agents**

Targeted therapy using epidermal growth factor receptor (EGFR) agents showed some promising results in advanced

pancreatic cancer. Overexpression of EGFR and gene amplification were detected in 60% of the patients with pancreatic carcinoma. Erlotinib is a reversible tyrosine kinase inhibitor of EGFR. Erlotinib in combination with chemoradiotherapy (capecitabine with or without gemcitabine or paclitaxel with IMRT) has been evaluated various trials for the treatment of pancreatic carcinoma.

Cetuximab is a monoclonal antibody that specifically binds to EGFR. Results of in-vivo and in-vitro studies have shown that cetuximab enhances radiosensitivity, promotes radia-tion-induced apoptosis, decreases cell proliferation, inhibits regeneration of radiation-induced defect site and tumour angiogenesis. Bevacizumab is a monoclonal antibody related to vascular endothelial growth factor (VEGF). Studies of bevacizumab with chemo-radiation showed some promising results in locally advanced pancreatic cancer.

**Further Reading**

1. Lowenfels AB. Epidemiologic and etiologic factors of pancreatic cancer. *Hematol Oncol Clin North Am* 2002;16:1–16.

2. Levy MJ, Wiersema MJ. Pancreatic neoplasms. *Gastrointest Endosc Cli N Am* 2005;15:117–42.

3. Cleary SP. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. *J Am Coll Surg* 2004;198:722–31.

4. Juan MS, David MN, Michael GS, Michael Farnell. Periampullary cancers: Are there differences? *Surgical Cli N America* 2001;81:543–555.

5. Castellanos E, Berlin J, Cardin DB. Current treatment options for pancreatic carcinoma. *Curr Oncol Rep* 2011;13:195–205.

6. Springett GM, Hoffe SE. Borderline resectable pancreatic cancer: on the edge of survival. *Cancer Control* 2008;15:295–307.

7. Patel M, Hoffe S, Malafa M, Hodul P, et al. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. *J Surg Oncol* 2011 1;104:155–61.

8. Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010;362:1605–17.

9. Saif MW. Palliative care of pancreatic cancer. Highlights from the “2011 ASCO Annual Meeting”. Chicago, IL, USA; June 3–7, 2011. *JOP* 2011 Jul 8; 12(4):355–7.

10. Gastrointestinal Tumor Study Group: Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer: Gastrointestinal tumor study group. *Cancer* 1987;59:2006–10.

11. Garofalo MC, Regine WF, Tan MT. On statistical re-analysis, the EORTC trial is a positive trial for adjuvant chemoradiation in pancreatic cancer. *Ann Surg* 2006; 244:332–3.

12. Wolfgang CL, Herman JM, Laheru DA, et al. Recent prog-ress in pancreatic cancer. *CA Cancer J Clin* 2013;63:318–48.

13. Becker AE, Hernandez YG, Krucht H, et al. Pancreatic ductal adenocarcinoma: risk factors, screening and early detection. *World J Gastroenterol* 2014;20:11182–98.

14. Morganti AG, Falconi M, van Stiphout RG, et al. Multi-institutional pooled analysis on adjuvant chemoradia-tion in pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2014;90:911–7.

**Chapter 15.**

**Ampullary Tumours**

**Introduction**

The ampulla of Vater is the junction of the main pancreatic and the distal bile ducts within the head of the pancreas. The common channel of the ampulla empties into the duodenum through the papilla. This area is surrounded by the parenchyma of the pancreatic head and the duodenum. This area, within 1–2 cm of the ampulla is known as the periampullary region. Adenocarcinoma of the ampulla of Vater or ampullary carcinoma is a relatively rare cancer comprising 0.5% of all gastrointestinal cancers and approximately 7% of all periampullary cancers. Periampullary cancer occurs in 5% of all gastrointestinal cancers and pancreatic cancer is the most common followed by distal bile duct cancer. Before surgical resection, the exact origin of a periampullary tumour is often not clear. However, the tissue of origin has important prognostic implications; tumours arising from the pancreas have a worse prognosis. Ampullary cancers are rare except in the case of patients with familial adeno-matous polyposis (FAP) syndrome. Tumours at the ampulla often present relatively early because of biliary and/or pancreatic obstruction, and therefore, have a better prognosis than pancreaticobiliary malignancy.

**Clinical History**

(See details in Jaundice, ch. 13)

n Cancer located in the distal portion of the bile duct and ampulla of Vater presents with jaundice followed by cancer-related constitutional symptoms. Fluctuating jaundice is seen in 20% of cases.

n Cancer located in the head of pancreas presents with abdominal pain, weight loss, anaemia, vomiting usually precede jaundice.

n Features of gastric outlet obstruction are observed in 10–15% of patients.

**Abdominal Examination**

n Abdominal examination may be normal in ampullary or distal cholangiocarcinoma.

n Palpable gallbladder is seen in around 35% of patients with periampullary cancer.

n Large pancreatic head mass can be palpable.

**Investigations**

1. ***Biochemistry***

n Leukocytosis (indicating cholangitis).

n Direct hyperbilirubinemia with raised alkaline phosphatase.

n Elevated prothrombin time, secondary to cholestasis, which is vitamin K responsive.

2. ***USG abdomen***

n Initial investigation of choice.

n Dilatation of bile duct till lower end, with dilatation of biliary radicals.

n Ampullary tumour can be visualized.

n Can identify liver metastasis.

3. ***Spiral CT scan***

n Sensitivity of resectability is around 90%.

n Helps in by detecting vascular and adjacent organ invasion as well as distant metastasis.

4. ***EUS***

n Endoscopic ultrasound provides transmural details, so it can assess the depth of the tumour invasion and peri-pancreatic lymph nodes.

n Best modality for local staging of periampullary tumour.

n Linear EUS-guided biopsy from lymph node and mass lesion is possible.

n EUS is helpful in staging ampullary malignancy according to the TNM staging system. Compared with CT and MRI, EUS is the most accurate tool for preoperative T staging.

n The prediction of local lymph node metastasis by EUS is only 60–80%.

n Intraductal ultrasounds (IDUS), by inserting the echo probe inside the ducts, has further increased diagnostic accuracy of endoscopic imaging modalities.

5. ***MRI***

n MRI accurately stages the disease.

n MRCP identifies dilatation of pancreatic duct and common bile duct.

n Vascular encasement can be identified by MR angiogram.

6. ***Forceps biopsy with duodenoscope***

n Observation of ampulla by duodenoscope is most important **(Fig. 15.1)***.*

n Endoscopic forceps biopsy, taken from the surface of an ampullary lesion, is the usual mode of diagnosis. It can be false-negative for malignancy. To reduce the sampling error, it is recommended that multiple biopsies should be obtained, taking care to avoid the pancreatic orifice.

n Malignant change within an ampullary adenoma may be seen in up to 30% of patients.

n Biopsy performed after a sphincterotomy may have a higher yield for malignancy. The best yield of biopsy is seen when the sample is obtained after 10 days of sphincterotomy (reduces diathermy artifact).

7. ***Tumour marker***

n Tumour marker like CA 19-9 has low sensitivity.

n When CA 19-9 is combined with abdominal CT scan and reference value is set at 100–120 U/mL, the positive predictive value increases to 99–100%.

8. ***Colonoscopy***

n Ampullary adenoma may be the presenting feature of attenuated FAP syndrome. Ampullary adenoma may increase risk of colorectal cancer even in the absence of FAP, thus colonoscopy is indicated in all patients of ampullary adenoma.

**Staging**

Periampullary cancers have different prognosis, thus the TNM classification describes ampullary cancers separately from pancreatic and duodenal cancers. Revised TNM classification includes:

T1 - Tumour limited to the ampulla of Vater

T2 - Tumour infiltrating the duodenal wall

T3 - Tumour infiltrating the pancreas <2 cm

T4 - Tumour infiltrating the pancreas >2 cm or

peripancreatic tissue

N0 - No regional lymph node metastasis

N1 - Regional lymph node metastasis

M1 - Distant metastasis

**Risk of Lymph Node Metastasis**

1. Risk of lymph node metastasis is correlated with the size of the tumour. Tumour <1 cm size has 9%, 1–1.5 cm has 25% and >1.5 cm size has 40% chances of lymph node metastasis.

2. The depth of invasion dose not correlate equally well with the presence of lymph node metastasis.

3. The degree of differentiation on histology correlates with lymph nodes metastasis: well-differentiated tumour has 23%, whereas poorly differentiated cancer has 50% of the patients.

**Management**

Local resection is sufficient for non-invasive tumours, whereas for invasive tumours, radical surgery is required. Around 80% of pancreatic tumours are unresectable at the time of the diagnosis. Whereas around 15% of ampullary tumours are unresectable at the time of diagnosis.

**Surgical Management**

1. **Pancreaticoduodenectomy (Kausch-Whipple’s resection)**

n En-block resection of pancreatic head, duodenum, distal common bile duct, proximal jejunum, cholecystectomy, partial gastrectomy and regional lymph nodes.

n Morbidity 30–60% with <5% mortality.

n Pancreaticojejunostomy leak rate is around 10%.

n Wider resection margin along the duodenum.

n Resection in the presence of portal vein encasement on preoperative imaging is rarely justified.

2. **Pylorus preserving Whipple’s resection (PPPD)**

n Helps to preserve more gastrointestinal function

n Leads to transient gastric stasis

n Literature does not support advantage of PPPD over classic Whipple’s procedure.

n Operative results are similar to Whipple’s resection

3. **Local excision of ampullary tumour**

n Local excision of tumour is reserved for patients with ampullary neuroendocrine tumour, benign adenoma and for highly selected patients with ampullary adenocarcinoma.

n Local excision of ampullary tumour is done only in old and frail patient with T1 stage.

n Local excision can be performed by endoscopic snare removal, endoscopic ablation and surgical ampullec-tomy. Risk of incomplete resection and recurrence is around 20%.

n If the tumours are polypoid and papillary in appearance, the results after local excision are better than in tumours with other characteristics.

n Around 5–10% of ampullary cancer with T1 harbour lymph node metastasis.

**Palliative Management**

There are three main symptoms that need palliation: obstructive jaundice, duodenal obstruction and pain.

1. Palliation of obstructive jaundice can be done by surgical means like cholecystojejunostomy, Roux-en-Y choledochojejunostomy **(Fig. 15.2)**.

2. Relief from jaundice can be achieved by placing endoscopic prosthesis (plastic as well as metallic stents). Metal stent is preferred over plastic stent if life expectancy of the patient is more than 6 months **(Fig. 15.3)**.

3. Results of endoscopic stenting are similar to palliative surgery.

4. Celiac ganglion block to relieve abdominal pain secondary to inoperable pancreatic head malignancy.

5. Gastric outlet obstruction (10–15%) – Palliative gastrojejunostomy or metal endosprothesis. Duodenal bypass should be performed in case of inoperable duodenal malignancy. Insertion of endoluminal self-expanding metal stent may palliate duodenal narrowing **(Fig. 15.3)**.

**Adjuvant Therapy**

1. Beneficial role of adjuvant therapy has not been established.

2. Role of external beam radiation (EBRT) and systemic chemotherapy (5-FU, mitomycin C) have not been proven to improve the survival.

**Role of preoperative biliary decompression in a jaundice patient in periampullary tumour**

1. Bile stasis leads to endothelial dysfunction leading to absorption of endotoxin, which increases portal pressure and reduces hepatic blood flow. Biliary decompression reduces portal pressure and improves hepatic blood flow.

2. Infectious complications are the most serious complications encountered following biliary decompression thus usually not recommended.

3. Usual indications of preoperative bililary decompressions are: presence of cholangitis, poor nutritional status leading to delay in definitive surgery, level of bilirubin more than 20 mg/dL.

4. Ideally definitive surgical intervention should be performed 4 weeks after biliary decompression.

**Pathology**

1. Ninety-five percent of neoplasms of the ampulla consist of adenomas or adenocarcinoma. Other differential diagnoses of ampullary lesions are neuroendocrine tumour (NET), gastrointestinal stromal tumour (GIST), lymphoma, lipoma and leiomyoma. Ampullary tumours are increasingly recognized as sporadic lesions.

2. Macroscopically, ulcerative tumours can be differentiated from intramural protruding and exposed protruding tumours. Microscopically, most ampullary tumours are adenocarcinoma as they arise from the epithelial cells.

3. Ampullary cancer is subdivided into intestinal and pancreaticobiliary type based on the differences in immunohistochemical findings.

4. Several immunohistochemical markers such as cyto-keratins (CK), apomucin (MUC) and caudal homeobox gene transcription factor (CDX) are used to differentiate the tumours. The intestinal type of ampullary cancer expresses CK-20 and CDX2, whereas pancrea-ticobiliary type expresses MUC1 and CK7. Intestinal type typically contains microsatellite instability as a biomarker similar to that in colon cancer.

**Cancer Syndromes Associated With Ampullary Carcinoma**

1. Familial adenomatous polyposis

2. HNPCC

3. Neurofibromatosis type 1

4. Muir-Torre syndrome

**Factors Influencing Survival in Patients with ampullary cancer**

1. **Early vs late jaundice**

n Most ampullary, duodenal and distal bile duct obstruction present with the jaundice, so they present much earlier.

2. **Intraluminal growth**

n Intraluminal growth is present in 40% of patients with ampullary cancer, but only in 2% patients with pancreatic cancer.

n Extraductal involvement seen in 60% of ampullary cancer and 98% of pancreatic cancer.

3. **Lymphatic spread**

nIn patients with pancreatic cancer, 55–80% and in other periampullary cancers, 30–50% would have lymph node metastasis.

n Patients without lymph node metastasis have median survival of 60–70 months, whereas those with lymph node metastasis survive for 20–30 months.

4. **Perineural spread**: Most patients with pancreatic carcinoma have perineural spread, whereas only 5–15% of other periampullary carcinoma has perineural involvement.

5. **Immunohistochemical differentiation**: Ampullary cancer with intestinal differentiation appears to have comparable survival to duodenal cancer (60%), whereas pancreaticobiliary differentiation has survival comparable to pancreatic cancer (20%).

**Survival in Periampullary Tumour after Pancreaticoduodenectomy**

n Overall 5-year survival rates are best for duodenal and ampullary cancers, worst for pancreatic cancer and intermediate for distal cholangiocarcinoma **(Table 15.1)**.

n Although the fundamental surgical approach is similar (pancreaticoduodenectomy) for patients with periam-pullary cancers. Pancreaticoduodenectomy for pancreatic cancer is more frequently combined with neo-adjuvant or adjuvant chemoirradiation or more extensive regional lymphadenectomy than for non-pancreatic periampullary cancers.

**Type of peri- Frequency 5-yr**

**ampullary cancer (%) survival (%)**

1. Pancreatic head 60 10–26

cancer

2. Ampullary 20–25 33–48

malignancy

3. Distal cholangio- 10–15 13–40

carcinoma

4. Second part of 5–10 30–60

duodenum

**Familial Adenomatous Polyposis (FAP) and Ampullary Neoplasm**

n Around one-third of patients with FAP harbour ampullary adenoma. Periampullary cancer is often preceded by ampullary or duodenal adenomas. Thus, examination and biopsy of the periampullary region is very important in patients with FAP. To prevent duodenal malignancy in patients with FAP syndrome, various screening strategies have been developed. Spigelman and co-workers developed a staging system for ampullary adenomas in FAP patients to stratify their risk of developing cancer **(Table 15.2)**.

n The median interval between colectomy for FAP and development of upper gastrointestinal cancer is 22 yrs.

n The frequency of surveillance endoscopy is determined by severity of the duodenal polyposis. Patients with stage 4 duodenal polyposis can undergo resection. Duodenoscopy should be performed after the patient has been diagnosed with colorectal polyps. Stage 0/1 polyposis (repeat endoscopy after 5 yrs), stage 2 (after 3 yrs) and stage 3 (after 1–2 yrs).

**Points 1 2 3**

Polyp number 1–4 5–20 >20

Polyp size (mm) 1–4 5–10 >10

Histology Tubular Tubulo Villous

villous

Dysplasia Mild Moderate Severe

Stage I = 1–4 points, Stage II = 5–6 points, Stage III = 7–8 points, Stage IV = 9–12 points

**Treatment of Ampullary Adenomas**

n The aim of treatment of adenomas differs between FAP patients and those with sporadic lesions. In those with a sporadic lesion, the aim is to complete excision of all adenomatous tissues followed by close endoscopic surveillance depending on the histology. The aim with FAP

patients is to “control” the disease through the removal of all significant-sized lesions.

n Adenomas in the region of the major duodenal papilla can be both diagnosed and treated via endoscopic retrograde cholangiopancreatography (ERCP).

n Snare ampullectomy combined with biliary and/or pancreatic sphincterotomy allows complete removal of the adenoma in approximately 80–90% of patients without intraductal extension. Recurrence is more common in patients with familial adenomatous polyposis syndrome.

n Endoscopic ampullectomy is associated with up to a 20% risk of post-ERCP pancreatitis, which appears to be reduced by placement of a pancreatic duct stent at the time of resection.

n Close endoscopic follow-up is necessary to ensure complete resection and detect recurrence.

n Successful resection of non-ampullary duodenal adenomas is feasible using endoscopic mucosal resection (EMR) techniques developed for the removal of large colonic polyps.

**Further Reading**

1. Juan MS, David MN, Michael GS, et al. Periampullary cancers: are there differences? *Surgical Cli N America* 2001; 81:543–555.

2. Winter JM, Cameron JL, Olino K, et al. Clinicopathologic analysis of ampullary neoplasms in 450 patients: implications for surgical strategy and long-term prognosis. *J Gastrointest Surg* 2010;14:379–87.

3. Yeo CJ, Sohan TA, Cameron JL, et al. Periampullary adnocarcinoma. Analysis of 5-year survivors. *Ann Surg* 1998;227:821–31.

4. Seiler CA, Wanger M, Sadowski C, et al. Randomized prospective trial of pylorus preserving vs classic duodeno-pancreatectomy (Whipple procedure): initial clinical results. *J Gastrointest Surg* 2000;4:443–52.

5. Westgaard A, Tafjord S, Farstad IN, et al. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. *BMC Cancer* 2008;8:170.

6. Heinrich S, Clavien PA. Ampullary cancer. *Curr Opin Gastroenterol* 2010;26(3):280–5.

7. Hamaloglu E, Yildiz BD, Karakoc D. Controversies in periampullary tumors. *Hepatogastroenterology* 2009;56:54–8.

8. Bettschart V, Rahman MQ, Engleken FJ, et al. Presentation, treatment and outcome in patients with ampullary tumors. *Br J Surg* 2004;91:1600–7.

9. Kimura W, Futakawa N, Zhao B. Neoplastic diseases of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004; 11:223–31.

10. Fischer HP, Zhou H. Pathogenesis of carcinoma of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004;11:301–9.

11. Kamarajah SK. Pancreaticoduodenectomy for periampullary tumours: a review article based on surveillance, end results and epidemiology (SEER) database. *Clin Transl Oncol* 2018; 20:1153–60.

**Chapter 16.**

**Cholangiocarcinoma**

**Introduction**

Cholangiocarcinoma (CCA) is a malignancy arising from the epithelial cells of the biliary tract (cholangiocytes). Cholangiocarcinomas are classified as intrahepatic (iCCA), perihilar (pCCA, Klatskin tumour) or distal (dCCA). Perihilar is the most common type and accounting for 60–80% of CCAs, whereas dCCA account for 10–30% of CCAs. Intrahepatic is the least common and is seen only a minority of cholangiocarcinomas. The prognosis of cholangio-carcinoma is dismal. Surgery is the only potentially curative treatment, but the majority of patients present with advanced stage disease and recurrence after resection is common.

**Clinical History**

The clinical features of cholangiocarcinoma depend on the location of the tumour. Tumour arising from extrahepatic biliary ducts presents with painless cholestatic jaundice, whereas patients with intrahepatic tumours rarely present with jaundice, they usually present with abdominal pain.

1. Cholestatic jaundice (Chapter 13)

2. Fever with chills indicates cholangitis – Cholangitis is unusual in malignant biliary obstruction without intervention, whereas cholangitis is very common in stone disease as obstruction is incomplete obstruction

3. Anorexia and weight loss

4. Abdominal pain – Predominant feature of intrahepatic cholangiocarcinoma

**Past History**

1. Past history suggestive of recurrent cholangitis indicates hepatolithiasis or choledochal cyst.

2. History suggestive of ulcerative colitis indicates primary sclerosing cholangitis.

**Abdominal Examination**

1. Hepatomegaly – more commonly seen in intrahepatic cholangiocarcinoma

2. Enlarged gallbladder, caused by obstruction at or distal to the origin of the cystic duct (Courvoisier law)

**Differential Diagnosis**

1. Pancreatic head carcinoma

2. Ampulla of Vater carcinoma

3. Duodenal carcinoma

4. Gallbladder carcinoma

5. Benign biliary stricture (usually postoperative)

6. Choledocholithiasis

**Investigations**

1. ***Biochemistry***

n Elevated ESR

n Elevated WBC indicates cholangitis

n Direct hyperbilirubinemia with raised SAP with GGT

2. ***USG abdomen***

n Non-invasive test

n An obstructing lesion of biliary tract is suggested when intra- or extrahepatic bile duct dilatation (>6 mm is normal in adult) in the absence of stones.

n Dilatation of intrahepatic biliary ducts with normal diameter extrahepatic ducts indicates hilar (proximal) lesions, dilation of both extra- and intrahepatic bile duct indicates more distal lesion.

n Poor sensitivity to detect vascular invasion.

3. ***Spiral CT abdomen***

n Computed tomography (CT) and magnetic resonance imaging (MRI) can accurately distinguish intrahepatic cholangiocarcinoma from HCC in tumours >2 cm.

n Can detect the level of biliary obstruction, presence of liver metastasis, liver atrophy, and lymph node involvement.

n Sensitivity to detect portal vein invasion is around 86%.

4. ***MRI***

n MR imaging provides all the information that is necessary to stage patients.

n MRCP correctly identifies the nature and the level of obstruction in 95% of patients.

n Vascular encasement can be identified by MR angiogram.

n MRCP is highly accurate in evaluation of the extent of hilar strictures and forms a road map of biliary anatomy before any interventions.

5. ***PET***

n Can detect less than 1 cm size cholangiocarcinoma in patients with primary sclerosing cholangitis (PSC), does not provide advantage over CT/MRI.

6. ***ERCP/PTC***

n No role of diagnostic ERCP or PTC

n PTC defines the proximal end of the extent of the tumor, particularly of intrahepatic cholangiocarcinoma

n Double duct sign on ERCP (dilatation of CBD and PD) is seen in pancreatic cancer, not in distal cholangiocarcinoma

7. ***Cytology and biopsy***

n Bile cytology is positive in around 30%; brush cytology is positive in around 40%, whereas percutaneous FNA is positive in 67% of patients.

n Preoperative tissue diagnosis is often unsuccessful, and surgical therapy may be performed without a histological confirmation.

n Fluorescence in-situ hybridization (FISH) has improved the diagnostic performance of conventional cytology for the detection of pCCA and dCCA; several emerging diagnostic modalities, including liquid biopsy techniques, might further improve the diagnosis of CCA.

8. ***Tumour markers***

n Both CEA and CA 19-9 can be elevated in cholangio-carcinoma.

n CEA as well as CA 19-9 levels are neither sensitive nor specific for cholangiocarcinoma.

9. ***Cholangioscopy***

n Single-operator peroral cholangioscopy (SOP) allows direct visualization of biliary defects, and guided brushings and biopsies. The accuracy of SOP with tissue sampling in patients in whom ERCP-guided tissue sampling was inconclusive is 58–95%.

**Staging of Cholangiocarcinoma**

Tis - Carcinoma in situ

T1 - Tumour invades the subepithelial connective tissue

T2 - Tumour invades perifibromuscular connective

tissue

T3 - Tumour invades adjacent organs

N1 - Metastasis to hepatoduodenal ligament lymph

nodes

N2 - Metastasis to peripancreatic, periduodenal, periportal, celiac lymph nodes

M0 - No distant metastasis

M1 - Distant metastasis

**Stage TNM grade**

0 Tis N0 M0

I T1 N0 M0

II T2 N0 M0

III T 1-2 N 1-2 M0

IVA T3 Any N M0

IVB Any T Any N M1

**Bismuth-Corlette classification Scheme of Perihilar Cholangiocarcinoma (Fig. 16.1) (Fig. 16.2a & b)**

Type I - Tumour involves common hepatic duct

Type II - Tumour involves the bifurcation of common

hepatic duct

Type IIIa - Tumour involves the right hepatic duct

Type IIIb - Tumour involves the left hepatic duct

Type IV - Tumour involves both the right and left

hepatic ducts

**Histology**

1. Adenocarcinoma 95%

2. Others:

n Small cell carcinoma

n Papillary adenocarcinoma

n Signet ring cell carcinoma

n Clear cell carcinoma

**Types of tumour**

1. Mass forming – Usually intrahepatic cholangiocarcinoma

2. Periductal-infiltrating – Usually perihilar cholangiocarci-noma

3. Intraductal – Papillary

**Radiological Criteria that Suggest Unresectibility**

1. Bilateral hepatic duct involvement up to secondary radicals

2. Bilateral hepatic artery involvement

3. Encasement of the portal vein proximal to its bifurcation

4. Distant metastasis

5. Atrophy of one hepatic lobe with contralateral portal vein encasement

**Management**

n Making a definitive tissue diagnosis of cholangio-carcionoma is difficult.

n In clinically suspected cholangiocarcinoma, assessment of operability and resection should not be delayed due to the absence of a tissue diagnosis.

n Around 45–50% of perihilar and 10% of distal cholangio-carcinoma are inoperable.

n 10–20% have peritoneal involvement.

n Surgery is the only curative treatment with chol-angiocarcinoma.

n 5-year survival rate is better in distal lesion than perihilar lesion **(Table 16.1)**.

n Aim of the surgery is tumour-free margin of more than 5 mm.

n Segment 1 of the liver may preferentially harbour metastasis.

1. *Distal cholangiocarcinoma*: Whipple’s resection (see Chapter 14)

2. *Intrahepatic cholangiocarcinoma*: Hepatic resection

3. *Perihilar cholangiocarcinoma*:

n pCCA is the most difficult to manage form of CCA. Radical resection of the tumour is the most important treatment modality, but the assessment of the need of surgical resection in patients with pCCA is complex. Risk factors for recurrence include size of the lesion, perineural invasion, presence or absence of lymph node metastases, vascular encasement and preoperative serum CA 19–9 levels.

n Bismuth I and II: En-block resection of the extrahepatic bile ducts and gall bladder; regional lymph node removal and Roux-en-Y hepaticojejunostomy.

n Bismuth III: Above + right or left hepatectomy (depends on the involvement).

n Bismuth IV: Above + extended right or left hepatectomy

n Lymph node metastases and R0 status are the two major prognostic factors influencing outcomes after resection. Approximately 45% of patients undergoing resection are found to be lymph node positive (N+). Five-year survival of N+ vs N0 disease is 0–9% vs 36–43% in iCCA, 0–29% vs 32–67% in pCCA and 16–21% vs 42–61% in dCCA. On the basis of the results of a recent meta-analysis, the National Comprehensive Cancer Network (NCCN) recommends adjuvant chemotherapy with fluoro-pyrimidine- or gemcitabine-based regimens for patients with R1-resection and/or N1 disease with marginal survival benefit.

n Photodynamic therapy plays a role in small perihilar cholangiocarcinoma or PSC patients with local high- grade dysplasia whose combined status, including age precludes more aggressive therapy.

n Emerging evidence indicates that high-dose, conformal external-beam radiation therapy is a potential treatment option for patients with localized unresectable iCCA.

n Chemotherapy has no survival advantage, but the results of two recent trials showed a survival benefit of around 3 months with combination therapy using gemcitabine plus cisplatin vs gemcitabine alone.

n Preclinical and early clinical trials support targeting EGFR in combination with other molecular targets (i.e., HER2 and VEGFR) and/or chemotherapeutics. Mutations in KRAS are associated with resistance to receptor tyrosine kinase inhibition and poor survival.

**Liver Transplantation for Perihilar Cholangiocarcinoma**

Orthotopic liver transplantation (OLT) is not recoom-mended as monotherapy for CCA because of high recurrence rates and long-term survival of less than 20%. Recently, neoadjuvant chemoradiation followed by OLT has been established as an effective treatment for pCCA. Recurrence rates following this transplant protocol are 20% and the rate of recurrence-free 5-year survival is 68%. Patient selection criteria for this procedure are stringent, and 25–31% of patients develop progression of their disease while awaiting OLT, which results in exclusion from the protocol. OLT is currently not recommended for iCCA and dCCA.

**Palliative Biliary Drainage**

1. As majority of patients with cholangiocarcinoma are inoperable and have short life expectancy, palliative biliary decompression improves their quality of life.

2. Palliative biliary decompression either surgical bypass (hepaticojejunostomy or intrahepatic segment III/IV bypass) or non-surgical biliary decompression (either percutaneous or endoscopic).

3. As the survival after palliative drainage is similar after surgical and non-surgical methods, the indications for operative drainage have narrowed.

4. Placement of a metallic stent is more cost effective than placement of a plastic stent if the survival of a patient is expected to be more than 6 months.

5. Around 25% of liver drainage is sufficient to relieve pruritus. Single SEMS (metal stent) for lower cholangio-carcinoma **(Figs 16.2a,b)**, whereas double stenting (one metal and one plastic or metal Y stent) for perihilar lesions **(Fig. 16.3)**.

6. In type IV hilar cholangiocarcinoma, transhepatic biliary drainage is more feasible as both the hepatic ducts are isolated. Transhepatic metal stent is advocated when the life expectancy is more than 6 months.

7. Preoperative biliary drainage is not indicated except in the case of cholangitis or to improve nutrition before drainage in patients with severe malnutrition.

8. For proximal (Klatskin) lesions, success rates are lower, biliary drainage may be incomplete, and the incidence of

early cholangitis is higher. Such tumours may require the placement of stents into both right and left hepatic ducts to achieve adequate drainage. Minimal contrast injection and the use of preprocedural imaging studies to direct unilateral drainage of patients with hilar tumours may decrease the rate of cholangitis.

**Risk Factors of Cholangiocarcinoma**

1. Primary sclerosing cholangitis

n Most important risk factor

n PSC patients have a 5–20% lifetime risk to develop cholangiocarcinoma. However, only 10% of cholan-giocarcinoma are attributed to PSC. Usually, cholan-giocarcinoma is diagnosed after a median of 4 yrs following the PSC diagnosis.

n Occult cholangiocarcinoma in patients with PSC has been reported as 30–40%.

2. Choledochal cyst (type I and IV)

n Uncommon in patients diagnosed and treated before the age of 20 yrs.

n Untreated patients at third decade have a 15–20% incidence of malignant degeneration

3. Hepatolithiasis

4. Bile duct adenoma

5. Biliary papillomatosis

6. Caroli’s disease

7. Thorotrast

8. Age >65 yrs

9. Smoking – risk increases associated with PSC

10. Liver flukes like *Clonorchis sinensis* and *O. viverrini*

**Further Reading**

1. SA Khan, BR Davidson, R Goldin, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document *Gut* 2002;51:1–9.

2. Coelho-Prabhu N, Baron TH. Endoscopic retrograde cholangiopancreatography in the diagnosis and management of cholangiocarcinoma. *Clin Liver Dis* 2010;14:333–48.

3. Gores GJ. Cholangiocarcinoma: current concepts and insights. *Hepatology* 2003;37:961–9.

4. Jarnagin WR, Shoup M. Surgical management of cholangiocarcinoma. *Semin Liver Dis* 2004;24:189–99.

5. Baron TH. Photodynamic therapy: standard of care for palliation of cholangiocarcinoma? *Clin Gastroenterol Hepatol* 2008;6:266–7.

6. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010 8;362:1273–81.

7. Rea DJ, Rosen CB, Nagorney DM, et al. Transplantation for cholangiocarcinoma: when and for whom? *Surg Oncol Clin N Am* 2009;18:325–37.

8. Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2013;11:13–21.

9. Chaiteerakij R, Harmsen WS, Marrero CR, et al. A new clinically based staging system for perihilar cholangio-carcinoma. *Am J Gastroenterol* 2014;109:1881–90.

10. Nagino M, Ebata T, Yokoyama Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 2013;258:129–140.

11. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013;145: 1215–1229.

**Chapter 17.**

**Gallbladder Cancer**

**Introduction**

Gallbladder (GB) cancer is an infrequent biliary tract malignancy worldwide; the incidence of GB cancer is low in developed countries, but it is common in some specific geographical regions of developing countries including North India. GB carcinoma occurs primarily in the elderly and is 3–4 times as common in women as in men. Delayed diagnosis is the major factor, which leads to an unfavour-able outcome in patients with GB carcinoma. Lack of the serosal layer leads to rapid local invasion to adjacent liver tissue and this makes operation difficult in patients.

**Clinical History**

1. Common in the 6th and 7th decade. But it can occur in even the 5th decade.

2. M: F–1:3

3. Right hypochondrium pain (80%) – Dull, continuous (unlike biliary colic)

4. Anorexia and weight loss (75%)

5. Lump in right hypochondrium (65%)

6. Progressive obstructive jaundice (45%) – Due to infiltration of common hepatic and bile ducts or nodes in the hepatoduodenal ligaments

7. Cholangitis, pruritus (20%)

8. Postprandial fullness, nausea, vomiting (gastroduodenal obstruction, 20%)

**Past History**

1. Past history of recurrent biliary colics due to gall stones

**General Examination**

1. Icterus

2. Left supraclavicular lymph node

**Abdominal Examination**

1. Hepatomegaly

2. Umbilical nodule

3. Palpable GB mass in the right hypochondrium

4. Ascites

5. Pelvic deposits by digital rectal or vaginal examination

**Differential Diagnosis**

1. Xanthogranulomatous cholecystitis/chronic cholecystitis

2. Mirizzi syndrome

3. Cholangiocarcinoma

**Investigations**

1. ***USG abdomen***

n Thickened wall (>3 mm), either diffuse or localized

n Discontinuous mucosa

n Echogenic mucosa

n Submucosal echolucency

n Intraluminal mass, polypoidal mass replacing GB without posterior acoustic shadow

n Poor to define lymph nodes and duodenal infiltration

n USG may miss early lesions. But it is good to detect liver infiltration, metastasis and ascites.

2. ***CT scan abdomen***

n Seen as a thick wall, intraluminal mass and mass replacing GB.

n Extent of tumour growth.

n Infiltration into adjacent structures including liver, duodenum, bile duct and vascular invasion like portal vein and hepatic artery.

n Detection of lymph nodes and distant metastasis.

3. ***EUS***

n EUS is useful for the evaluation of early lesion and lymph node metastasis.

n EUS is useful to evaluate the depth of tumour invasion and to differentiate between neoplastic versus non-neoplastic polyp.

4. ***MRI***

n MRCP can be used to delineate biliary anatomy in patients with jaundice due to obstructive biliary system.

n MR angiogram can be used to assess vascular (hepatic artery and portal vein) invasion by the tumour. Thus, MRI permits noninvasive assessment of the hepatic parenchyma, biliary tree, vasculature and lymph nodes.

5. ***PET***

n PET/CT has limited sensitivity but high specificity for the detection of regional lymph nodes and

metastasis. The routine use of preoperative CT/PET is not recommended but it should be performed if a major resection is planned.

6. ***Selective angiography***

n Accurate way to diagnose invasion of blood vessels (hepatic artery and portal vein)

n Replaced by CT arteriography/MR angiogram

7. ***Cholangiography***

n Either PTC or ERCP. Long stricture involving the common hepatic duct is the typical finding in cholangiogram.

n Invasive cholangiography has limited role for diagnosis alone (MRCP is preferred); it should be performed only as a part of a therapeutic intervention for biliary drainage.

8. ***Cytology***

n Tissue diagnosis is not essential if the disease is resectable USG/CT-guided FNAC from GB mass sensitivity is 88%.

n Brush cytology is performed via ERCP or PTC, but has low yield.

n Ascitic fluid cytology.

n FNAC from supra-clavicular LN, umbilical nodule.

9. ***Tumour markers***

n Negligible role.

n CEA >4 ng/m; specificity 90% and sensitivity 50%.

n CA19-9 >20 unit/mL; specificity and sensitivity both 80%.

10.***Other investigations***

n Upper endoscopy to look for duodenal infiltration.

n Staging laparoscopy is strongly recommended to detect surface peritoneal and liver deposits.

**Staging of Gallbladder Cancer AJCC UICC 8th edition, 2017**

1. **Nevin staging system** – not used now

n Stage 1: Mucosal invasion

n Stage 2: Extension into muscularis

n Stage 3: Extension through muscularis

n Stage 4: Involvement of regional nodes

n Stage 5: Adjacent organ

2. **TNM staging** – most commonly used

n T is: Tumour in situ

n T1a: Invade lamina propria (mucosa)

n T1b: Involvement of muscular layer

n T2: Involvement of perimuscular connective tissue

- T2a on peritoneal side of GB

- T2b on hepatic side of GB

n T3: Serosa; liver invasion or one organ invasion

n T4: Hepatic artery or portal vein involvement, two organs involvement

n N0: No lymph node involvement

n N1: 1–3 lymph nodes

n N2: More than 3 lymph nodes

n M0: No distant metastasis

n M1: Distant metastasis

**Stage TNM** **stage** **5-yr survival**

Stage I T1 N0 M0 96%

Stage IIA T2a N0 M0 56%

Stage IIB T2b N0 M0

Stage IIIA T3 N0 M0 16%

Stage IIIB T1–3 N1 M0

Stage IVA T4 N0-1 M0 6%

Stage IVB Any T N2 or M1 < 1%

3. **Japanese Society of Biliary Surgery Staging System –** used by some Japanese surgeons

Takes into account depth of GB wall invasion, liver, hepato-dudoenal ligament, hepatic artery and portal vein involvement and lymph nodes.

**Criteria for Unresectibility**

n Distant spread like supraclavicular lymph nodes, umbilical nodule and pelvic deposits

n Hepatic/peritoneal deposits

n Malignant ascites

n Extensive involvement of hepatoduodenal ligament

n Encasement of major vessels (portal vein or hepatic artery)

n Duodenal infiltration (unless pancreaticoduodenectomy planned)

n Para-aortic or aorto-caval lymph nodes

n Poor performance status

**Surgical Management**

Surgical management depends on the stage of the tumour. Survival is excellent in patient with malignancy limited to gallbladder. Survival reduces markedly in hepatic and bile duct invasion and in the presence of lymph nodes **(Table 17.1)**. Laparoscopic cholecystectomy should be avoided in patients with suspected gallbladder cancer because incomp-lete excision of the tumour and spillage of bile results in inevitable recurrence.

1. **Simple cholecystectomy**

n For T1a disease (mucosal disease) only

2. **Extended cholecystectomy**

n Removal of 2 cm wedge of gallbladder bed in segments IVB and V of liver with removal of lymph nodes from hepatoduodenal ligament

n With or without CBD resection

3. **Extended cholecystectomy + Liver resection**

n Removal of segment IVB and V, or extended right hepatectomy

4. **Extended cholecystectomy + extensive retroperitoneal lymph node resection** (not recommended because of poor outcome)

5. **Extended cholecystectomy + pancreaticoduo-denectomy** (may be performed in highly select patients)

n For associated duodenal-pancreatic infiltration

**Stage Surgery 5-yrs survival**

Stage I Simple or extended 90–100%

cholecystectomy

Stage II Extended cholecys- 90–100%

tectomy

Stage III Above + liver resection 40–80%

Stage IV Above + multi-organ 10–20%

a) Resection

b) Palliative therapy < 5%

***Different Situations in Management of Gallbladder Malignancy***

1. Carcinoma discovered during laparoscopic cholecystectomy

n Assess extent of the disease and decide whether curative surgery is possible

n Confirmation of the diagnosis

n If tumour is resectable, convert to open operation and perform extended cholecystectomy.

2. Incidental detection of gallbladder malignancy on pathological examination of specimen after laparoscopic cholecystectomy.

n If margins are negative and tumour stage T1a (mucosal disease), simple cholecystectomy is the cure.

n If tumour is T1b or beyond – Re-exploration for completion extended cholecystectomy. Port sites (all ports or port of GB extraction) must be excised full thickness (skin to peritoneum).

3. Tumour at neck of gallbladder

n Extended cholecystectomy with CBD resection and hepaticojejunostomy

4. Advanced tumour (stage III/IV)

n Extended cholecystectomy + Multi-organ resection in the form of hepatic resection and/or pancreatico-duodenectomy.

5. Involvement of colon is not a contraindication for surgery.

**Neoadjuvant and adjuvant Therapy**

1. Neoadjuvant chemotherapy should be considered for locally advanced disease (big mass invading liver and/or nodal mass, including positive cystic duct nodes) to assess aggressiveness of the tumour and to avoid futile surgery. Gemcitabine-based or fluoropyrimidine-based chemotherapy used the most as chemotherapy.

2. Adjuvant chemotherapy for T2+, node-positive, margin-positive disease.

3. Imaged-guided radiotherapy using EBRT, IMRT and SBRT used as adjuvant therapy as well as palliative therapy.

4. Intraluminal brachytherapy may help to increase stent patency in patients with biliary obstruction.

**Follow-up following surgical resection**

1. R0 Resection (resected negative margin, negative nodes) – observe – considered imaging every 6 mo for 2 yrs then annually for 5 yrs.

2. R1 Resection (resected positive margin, positive nodes) – adjuvant chemotherapy.

3. R2 Resection (resected gross residual disease) – adjuvant chemotherapy + RT.

4. The presence of port site implants suggests disseminated disease, thus port site resection has not shown to be beneficial.

**Palliative Management**

**Non-surgical**

1. For poor-risk patients or patients with metastatic disease. The presence of jaundice is a contraindication for curative resection. Biliary decompression is required before palliative chemotherapy.

2. Endoscopic or percutaneous biliary decompression by stenting, preferably metal stent if the life expectancy of the patients is more than 6 months.

3. Endoscopic gastro-duodenal metal stenting in case of duodenal obstruction secondary to tumour infiltration.

4. Celiac plexus block for pain relief.

**Surgical**

Good risk patient with non-metastatic disease can be treated with palliative intrahepatic segment III cholangio-jejunostomy with or without gastro-jejunostomy.

**Pathology**

1. Adenocarcinoma 90%

n Well/moderately differentiated 75%

n Fundus (60%); Body (30%); Neck (10%)

2. Intestinal type of adenocarcinoma

3. Mucinous carcinoma

4. Squmous cell carcinoma (16%)

5. Clear cell carcinoma

**Risk Factors for Gallbladder Cancer**

1. **Gallstone**

n More than 70% of patients with gallbladder cancer have coexisting gallstones and chronic cholecystitis.

n 7 times higher risk of developing cancer.

n More often associated with single large stone (size >3 cm diameter) or GB packed with stones.

n Chronic inflammation leads to epithelial dysplasia – carcinoma.

n Only 1% patients with cholelithiasis have gallbladder cancer (incidental detection).

2. **Choledochal cysts**

n Risk increases with age.

n Reflux of pancreatic juice into the gallbladder is suggested as contributing factor for cancer.

3. **Porcelain gallbladder**

n Calcification of gallbladder wall.

n Type I (diffuse calcification), type II/III (selective calcification).

n Type II or type III – more chances of gall bladder cancer than type I.

n Prophylactic cholecystectomy indicated.

4. **GB polyp**

n Single, sessile polyp >1 cm in diameter increases the risk for cancer.

5. **Anomalous pancreatico-biliary duct junction (APBDJ)** without choledochal cyst.

6. **Typhoid carrier**

n Bile stasis, bacterial contamination and chronic irritation lead to carcinogenesis.

**Further Reading**

1. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. *Lancet Oncol* 2003;4:167–76.

2. Agrawal S, Kapoor VK. Thick walled gall bladder. *National Medical Journal of India* 2006;19:37–8.

3. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014;6:99–109.

4. Shrikhande SV, Barreto SG, Singh S, Udwadia TE, Agarwal AK. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause! *Eur J Surg Oncol* 2010;36:514–9.

5. Shukla HS, Guest Editor. Gall bladder cancer. *J Surg Oncol* 2006;93:597–708.

6. Bihar A, Kapoor VK. Gall bladder cancer with jaundice: the unscaled frontier. In: Peush Sahni, Sujoy Pal, eds. GI Surgery Annual. New Delhi: Springer; 2018:119–130.

7. Behari A, Kapoor VK. Incidental gall bladder cancer. In: Cameron John L, ed. *Advances in* *Surgery* 2013;47:227–49.

8. Shukla HS, Sirohi B, Behari A, et al. Indian Council of Medical Research consensus document for the management of gall bladder cancer. *Indian J Med Paediatr Oncol* 2015;36:79–84.

9. Qadan M, Kingham TP. Technical aspects of gallbladder cancer surgery. *Surg Clin North* *Am* 2016;96:229–45.

10. Kanthan R, Senger JL, Ahmed S, et al. Gallbladder cancer in the 21st century. *J Oncol* 2015;96:72–4.

**Chapter 18.**

**Achalasia Cardia**

**Introduction**

Achalasia is a Greek term, which means “does not relax.” Primary or idiopathic achalasia is characterized by oesophageal body aperistalsis and incomplete or absence of relaxation of the lower esophageal sphincter (LES) in response to swallowing, which leads to impaired propulsion of food bolus. The incidence of achalasia is 1.6 per 100,000 per year. Achalasia cardia typically occurs between 25 and 60 yrs of age, and men and women are equally affected. The most important feature of this condition is the absence or near absence of LES relaxation. Persistent contraction of the LES causes functional obstruction that remains till hydrostatic pressure generated by retained material exceeds the pressure generated by LES. Management of achalasia is palliative and mainly involves improving the oesophageal outflow to provide symptomatic relief to patients.

**Clinical Presentation**

1. Dysphagia to solids and liquids are most common presentation

n Dysphagia for liquids happens in oesophageal dysmotility syndrome like progressive systemic sclerosis but it is also strongly suggestive of achalasia and should always be considered first.

n Postural changes may improve dysphagia by increasing intraesophageal pressure like lifting the neck and throwing the shoulders back frequently.

2. Regurgitation of undigested food and fluid

3. Weight loss

4. Nocturnal coughing

5. Recurrent pulmonary aspiration

6. Retrosternal chest pain

n Types of retrosternal pain – Pain associated with dysphagia is primarily due to pressure generated by food material; Pain unrelated to meals may represent neuropathic origin.

n Often affects younger patients and usually nocturnal.

**Physical Examination**

n Symptoms are disproportionate to physical findings

n Mild pallor is observed in some patients

**Investigations**

1. ***Routine biochemistry***

n Usually normal except mild anaemia

2. ***Chest X-ray PA view***

n Absence of gastric bubbles due to failure of LES relaxation that prevents air from entering the stomach.

n Widening of mediastinum due to dilated oesophagus.

3. ***Barium swallow with fluoroscopy***

n Diagnostic accuracy is 95%.

n Oesophageal dilation – Mainly distal oesophagus, profound oesophageal dilatation looks like sigmoid colon.

n Smooth tapered barium column at tight non-relaxing sphincter with dilated distal oesophagus gives ‘bird’s-beak’ appearance **(Fig. 18.1)**.

n Fluoroscopy shows absence of peristalsis and sometime sporadic spastic contractions.

n Upright film shows esophageal air-fluid level.

n Lower and mid-oesophageal pulsion diverticula.

n Tortuous dilated oesophagus >7 cm is called advanced megaesophagus or sigmoid oesophagus.

n The water flush technique (patients drink tap water at end of esophagography in an attempt to clear the

standing barium column) is a simple, noninvasive maneuver that improves the extent of diagnostic visualization of the distal oesophageal mucosa in patients with moderate-to-severe primary achalasia. It facilitates detection of a tumour.

4. ***Endoscopy***

n Upper endoscopy should be performed in all patients (retroflexion view is very critical).

n It excludes secondary causes of achalasia, especially cancer of the gastroesophageal junction that mimic achalasia hence named pseudoachalasia **(Fig 18.2)**.

n It helps to evaluate oesophageal mucosa before therapeutic interventions.

n Endoscopy shows dilated oesophageal body with tight LES, which can be negotiated with gentle pressure on endoscope.

5. ***Manometry***

n Gold standard for the diagnosis of achalasia cardia.

n Three main elements of high-resolution esophageal manometry (HREM) are elevated resting LES pressure, incomplete LES relaxation and aperistalsis.

n Based on the HREM findings, achalasia is classified into three types, as outlined in the Chicago classification: type I, type II and type III. Along with impaired relaxation of LES, type I achalasia is characterized by a complete absence of oesophageal peristalsis on HREM, type II is characterized by pan-esophageal pressurization and type III is characterized by spastic contractions in the oesophagus.

n Vigorous achalasia is an achalasia with high amplitude non-peristaltic oesophageal body contractions.

n High-resolution oesophageal manometry uses 36 sensors placed at 1 cm distance than usual manometry, which uses 8 sensors at 3–5 cm distance.

6. ***Oesophageal transit scintigraphy***

n Not routinely used. It is used for research purposes and to monitor the therapy.

n Non-invasive technique to examine oesophageal transit.

n Both oesophageal transit time and retention are prolonged in achalasia.

**Disorders Mimicking Primary Achalasia (Pseudoachalasia or secondary achalasia)**

1. Adenocarcinoma at gastroesophageal junction

2. Oesophageal squamous cell carcinoma

3. Lymphoma

4. Post vagotomy dysphagia

5. Amyloidosis

6. Duodenal carcinoma

7. Pancreatic malignancy

**Diseases Associated with Achalasia**

1. Chagas’ disease

2. Chronic idiopathic intestinal pseudo-obstruction

3. Sarcoidosis

4. MEN type II B neoplasia

5. Neurofibromatosis

6. Eosinophilc gastroenteritis

7. Fabry’s disease

8. Juvenile Sjogren’s syndrome

**Management**

1. Management is aimed at palliating dysphagia by reducing the resistance to flow at the level of the gastroesophageal junction.

2. This can be achieved by relaxing LES with pharmacological agents like nitrates and calcium channel blockers. Current guidelines recommend the use of nifedipine 10–30 mg, sublingually 30–45 min before meals or isosor-bide dinitrate 5 mg, 10–15 min before meals for best response. Oral pharmacological therapy is generally only reserved for those patients who are not candidates for other therapies.

3. Injection of botulinum toxin (100 units of toxin diluted in normal saline and injected in four quadrants just above the squamocolumnar junction) into the LES *via* upper endoscopy has been shown to be a useful treatment option for achalasia. By causing presynaptic inhibition of acetylcholine release, botulinum toxin blocks the unopposed excitatory cholinergic stimulus to the LES, which is characteristic of achalasia. This leads to paralysis of the LES muscle due to neuronal inhibition but has no effect on the resting muscle tone, which is mostly driven by myogenic influence. Thus, the overall effect

of botulinum toxin injection is an approximate 50% reduction in LES pressure. Most patients require repeated injection every 6–24 months.

4. LES pressure can be reduced by endotherapy using pneumatic balloon or peroral endoscopic myotomy (POEM) or by surgical myotomy.

**Pneumatic Balloon Dilatations Using Rigiflex Balloon**

1. The patient is on clear liquids for at least 24 hrs with nil per orally past midnight.

2. Upper endoscopy is performed on the fluoroscopy table in the left lateral position using conscious sedation to exclude pseudo-achalasia.

3. The Savary guide wire with flexible tip is then advanced through the endoscope and placed in the stomach under combined endosocpic and fluoroscopic control.

4. Radiopaque marker marks the LES. The best way to mark the gastroesophageal (GE) junction is measuring it on the balloon catheter and marking the spot. External markers are not reliable because of patient movements.

5. The Rigiflex balloon **(Fig. 18.3)** is advanced over the guide wire and positioned at the gastroesophageal junction.

6. The balloon is then partially inflated with air using the manometer until the waist is visible.

7. The final position of the balloon is when half of the partially inflated balloon is above the waist and half below the waist **(Fig. 18.4)**.

8. The balloon is then inflated under fluoroscopic control between 8 and 12 psi until the waist is completely obliterated.

9. The inflation is maintained for 60 sec.

10. Water-soluble contrast is given to patients in whom symptoms are suggestive of oesophageal perforation.

11. Patient is kept nil orally for 6 hrs and then liquid diet is started, followed by regular diet as tolerated.

12. Pneumatic balloon dilation should be done in graded manner using 30 mm Rigiflex balloon, followed by 35 mm and 40 mm in case of unsuccessful first dilation.

13. Complication includes symptomatic oesophageal perforation and heart burns.

14. Use of the 30 mm balloon as opposed to the larger sizes was associated with PD failure for younger patients (especially male) in some studies.

15. Young men seem to be especially prone to failure with PD, and consideration should be given to starting with larger balloons. Those patients with achalasia with ‘end-stage’ disease signified by a dilated sigmoid-shaped

oesophagus usually do not respond well to PD (or other treatments for that matter).

16. Oesophageal perforation is a dreaded complication of PD but, fortunately, this occurred in less than 5% of dilations in most recent studies.

17. The effects of PD or any intervention for achalasia have been assessed clinically by a simple quantitative measurement known as the Eckardt score, which assesses the symptoms of dysphagia, chest pain, regurgitation and weight loss **(Table 18.1)**.

**Surgical Myotomy**

1. Laparoscopic Heller’s myotomy (LHM) involves the surgical division of the circular (full thickness) or both circular and longitudinal muscle fibres of the LES.

2. Myotomy decrease the LES pressure more effective than pneumatic dilation.

3. Results from a European randomized controlled trial comparing the efficacy of pneumatic dilation *versus* LHM showed no significant difference in the efficacy of the two modalities after 5 yrs of follow-up. Additionally, no significant differences were observed in post-procedural LES pressure, height of barium-contrast column or quality of life between the two groups. However, 25% of patients treated with pneumatic dilation required repeat dilation.

**Technical Issues with Heller’s Myotomy**

1. ***Length of the myotomy***

n Myotomy on the gastric site is the most critical part. More the distal length, effective palliation of dysphagia, but at the expense of postoperative gastroesophageal reflux.

2. ***Type of anti-reflux surgery***

n In achalasia, lower end of oesophagus is aperistaltic, so 360° complete Nissen’s fundoplications is not required. Partial (180°) fundoplication is sufficient to prevent reflux postoperative.

n Partial posterior wrap (Toupet fundopliocation) – wrapping the fundus of the stomach behind the oesophagus.

n Partial anterior wrap (Dor fundoplication) – wrapping the fundus of the stomach anterior to the oesophagus.

n Technically, Dor fundoplication is easy but higher incidence of postoperative reflux.

3. ***Effects of previous interventions***

n Balloon dilatation does not have any effect on surgical myotomy.

n Botulinum toxin injection leads to technical difficulty, but outcome is not affected.

4. ***Sigmoid oesophagus***

n Dilatation of oesophagus has no effect on the outcome following surgery. Anatomical distortion of the GE junction in a horizontal alignment with sump effect may not respond to nonsurgical therapy.

5. ***Role of intraoperative manometry***

n Useful to identify high-pressure zone.

n Helps to guide the extension of myotomy.

**Endoscopic Myotomy**

Peroral endoscopic myotomy (POEM) is a hybrid endoscopic procedure, which uses the concept of natural orifice transluminal endoscopic surgery (NOTES) to perform endoscopic myotomy. The procedure is performed under general anaesthesia, with the patient in the supine position on positive pressure ventilation. The endoscope is posi-tioned at 10 cm above the gastroesophageal junction (GEJ) and mucosotomy was performed at the 2 o’clock position (for anterior myotomy) and 5 o’clock position (for posterior myotomy) and a submucosal space was developed caudally creating a controlled submucosal tunnel extending 2 cm distal to the GEJ. Upon completion of this tunnel the gastroesophageal lumen was inspected for mucosal integrity. The scope was then reinserted into the submu-cosal tunnel and using a triangle-tip knife, and myotomy was performed starting at 5 cm above the GEJ and ending at 2 cm below the GEJ **(Fig. 18.5)**. During this process, the circular muscle layer of the oesophagus was carefully divided while preserving the longitudinal layer. At the end of the procedure, the mucosal incision was closed longitudinally with endoscopic clips. POEM is contra-indicated in patients who are unable to tolerate general anaesthesia or in those who have coagulopathy, portal hypertension or previous exposure to radiation, ablation, or mucosal resection in the planned operative field. The efficacy of POEM is >90%. In addition, the length of hospital stay after POEM is significantly lower than that after LHM. In addition, POEM is remarkably safe and well tolerated. Gastroesophageal reflux disease (GERD) was reported in 10–30% of the patients and the incidence of severe side effects was as low as <1%.

**Esophagectomy**

Patients unresponsive to other forms of therapy may require esophagectomy for relief of symptoms. However, due to its significant morbidity and mortality, esophagectomy is generally reserved for patients with end-stage achalasia who are good surgical candidates and who have previously failed pneumatic dilation with or without Heller’s myotomy. Although esophagectomy shows symptomatic improve-ment in more than 80% of patients, complications include postoperative dysphagia requiring dilation in up to 50% of patients, and the risk of mortality is up to 5.4%.

**Pathophysiology**

Degeneration of neurons in the oesophageal wall is the main feature observed on histological examination. The number of ganglion cells in the myenteric plexuses in the wall of oesophagus is decreased and most remain surrounded by lymphocytes and eosinophils, which cause inflammatory degeneration of nitric oxide producing inhibitory neurons that result in improper relaxation of the oesophageal wall hence aperistalsis. Most cholinergic neurons that contribute to the LES tone by smooth muscle contraction are spared from this degeneration thus resulting in the absence of LES relaxation. Loss of inhibitory innervations in the oesophagus can be identified using the cholecystokinin or CCK test.

**aetiology**

Main cause of inflammatory degeneration of neurons is not known. There has been association observed with HLA-DQw1 suggesting association with autoimmune process. Few have observed association with herpes virus and measles. One study found reactivity of T cells in achalasia patient to HSV-1 infection suggesting that HSV-1 might be triggering event.

**Achalasia Cardia and oesophageal Cancer**

n Achalasia is one of the risk factor for the development of squamous cell carcinoma of the oesophagus.

n Oesophageal adenocarcinoma is also linked with achalasia.

n Prevalence of carcinoma in patients with untreated achalasia is ranging from 2 to 7%.

n Food stasis and mucosal irritation may be the precipitating factors.

**Further Reading**

1. Spechler JS. American Gastroenterological Association medical position statement on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology* 1999;117:229–32.

2. Stavropoulos SN, Friedel D, Modayil R, et al. Endoscopic approaches to treatment of achalasia. *Therap Adv Gastroenterol* 2013;6:115–35.

3. Moonen AJ, Boeckxstaens GE. Management of achalasia. *Gastroenterol Clin North Am* 2013;42:45–55.

4. Eckardt VF, Kanzler G, Westermeler T. Complications and their impact after pneumatic dilation for achalasia: prospective long-term follow-up study. *Gastrointest Endosc* 1997;45:349–353.

5. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depends on manometric subtype. *Gastroenterology* 2013;144:718–25.

6. Stavropoulos SN, Modayil R, Friedel D. Achalasia. *Gastrointest Endosc Clin N Am* 2013;23:53–75.

7. Gheorghe C, Bancila I, et al. Predictors of short term treatment outcome in patients with achalasia following endoscopic or surgical therapy. *Hepatogastroenterology* 2012; 59:2503–7.

8. Moonen A, Annese V, Belmans A, et al. Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. *Gut* 2016;65:732–9.

9. Stavropoulos SN, Modayil R, Friedel D. Per oral endoscopic myotomy for the treatment of achalasia. *Curr Opin Gastroenterol* 2015;31:430–40.

10. Patel KS, Calixte R, Modayil RJ, et al. The light at the end of the tunnel: a single-operator learning curve analysis for per oral endoscopic myotomy. *Gastrointest Endosc* 2015*;* 81:1181–7.

11. Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastro-enterol* 2013;108:1238–49.

**Chapter 19.**

**Benign Oesophageal Stricture**

**Introduction**

Benign oesophageal strictures are presumed to develop as sequelae of deep oesophageal ulcerations that lead to fibrous tissue production and collagen deposition. However, the exact mechanisms that lead to stricture formation are not known, as some strictures develop because of chronic oesophageal inflammation even without mucosal ulceration. Benign oesophageal strictures arise from a diversity of causes, e.g., oesophagogastric reflux, oesophageal resec-tion, radiation therapy, ablative therapy or the ingestion of a corrosive substance. Most strictures can be treated successfully with endoscopic dilation using bougies or balloons, with only a few complications. Nonetheless, approximately one-third of patients develop recurrent symptoms after dilation within the first year.

**Causes**

1. Corrosive oesophageal stricture

2. Peptic oesophageal stricture

3. Post radiation

4. Post sclerotherapy

5. Post chemotherapy

6. Postoperative stricture (e.g., after hiatal hernia repair, gastric surgery, etc)

7. Secondary to infectious/inflammatory oesophagitis:

n Candidiasis

n Tuberculosis

n Histoplasmosis

n Crohn’s disease

n Eosinophilic oesophagitis

n Behcet’s syndrome

8. Stricture secondary to pill oesophagitis

**Clinical History**

n Dysphagia to solid and liquid (Ch. 1).

n Mild-to-moderate weight loss – weight loss is more profound in corrosive stricture.

n History of acid or alkali ingestion suggests corrosive oesophageal stricture.

n History of chronic heartburn indicates peptic oesophageal stricture.

n History of multiple sessions of endoscopic sclerotherapy suggests post-sclerotherapy stricture.

**Physical Examination**

n Physical examination may be normal in patients with benign oesophageal stricture.

n Stigma of corrosive ingestion like pigmentation or erythema of lips, oral cavity and pharynx.

n Stigma of chronic liver disease in who underwent multiple sessions of sclerotherapy.

**Investigations**

1. ***Haemogram***

n Usually normal in benign oesophageal stricture

2. ***Barium swallow***

n Corrosive stricture – Strictures can appear as soon as 2 weeks after the ingestion of a caustic substance. Strictures tend to be long, involve a large portion of the thoracic oesophagus, and occasionally extend the entire distance between the aortic knob and the diaphragm. Lye stricture is longer than acid stricture.

n Peptic stricture – Stricture secondary to reflux oeso-phagitis tends to be typically smooth, tapered and concentric narrowing is observed in the distal oesophagus with no demonstrable mucosal pattern.

n Radiation stricture – Benign strictures situated mostly in the mid oesophagus with tapered margins and relatively smooth mucosal surfaces.

n Post-sclerotherapy stricture – Fixed, non-collapsible, rather rigid-appearing filling defects in the barium column lead to complete fixation and lack of distensibility of the oesophagus. The stenotic zone may be asymmetric and even have overhanging edges mimicking carcinoma. If the overlying mucosa becomes denuded, ulceration may develop.

3. ***Upper GI endoscopy***

n Upper GI endoscopy is the procedure of choice to evaluate a suspected oesophageal stricture because of the high sensitivity associated with the ability to directly observe mucosal details; high specificity because of the ability to obtain endoscopic biopsies.

n Simple strictures are considered to be short, focal, and straight, and they allow passage of an endoscope with a normal diameter. Examples include Schatzki rings, oesophageal webs and peptic strictures.

- Complex strictures are usually longer (>2 cm), angulated, irregular or have a severely narrowed diameter. Complex stricture includes radiation-induced strictures, caustic strictures and photodynamic therapy-induced strictures.

- Endoscopic stricture dilation can be performed using Savary dilators or balloons.

- One to three dilations are sufficient to relieve dysphagia in simple strictures. Only 25–35% of patients require additional sessions, with a maximum of five dilations in more than 95% of patients. Complex strictures are more difficult to treat and have a tendency to be refractory or to recur despite dilation therapy.

**Management**

Management of benign oesophageal stricture depends on the cause (see below).

**Peptic stricture**

**Introduction**

It has been estimated that 60–70% of all benign oesophageal strictures in the United States are peptic in origin, secondary to gastroesophageal reflux disease (GERD). Risk factors for an oesophageal stricture from GERD include long history of GERD, old age and hypotensive LES.

**Clinical Features**

Progressive dysphagia, typically to solids and often with antecedent heartburn and regurgitation are the most common presenting symptoms in peptic stricture. Sometimes heart-burn may disappear once dysphagia develops. Marked weight loss associated with peptic stricture suggests oesophageal adenocarcinoma in the setting of chronic GERD.

**Investigations**

1. ***Barium oesophagogram*** shows smooth, tapered, and concentric narrowing located in the distal oesophagus. It may be associated with hiatus hernia.

2. ***Upper endoscopy*** to define the injury and obtain biopsy to exclude Barrett’s oesophagus and adenocarcinoma in the setting of chronic GERD. It is usually short stricture near the lower end oesophagus **(Fig. 19.1)**.

**Management**

***Lifestyle Modification***

1. Patients should strictly follow standard antireflux precautions like elevation of the head end of the bed, avoidance of meals at least 2–3 hrs before going to bed, weight reduction and reduction of alcohol intake and smoking.

2. Patients should chew the food properly, avoid eating hurriedly and should correct ill-fitting dentures.

***Acid-Suppression Therapy***

1. Mechanical dilatation is the mainstay of therapy in peptic stricture, but aggressive acid suppressive therapy using proton pump inhibitors heals oesophagitis and decreases the need for peptic stricture dilation.

2. H2 blockers or prokinetic agents do not decrease the need for subsequent stricture dilations.

***Mechanical Dilatation***

1. Mechanical dilatation is the most important treatment for peptic stricture. The initial choice of dilator size is based on an estimate of the stricture diameter determined using a barium swallow or an endoscopic examination.

2. The 3 commonly used devices for oesophageal dilation are: (a) mercury-filled bougies that are passed blindly through the mouth (e.g., tapered-tip Maloney dilators, blunt-tip Hurst dilators); (b) polyvinyl bougies that can be passed over a fine guide wire that is positioned within the stricture using either fluoroscopic or endoscopic guidance (e.g., Savary dilators); and (c) balloon dilators that are passed either over a guide wire (OTW) or through the endoscope (“through-the-scope” or TTS balloons).

3. Bougies are pushed through the stenotic segment and thus deliver axially as well as radially directed dilating forces to the stricture. Balloon dilators deliver only radially directed dilating forces. Thus, balloon dilators are believed to stretch the stricture uniformly minimizing complications associated with the application of shearing stresses. To date, no study has reported differences

between balloon and bougie dilation for alleviating dysphagia or preventing the recurrence of dysphagia. In addition, no differences have been reported in the risk of major complications.

4. A clear consensus has not been achieved thus far about the optimal size to which a peptic stricture should be dilated. Typically, it is recommended that the Savary dilator passed for the first time should have a diameter approximately equal to that estimated for the stricture. The “rule of threes” is that no more than three dilators of progressively increasing sizes should be passed during any one dilation session to minimize the risks of oesophageal perforation and haemorrhage.

5. Typically, strictures are dilated to a diameter much greater than that can be achieved by passing 3 bougies.

6. Perforation and bleeding are the major complications of oesophageal dilatation, and the frequency of these complications is 0.1 and 0.3%, respectively. Bacteremia develops in 20–45% of the patients following stricture dilatation, but infections develop very rarely.

7. Persistent heartburn following dilation is a strong predictor of early symptomatic recurrence.

8. Oesophageal dilation relieves the dysphagia in more than 80% of the patients. Approximately, 30% of patients require repeat dilation within 1 year of successful treatment despite optimal acid suppressive therapy. The recurrent stricture rate is 12–65%.

9. Results of previous studies indicate that injection of a steroid (intralesional triamcinolone) followed by dilation to avoid recurrent dysphagia prevents recurrence of the stricture. However, most of these studies were small and uncontrolled. The pathogenesis of anastomotic strictures differs from that of peptic strictures, in that the former are due to ischaemia, whereas the latter develop as a result of inflammation and ulceration from the reflux of gastric acid. Steroids locally inhibit the inflammatory response, which result in a decrease in the formation of collagen.

10.Incisional therapy with a needle knife is shown to be effective in short anastomotic strictures.

**Kochman Criteria**

Refractory or recurrent strictures are defined as an anatomic restriction because of a cicatricial luminal compromise or fibrosis, which result in clinical symptoms of dysphagia in the absence of endoscopic evidence of inflammation. This may occur as the result of either an inability to successfully address the anatomic problem to a diameter of at least 14 mm over five sessions at 2-week intervals (refractory) or because of an inability to maintain a satisfactory luminal

diameter for four weeks once the target diameter of 14 mm has been achieved (recurrent).

**Role of Endoscopic Stents**

1. Uncovered SEMS were initially used for the treatment of refractory benign oesophageal strictures. One of the major drawbacks of uncovered and partially covered SEMS is that they are associated with a relatively high complication rate, mostly due to hyperplastic tissue ingrowth through the stent mesh, which results in embedding of the stent in the mucosa. The complication rate associated with the placement of uncovered or partially covered stents are as high as 80%. The most common complications include the formation of a new stricture because of tissue ingrowth, stent migration, pain and gastroesophageal reflux if the stent is positioned across the gastroesophageal junction.

2. To overcome the problem of stent ingrowth, fully covered stents (SEMS or SEPS) are preferable for benign oesophageal strictures. However, results of fully covered stents are not very encouraging because dysphagia recurs in a majority of the patients following removal of the stent.

3. Biodegradable stents hold promise in the management of benign oesophageal stricture, but majority of the studies performed thus far have been in a small population.

***Surgical Treatment***

1. Surgery is reserved only in the case of patients with strictures that cannot be dilated, those with frequent recurrence of strictures after dilation, and those showing failure of healing of oesophagitis after maximal medical therapy.

2. The standard Nissen fundoplication is the most commonly performed operation. Partial fundoplication is indicated in patients with impaired oesophageal motility.

3. The results of a partial or complete fundoplication are good in about 77% of patients.

**Corrosive Stricture**

**Introduction**

Corrosive oesophageal stricture is the most common cause of benign oesophageal stricture in India. Corrosive agents produce extensive damage to the gastrointestinal tract. Severe corrosive ingestion can lead to perforation and even death in the acute phase. Oesophageal stricture and development of oesophageal carcinoma are the chronic sequelae of corrosive ingestion.

Corrosive agents can be either alkaline (lye) or acidic.

***Alkali/Lye***

1. Common in the Western world.

2. Commonly used alkalis are corrosive alkalis like sodium hydroxide (drain openers) and corrosive detergents (hydrogen peroxide 3% and sodium hypochlorite >1%).

3. Its pH is between 10.8 and 11.4.

***Acids***

1. Most common cause of corrosive stricture in countries like India.

2. Commonly used acids are hydrochloric acid, sulphuric acid (toilet cleaners, anti-rust compounds, battery fluids).

**Pathogenesis**

1. Solutions with pH less than 2 and more than 12 are highly corrosive.

2. Acid solutions usually cause immediate pain while alkalis are tasteless and odourless, causing extensive damage to esophagus and stomach.

3. Alkali penetrates tissue very rapidly and causes liquefaction necrosis. Thrombosis of adjacent vessels secondary to alkali ingestion exacerbates injury.

4. Acid produces coagulation necrosis that limits penetration.

5. Within seconds after corrosive ingestion, necrosis of the tissue occurs, which leads to either ulceration or perforation depending on the severity of necrosis. After few weeks, fibrous tissue proliferation and collagen deposition occur, which lead to stricture formation.

**Site of Stricture Formation Following Corrosive Ingestion**

Oesophagus At cricopharynx

At aortic arch

At tracheal bifurcation

At lower oesophagus

Stomach Antrum in fasting state

Mid-body postprandially

Degree 1°– Superficial injury produces

oedema and erythema of the mucosa

2° – Injury penetrates the mucosa,

involving the submucosa & muscle

layer producing deep ulceration

3° – Full thickness injury

**Clinical Features Following Corrosive Ingestion**

***Early***

1. Lip and oral cavity injury

2. Sialorrhea and drooling suggests oropharyngeal involve-

ment, hoarseness, stridor and dyspnea suggests laryngeal

injury, and persistent or severe chest or back pain suggests oesophageal perforation or mediastinitis.

3. 3° burns usually lead to ARDS and mediastinitis

4. Acute gastric perforation.

***Late***

*Oesophageal Stricture*

Presents most commonly at 2 months after injury, but can occur at any time from 2 weeks to many years after the initial injury. Stricture formation occurs more commonly following more severe (grade IIB or III) injuries than the milder forms (I or IIA). Lye strictures tend to be longer than acid strictures. The patient presents with dysphagia.

*Gastric Outlet Obstruction*

Usually develop 1–6 weeks after caustic ingestion but can also occur years later. Patients usually present with features of gastric outlet obstruction. The risk of antral stenosis is also related to the degree of injury. Endoscopic dilatation with the addition of acid suppression is successful in few patients, as most will require surgery.

*Carcinoma*

Long-standing corrosive stricture predisposes to oesopha-geal malignancy due to food stasis. About 3% of those with carcinoma oesophagus have past history of lye inges-tion. There is a 1000–3000-fold increase in the incidence of oesophageal carcinoma after lye ingestion. Patients with carcinoma of the oesophagus due to lye ingestion may have a better prognosis than other patients, as they have early symptoms and scar tissues limit spread of the cancer.

**Investigations**

At the time of admission:

n X-ray chest for mediastinitis.

n X-ray abdomen for free perforation. If there is suspicion of perforation, contrast CT thorax is required.

***Upper Endoscopy***

Upper endoscopy should be performed preferably within 24 hrs. Wound softening occurs after 3–4 days up to 2 weeks, which increases the risk of perforation during endoscopy. Thus, upper endoscopy should be avoided from 5 to 15 days. Absolute contraindication of upper endoscopy in corrosive ingestion is 3° burns to hypo-pharynx. Upper endoscopy should be performed preferably under sedation with airway protection. Risk of procedure related perforation is low. Endoscopy showed mild superficial ulceration to severe ulceration **(Fig. 19.2)**.

Role of EUS to assess the depth of injury has yet not been established.

***Endoscopic Grading of Severity of Oesophageal Injury***

Grade 0 - Normal

Grade I - Oedema; hyperemia of mucosa

Grade IIa - Friability, blisters, erosions,

superficial ulceration

Grade IIb - Grade IIa plus deep or

circumferential ulceration

Grade IIIa - Multiple ulcerations & areas of

necrosis

Grade IIIb - Extensive necrosis

Grade IV - Perforation

***Importance of Endoscopy and its Grading in Management of Corrosive Injury***

If endoscopy shows grade I or grade IIa injury, patients can be discharged immediately. Development of oesophageal stricture in these patients is very unlikely.

If endoscopy shows grade IIb to IV injury, patients should be managed very aggressively and may require intensive care. Development of oesophageal stricture in these patients is very high (70–100%).

**Management**

***Grade I and IIa***

n No aggressive treatment required. Can be discharged on same day.

***Grade IIb and III***

n Close monitoring and nutritional support

n May require intensive care monitoring

n Nil per orally for at least first 48 hrs

n Data regarding use of intravenous antibiotics are conflicting.

n Role of TPN and corticosteroid is not established.

n Volume repletion and airway protection is the most important part of management.

n If patient is stable after 48 hrs, oral fluids can be started.

***Role of Surgery***

n Emergency surgery is indicated only in case of oesophageal or gastric perforation. Higher incidence of anastomotic leak following emergency surgery.

***Early Dilation***

Early dilation increases the risk of perforation and hence is not recommended.

***Stricture***

n Dilatation can start at 3 weeks followed by either aggressive weekly dilation for 6 weeks or once 3 weeks dilation for 6 times.

n Role of self-expanding metallic stent is not yet proven in refractory cases of corrosive stricture.

n Maximum oesophageal wall thickness of more than 9 mm requires significant number of dilation, and is the most important predictor of response following stricture dilatation.

n More frequent dilation required compared with peptic stricture.

n Long, tight and eccentric stricture increases chances of perforation.

n 10–50% of patients require surgery.

***Gastric Outlet Obstruction***

Balloon dilation should be considered as the initial mode of therapy. Surgery is indicated when dilatation fails.

**Summary of the Management**

To date, no evidence-based treatment guideline is available for benign oesophageal stricture. Dilation remains the first choice for management as it is the least invasive approach with a low complication rate (0.001–0.040%). If a successful outcome is not achieved with dilation next steps, which include dilation with steroids, incisional therapy for selected strictures, or stent placement, should be discussed with the patients. In the case of patients with refractory strictures, self-bougienage can be proposed to patients with a stenosis in the proximal oesophagus. An ultimate step in the management of benign refractory oesophageal strictures includes surgery despite the fact that even after surgery, the risk of stricture formation remains high.

**Further Reading**

1. Kovil Ramasamy, Vivek Gumaste. Corrosive ingestion in adults. *J Clin Gastroenterol* 2003;37:119–24.

2. Zargar SA, Kochhar R, Nagar B, et al. Ingestion of corrosive acid. *Gastroenterology* 1989;97:702.

3. Mitchell S Cappell.Clinical presentation, diagnosis, and management of gastroesophageal reflux disease. *Medical Clin of N Am* 2005;89:243–91.

4. Heidelbaugh J. Medical and surgical management of gastroesophageal reflux disease. *Clin Fam Pract* 2004;6: 547–70.

5. ASGE Technology Committee. Tools for endoscopic stricture dilatation. *Gastrointest Endosc* 2004;59:753–60.

6. Broor SL, Raju GS, Bose PP, Lahoti D, Ramesh GN, Kumar A, Sood GK. Long-term results of endoscopic dilatation for corrosive oesophageal strictures. *Gut* 1993;34:1498–501.

7. Kochman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. *Gastro-intest Endosc* 2005;62:474–5.

8. Shah JN. Benign refractory esophageal strictures: widening the endoscopist’s role. *Gastrointest Endosc* 2006; 63:164–7.

**Chapter 20.**

**Esophageal Cancer**

**Introduction**

Squamous cell carcinoma (SCCA) occurs in the upper and middle third and adenocarcinoma is common in the lower third of oesophagus and GE junction. SCCA is the most common malignant tumour of the oesophagus, whereas incidence of esophageal adenocarcinoma (EAC) is increasing more rapidly due to the rising prevalence of gastroesophageal reflux disease and development of Barrett’s oesophagus. EAC, different from SCCA, affects the distal oesophagus of young patients and is usually detected in an early stage.

**Clinical History**

n Progressive, unremitting and short-duration dysphagia (90%).

n Odynophagia (50%) – Associated with ulcerated tumour.

n Chest pain or pain radiating to back due to invasion of neuromuscular structure.

n Cough and fever secondary to respiratory tract fistula:

- Weight loss

- Haematemesis or melena

n Hoarseness of voice due to recurrent laryngeal nerve involvement.

n Hiccups secondary to phrenic nerve involvement.

n History of squamous cell carcinoma of head and neck region.

n Long-standing heartburns, regurgitation and chest pain caused by long-standing GERD may be more common in adenocarcinoma.

**Past History**

n Achalasia cardia – 16-fold increased chance of SCCA

n Corrosive ingestion

n Dysphagia from postcricoid web and underwent multiple endoscopic dilation – Plummer-Vinson syndrome.

n Tylosis, a rare autosomal dominant condition characterized by hyperkeratosis of the palms and soles, has high association with oesophageal SCCA.

**Personal History**

Alcohol and smoking – Nitrosamines in alcohol and smoking predispose to SCCA in a dose-dependent manner. Populations that consume large quantities of green and yellow

vegetables rich in beta-carotene and vitamin C are protected from the development of oesophageal SCCA.

**Physical Examination**

n The physical examination is often normal in patients with oesophageal cancer.

n A generalized loss of muscle mass and subcutaneous fat is often evident.

n Lymph node in the supraclavicular fossae or axilla.

n Anaemia due to gastrointestinal blood loss/malnutrition/Plummer-Vinson syndrome.

n Koilonychia may point to Plummer-Vinson syndrome.

n Hyperkeratosis of palms and soles indicates tylosis.

**Investigations**

1. **Biochemistry**

n Anaemia with or without iron deficiency

n Elevated ESR

n Elevated liver enzyme indicates liver involvement

n Hypercalcaemia is either due to ectopic hormone production or bone metastasis

2. **Endoscopy**

n Proliferative mass occluding oesophageal lumen **(Fig. 20.1)**, early cancer can be detected as elevated plaque or small erythematous lesions.

n If the lumen is obstructed by tumour then an ultrathin endoscope (OD: 5.3–6 mm) should be used.

n Oesophageal dilatation for the purposes of diagnosis should be avoided due to the high risk of perforation, which may deny these patients a chance of cure.

n Endoscopically, Barrett metaplasia reveals circumferential or isolated islands (or tongue) of salmon-coloured mucosa proximal to oesophageaogastric junction **(Fig. 20.2)**.

n Histopathological confirmation by taking biopsy and biopsy samples of pieces 6 leads to >95% diagnosis.

n Yield of the biopsies can be enhanced by the advent of new endoscopic modalities such as narrow band imaging and autofluorescence and with the development of magnifying (zoom) and confocal endoscopes.

3. **Chest X-ray PA view**

n Oesophageal air-fluid level

n Lateral deviation of mediastinum

n Mediastinal widening

n Mediastinal air suggestive of fistula

n Bronchopneumonia in case of respiratory tract fistula

4. **Barium swallow**

n Barium examination can detect the level of obstruction and tracheo-esophageal fistula.

n Sensitivity of barium study to detect early lesions is only 75%. Advanced cancer appears as apple-core stricture **(Fig. 20.3)**.

5. **CT abdomen**

n Cannot distinguish between T1 and T2 lesions.

n Accurately predicts invasion of the adjacent structures by either mass effect or loss of fat planes.

n Poor sensitivity to predict lymph node metastasis; 94% accurate for liver metastasis.

6. **PET**

n Using 18F-fluorodeoxyglucose.

n For regional and distant nodal disease, PET-CT has been shown to have a similar or better accuracy than conventional EUS-CT.

n Thus a combined approach with CT, EUS and PET-CT has the highest possible yield for accurately assessing the nodal status.

n PET has similar limitations to CT in detecting peritoneal disease possibly due to lesion sizes of <5 mm and a low viable cancer cell to fibrosis ratio.

7. **EUS**

n Using radial scanner around 7.5–12 MHz.

n Most accurate modality to define the oesophageal wall.

n The only modality to distinguish between T1 and T2 lesions.

n More sensitive than CT scan to identify tumour invasion mainly to aorta and pulmonary vasculature.

n Can predict curative vs palliative resectability or unresectability.

n Accuracy for T-stage is 84% and for N-stage is 77%.

n It is very important to traverse the lesions by EUS, as inspection of celiac node is very important. Celiac node involvement in proximal oesophageal cancer is labeled as M1.

n Nodal metastases are suggested by four echo pattern characteristics: (a) size >10 mm; (b) well-defined

boundary; (c) homogeneously low echogenicity; and (d) rounded shape. All four may only be present in 25% of cases thus significantly reducing sensitivity. EUS fine-needle aspiration (FNA) cytology of potential nodal disease has been shown to improve the accuracy. At least three passes with the EUS-guided FNA needle are recommended to maximize sensitivity.

**Staging of oesophageal carcinoma**

All oesophageal tumours and tumours with epicentres within 5 cm of the oesophagogastric junction that also extend into the oesophagus are classified and staged according to the oesophageal scheme. All other tumours with an epicenter in the stomach >5 cm from the oesophago-gastric junction or those within 5 cm of the oesophago-gastric junction without extension into the oesophagus are staged using the gastric carcinoma scheme.

**Current TNM Staging**

Tis - Carcinoma in-situ/high-grade dysplasia

T1 - Lamina propria or submucosa

T1a - Lamina propria or muscularis mucosae

T1b - Submucosa

T2 - Muscularis propria

T3 - Adventitia

T4 - Adjacent structures

T4a - Pleura, pericardium, diaphragm or adjacent

peritoneum

T4b - Other adjacent structures (e.g., aorta, vertebral

body, trachea)

N0 - No regional lymph node metastasis

N1 - 1–2 regional lymph nodes (N1 is site dependent)

N2 - 3–6 regional lymph nodes

N3 - >6 regional lymph nodes

M1 - Distant metastasis (M1a and M1b are site

dependent)

**TNM Staging**

**Stage TNM stage**

Stage IA T1 N0 M0

Stage IB T2 N0 M0

Stage IIA T3 N0 M0

Stage IIB T1,T2 N1 M0

Stage IIIA T4a N0 M0

T3 N1 M0

T1,T2 N2 M0

Stage IIIB T3 N2 M0

Stage IIIC T4a N1,N2 M0

T4b Any N M0

Any T N3 M0

Stage IV Any T Any N M1

**Management**

The management of oesophageal cancer includes manage-ment of superficial tumours, role of surgery, role of chemo-radiation and endoscopic palliation. The overall 5-year survival of patients who undergo resection is 12–27%.

**Management of Superficial Tumours**

Patients with superficial lesions (T1) may be cured by endotherapy like endoscopic mucosal resection (EMR), photodynamic therapy, argon plasma coagulation or Nd:YAG laser (see Chapter 65). In EMR, saline is injected into the submucosa, which lifts the mucosa that can be snared with electrocautery using a cap-fitted endoscope.

**Role of Surgery**

Oesophageal resection (esophagectomy) remains a crucial part of the treatment of oesophageal cancer. Resection of the cancerous portion of the oesophagus can be done in the following three ways:

1. **Transhiatal technique** - The thoracic oesophagus is accessed by widening the oesophageal hiatus after a laparotomy and the upper stomach and thoracic oesophagus are resected. The cervical oesophagus is anastomosed to the pulled up part of the stomach through a neck incision.

2. **Ivor Lewis oesophagectomy** - This involves a laparotomy for mobilizing the stomach followed by right thoracic incision to access the oesophagus followed by anastomosis.

3. **McKeown or 3-field oesophagectomy technique** - Requires dissection in the abdomen, chest and neck, with a cervical anastomosis. It is preferential in patients with significant pulmonary risk factors.

Comparisons of the transhiatal technique with the other two (right thoracotomy) shows that the latter are superior in terms of better overall survival and disease-free survival especially where lymph nodes are involved or better resection margin are concerned.

***Indications for surgery include the following***

1. Diagnosis of oesophageal cancer must be made in a patient who is a candidate for surgery.

2. Surgery is indicated when high-grade dysplasia is present in a patient with Barrett oesophagus. As many as 50–70% of such patients are found to have cancer when the oesophagus is resected.

***Contraindications to surgery include the following***

1. Metastasis to N2 nodes (means, celiac, cervical or supraclavicular lymph nodes) or solid organs (e.g., liver, lungs) is a contraindication.

2. Invasion of adjacent structures (e.g., recurrent laryngeal nerve, tracheobronchial tree, aorta and pericardium) is a contraindication.

3. Severe associated comorbid conditions (e.g., cardiovascular disease, respiratory disease) can decrease a patient’s chances of surviving an oesophageal resection.

4. Cardiac function and respiratory function are carefully evaluated preoperatively. A forced expiratory volume in 1 sec of less than 1.2 L and a left ventricular ejection fraction of less than 0.4 are relative contraindications to the operation.

**Minimally Invasive Esophagectomy (MIE)**

1. Laparoscopy and video-assisted thoracic surgery (VATS) has constantly progressed. Advantages of MIE when compared to open surgery are less blood loss and lower requirement of ventilator therapy after surgery. The disadvantages are longer operation times and significantly higher re-operation rates.

2. Ivor-Lewis procedures have been done using a robot called the da Vinci Surgical System in a few centres around the world and will continue to evolve.

3. Mediastinoscope-assisted transhiatal oesophagectomy is another approach that has been tried with satisfactory results.

**Complications of Surgery**

1. Anastomotic leak

2. Anastomotic stricture – Early stricture is due to technical error and late stricture is due to either tumour recurrence or scarring

3. Recurrent laryngeal nerve injury

4. Gastric reflux

5. Postoperative atelectasis

6. Gastric stasis

7. Conduit necrosis

8. Surgical mortality is around 2–13% in well-experienced centres

**Role of Chemoradiation**

1. Chemotherapy as a single modality has limited use.

2. Radiation therapy is successful in relieving dysphagia in approximately 50% of patients. In patients with advanced oesophageal cancer, the preoperative combination of chemotherapy and radiotherapy has shown good results.

3. The aims of preoperative (neoadjuvant) chemotherapy are to reduce the bulk of the primary tumour before surgery to facilitate higher curative resection rates and target micrometastases. Neoadjuvant therapy consists

of a combination of radiotherapy (approximately 45 Gy) and chemotherapy (cisplatin and 5-fluorouracil).

4. Radiotherapy acts locally at the tumour site, whereas the chemotherapy acts on tumour cells that have already spread. This combination therapy is usually administered over a 45-day period and is followed by oesophageal resection after an interval of 4–6 wks.

5. Neoadjuvant chemoradiotherapy (NCRT) was studied in landmark CROSS trial. Trial established that NCRT should be followed by surgery as the standard of care. Recurrence rates were 35% for NCRT and surgery versus 58% for surgery alone.

6. Perioperative chemotherapy is superior to preoperative chemotherapy alone. This was shown in a trial with paclitaxel, cisplatin and 5-FU (PCF).

7. Trials have also shown that surgery should be done on operable cases even if CRT does not show any response.

8. Cisplatin and 5-FU are used for unresectable non-metastatic disease.

9. Metastatic or recurrent adenocarcinoma can be managed by chemotherapy with any of the multiple drugs used in combination. Newer monoclonal antibodies like ramucirumab and trastuzumab have also been tried in those with specific genetic markers.

10. Perioperative chemoradiotherapy is recommended for adenocarcinoma. The drugs used are leucovorin plus 5-FU or capecitabine.

There is no evidence to support routine use of adjuvant chemotherapy in oesophageal squamous cell carcinoma.

**Novel Drug Approaches**

1. **Monoclonal antibodies**: Many monoclonal antibodies acting against specific growth factors have been tried in cancers and in oesophageal cancers as well. These include ramucirumab, trastuzumab and bevacizumab.

2. **Immune checkpoint inhibitors**: These drugs inhibit the expression of programmed cell death protein 1(PD-1) on the T-cells. Nivolumab and Pembrolizumab are the drugs that have been trialled.

**Palliative Therapy**

Palliative therapy is either ablative therapy or endoscopic stenting. Ablative therapy destroys the tissue and relieves dysphagia, whereas stenting palliates the dysphagia by widening the lumen.

Following ablative therapies are available to palliative dysphagia:

1. Contact thermal therapy.

2. Non-contact thermal therapy includes endoscopic laser therapy or APC.

3. Endoscopic cytotoxic therapy injection into the tumour, which causes tissue destruction by chemical necrolysis.

4. Photodynamic therapy.

5. Tumour injection – Leads to sloughing of tumour by endoscopic injection of absolute alcohol, polidocanol or sodium morrhuate.

**oEsophageal Stenting**

1. Oesophageal metal stenting **(Fig. 20.4)** is most important to palliate dysphagia with technical success 98%. tumour should be 2 cm below the cricopharyngeus.

2. Dysphagia relieved by one/two grade.

3. Minor complications like chest pain in 30%.

4. Palliation of respiratory fistula is around 100%.

5. Tumour overgrowth 10%.

6. Stent migration 5%.

7. Antireflux stents confer no added benefit above standard metal stents.

8. Covered expandable metal stents are the treatment of choice for malignant tracheo-oesophageal fistulation or following oesophageal perforation sustained during dilatation of a malignant stricture.

**Palliative Chemoradiation**

1. Palliative external beam radiotherapy can relieve dysphagia with few side effects, but the benefit is slow to achieve.

2. Palliative brachytherapy improves symptom control and health-related quality of life (HRQL) where survival is expected to be longer than 3 months.

3. Palliative chemotherapy provides symptom relief and improves HRQL in locally advanced or metastatic oesophageal cancer.

4. Palliative combination chemotherapy improves survival compared with best supportive care in oesophageal squa-

mous cell carcinoma, adenocarcinoma and undifferentiated carcinoma.

**Classification of oEsophageal Cancer**

1. Squamous cell carcinoma

2. Adenocarcinoma

3. Adenoid cystic cancer

4. Carcinosarcoma

5. Choriocarcinoma

6. Leiomyosarcoma

7. Verrucous carcinoma

8. Small cell carcinoma

**Oesophageal Cancer and High-grade Dysplasia**

The pathology of early cancer of the oesophagus varies with histological subtype. Literature showed that submu-cosal infiltration was more frequent in T1 squamous cancers (80.5%) than in T1 adenocarcinomas (55.4%). The risk of lymph node involvement is also greater in squamous cell carcinoma. An analysis of 1690 lesions has reported the risk of lymph node metastases with early oesophageal squamous carcinomas as being 19% for lesions invading the muscularis mucosa and 44% for lesions invading deeper than the superficial one-third of the submucosa. In contrast, the risk of nodal disease in adeno-carcinoma limited to the muscularis mucosa is negligible. In submucosal infiltration of adenocarcinoma, the risk of lymph node spread reflects the depth of invasion. Once penetration into the superficial third (sm1) has occurred, the risk is 0–8% and once through into sm2 and sm3, it rises to at least 26%.

**Types of Oesophageal Growth**

1. Fungating (60%)

2. Ulcerating (25%)

3. Infiltrating (15%)

**Risk Factors of Squamous Cell Carcinoma**

1. Diet and nutrition – Food deficient in vitamins and minerals

2. Alcohol and smoking

3. Achalasia – May be due to prolonged contact with noxious substances

4. Corrosive oesophageal stricture – Long-standing corrosive stricture predisposes to oesophageal malignancy due to food stasis

5. Plummer-Vinson syndrome

6. Tylosis palmaris et plantaris

7. Human papilloma virus (HPV) infection – A lot of data that has accumulated has shown association between HPV16 and HPV18 with oesophageal SCCA of which the association of HPV16 is stronger. Nevertheless, the evidence is not very robust to demonstrate causation.

8. Current squamous cell carcinoma in head and neck.

**Risk Factors of Adenocarcinoma**

1. Barrett’s oesophagus – The risk of adenocarcinoma among patients with Barrett metaplasia has been estimated to be 30–60 times that of the general population but the absolute risk is only 0.12% per year. Studies have shown that genetic features like loss of heterozygosity mutations and microsatellite instability can predict, which among those with dysplasia will progress to cancer.

2. Gastroesophageal reflux.

3. *H. pylori* infection has a negative association - The role of *Helicobacter pylori* infection in the aetiology of oesophago-gastric junctional cancer is evolving. The hypochlorhydria associated with *H. pylori* due to ammonia production from urea by the bacteria and atrophic gastritis may protect the lower oesophagus by decreasing the acid exposure. In countries with an increase in oesophago-gastric junctional cancer, there has been a corresponding decrease in the incidence of *H. pylori* infection. Furthermore, community-based approaches to eradicate *H. pylori* infection in the treatment of ulcer and non-ulcer dyspepsia may be inadvertently contributing to the increase in these cancers.

4. Role of alcohol is yet to be proven.

5. Obesity - A BMI of 30 or more increases the risk of EAC by 16 times compared with a BMI of 22 or less. This effect was noted irrespective of the presence of reflux symptoms.

6. Smoking

7. NSAID – negative association

**Screening and Surveillance of Oesophageal Cancer**

1. Endoscopic screening and surveillance programme are indicated as there is definitive association between adenocarcinoma of oesophagus and Barrett’s metaplasia.

2. Medical as well as surgical therapy do not regress the Barrett’s metaplasia, thus surveillance programmes usually extend lifelong **(Fig. 20.5)**.

3. For metaplasia, the common recommendation is to perform routine endoscopy every 12–24 months because no evidence suggests that either medical or surgical therapy can stop the progression to high-grade dysplasia and cancer.

4. For high-grade dysplasia, the protocol suggested by investigators at the University of Washington in Seattle proposes endoscopy every 3 months with jumbo forceps and 4-quadrant biopsy samples taken at 1 cm intervals. The rationale is to avoid esophagectomy in patients who will not progress to cancer, based on the belief that this protocol will identify carcinoma in situ before it becomes invasive with lymph node metastases.

5. When an esophagectomy is performed for high-grade dysplasia detected using endoscopy, adenocarcinoma is found in approximately 40% of cases (range of 30–73%). Thus, it is strongly recommend that oesophagec-tomy be performed once high-grade dysplasia is detected.

**Survival of Oesophageal Carcinoma**

The overall 5-year survival rate for oesophageal cancer remains approximately 20–25% for all stages. Patients without lymph node involvement have a significantly better prognosis and 5-year survival rate compared to patients with involved lymph nodes. Stage IV lesions are associated with a 5-year survival rate of less than 5%. Transhiatal and transthoracic procedures have equivalent survival rates. Squamous cell carcinoma and adenocarcinoma, stage-by-stage, have equivalent survival rates.

**Relevant Anatomy of Oesophagus**

1. The oesophagus is a muscular tube that extends from the level of the 7th cervical vertebra to the 11th thoracic vertebra. The oesophagus can be divided into 3 anatomic parts: the cervical oesophagus, the thoracic oesophagus and the abdominal oesophagus.

2. The blood supply of the cervical oesophagus is derived from the inferior thyroid artery, whereas the blood supply for the thoracic oesophagus comes from the bronchial arteries and the aorta. The abdominal oesophagus is supplied by branches of the left gastric artery and inferior phrenic artery.

3. Venous drainage of the cervical oesophagus is through the inferior thyroid vein, whereas the thoracic oesophagus drains via the azygous vein, the hemiazygous vein or the bronchial veins. The abdominal oesophagus drains through the coronary vein.

4. The oesophagus is characterized by a rich network of lymphatic channels in the submucosa that can facilitate the longitudinal spread of neoplastic cells along the oesophageal wall. Lymphatic drainage is to cervical nodes, tracheobronchial and mediastinal nodes, and gastric and celiac nodes.

**Salient Points about Oesophageal Cancer**

1. In oesophageal cancer once dysphagia starts, tumour usually invades muscularis propria.

2. Tumour limited to mucosa has 3% chances to have lymph node metastasis, whereas that of submucosa and beyond submucosa have 30% and 60% chance to have lymph node metastasis, respectively.

3. 5-year survival following surgery is 5–20%.

4. No significant survival advantage of one surgical approach over others.

5. Postoperative chemoradiation shows marginal survival advantage.

**Further Reading**

1. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett’s esophagus. *N Engl J Med* 2011;365:1375–83.

2. Chang AC, Ji H, Birkmeyer NJ, et al. Outcomes after transhiatal and transthoracic esophagectomy for cancer. *Ann Thorac Surg* 2008;85:424–9.

3. Ellis FH Jr. Standard resection for cancer of the esophagus and cardia. *Surg Oncol Clin N Am* 1999;8:279–94.

4. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;8:226–34.

5. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. *Lancet Oncol* 2007;8:545–53.

6. Wang KK, Wongkeesong M, Buttar NS. American Gastroenterological Association technical review on the role of the gastroenterologist in the management of esophageal carcinoma. *Gastroenterology* May 2005; 128:1471–505.

7. Yoshihiro Tanaka, Kazuhiro Yoshida, Tomonari Suetsugu, et al. Recent advancements in esophageal cancer treatment in Japan. *Ann Gastroenterol Surg* 2018;2:253–65.

8. Ghulam Abbas, Mark Krasna. Overview of esophageal cancer. *Ann Cardiothorac Surg* 2017;6:131–6.

9. Rustgi AK, El-serag HB. Esophageal carcinoma. *N Engl J Med* 2014;371:2499–509.

10. Shapiro J, Lanschot JB, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long term results of a randomised controlled trial. *Lancet* 2015;16: 1090–98.

**Chapter 21.**

**Stomach Cancer**

**Introduction**

Gastric cancer (GC) is the second most common cause of cancer-related mortalities worldwide. The incidence of gastric cancer is highest in eastern Asia, Eastern Europe and South America. Recently, the incidence of gastric cancer has shown a steady decrease because of the increased standards of hygiene, better nutrition and eradication of *Helicobacter pylori*, which together constitute primary prevention. Adenocarcinoma is the most common form of gastric cancer. It occurs more commonly in men than in women, usually in their 60s and 70s. The disease becomes symp-tomatic in an advanced stage. Five-year survival rate is usually very low except in Japan because of their surveillance program.

**Clinical History**

1. Abdominal pain (50%)

n Postprandial worsening

n Acid peptic disease like symptoms

2. Weight loss (80%)

3. Dysphagia (25%) – cancer involves cardia of the stomach

4. Vomiting

5. Gastrointestinal haemorrhage and gastric outlet obstruction are rarely the initial manifestation of gastric tumour.

6. Abdominal mass (5%)

7. Jaundice – liver metastasis or nodes in hepatoduodenal ligament.

**Past History**

1. Peptic ulcer disease

2. Surgery for peptic ulcer disease

**Family History**

1. History of gastric cancer in the family – intestinal type

**Personal History**

1. Smoking – probable risk factor for carcinoma stomach

2. Alcohol

**Examination**

1. Pallor indicates overt or occult blood loss from the tumour.

2. Icterus: Liver metastasis, lymph nodes at hilum causing biliary obstruction

1. Lymphadenopathy: Left supraclavicular (Virchow’s node); left axillary (Irish node)

**Paraneoplastic Manifestation**

1. Thrombophlebitis (Trousseau’s sign)

2. Seborrheic keratoses (sign of Leser-Tre’lat)

3. Dermatomyositis

**Abdominal Examination**

1. Abdominal examination may be normal.

2. Umbilical nodules (Sister Mary Joseph’s nodules) indicate abdominal metastatic disease.

3. Visible peristalsis (from left to right) in case of gastric outlet obstruction.

4. Epigastric mass – falling forward and moves with respiration

5. Hepatomegaly indicates tumor infilteration in the liver.

6. Ascites is secondary to peritoneal involvement.

7. Enlarged ovary (Krukenberg’s tumour)

8. P/R – Blumer’s shelf due to drop metastasis

**Respiratory System Examination**

1. Pleural effusion

**Investigations**

1. ***Serum chemistry***

n Anaemia suggests blood loss

n Altered LFT suggestive of liver metastasis or hilar obstruction secondary to lymph node

2. ***Upper endoscopy***

n Malignant ulcer or ulceroproliferative growth **(Fig. 21.1)**

n Location of the lesion

n Involvement of lesser curve

n Distance of tumour from gastroesophageal junction

n Distance of tumour from pylorus

n Posterior wall involvement

n Lack of peristaltic activity due to muscular wall infiltration.

n At least 4–6 biopsy specimens should be obtained from the margin or edge of the ulcer.

n Involvement of duodenum suggests gastric lymphoma.

n Evidence of gastric outlet obstruction.

n Biopsy from the proliferative growth (friable mucosa) yield 90% sensitivity.

n Chromoendoscopy or magnifying endoscopy is useful for early gastric cancer.

3. ***Endoscopic adjuncts***

n Chromoendoscopy and high-resolution endoscopy have been introduced in selected centres although their role has yet to be defined.

n Contrast-enhancing and vital dyes sprayed onto the oesophago-gastric mucosa can aid in the detection of early lesions.

n The most well established are Lugol’s iodine for dysplastic and malignant squamous and indigo carmine for early cancer in gastric mucosa.

4. ***USG***

n Thickening of stomach

n Liver metastasis or hilar obstruction due to lymph node

n Ascites indicates peritoneal involvement.

n Lymph node assessment (66% accuracy)

5. ***CT abdomen***

n Multiple detector computed tomography (MDCT) images of the chest, abdomen and pelvis are acquired at fine collimation enabling multiplanar reformats to be performed with the same resolution as that of axial images (slice thickness should be 2.5–5 mm).

n The studies should be performed after intravenous contrast unless contraindicated. 1 liter of water can be used as an oral contrast agent. Approximately 200 mL and 400 mL of water can be given just before the scan for oesophageal cancer and gastric cancer, respectively.

n Antiperistaltic agent together with gas-forming granules can be administered before scanning to achieve maximum distension although generally sufficient distension is achieved using water alone.

n Tumours near the oesophagogastric junction can be better imaged in the prone or in the decubitus position. Tumour is seen as increased stomach wall thickness.

n Invasion to adjacent organs like the pancreas can be seen by loss of fat plane. Hepatic metastasis (sensitivity 65–90%) and accuracy of N-stage 40–70%.

6. ***EUS***

n Best modality to determine depth of invasion (T-stage).

n Best to differentiate between T1 and T2 (EGC versus AGC).

n Accuracy of perigastric lymph node is comparable with CT abdomen.

n EUS may overestimate T stage, but can under stage N stage.

n Cannot replace CT-scan for detection of distant metastasis.

n Lymph node biopsy is also possible with linear array equipment.

7. ***Barium meal***

n Sensitivity to detect EGC is poor.

n Seen as filling defect or ulceration.

**Benign ulcer Malignant ulcer**

n Symmetrical ulcer n Asymmetrical ulcer

n Smooth margin n Irregular margin

n Radiolucent band n Loss of distensibility

between ulcer & lu- & nodularity

men (Hampton line)

n Symmetrical n Asymmetrical folds

radiating folds

8. ***Tumour markers***

n No reliable tumour markers identified for gastric cancer.

9. ***Diagnostic laparoscopy***

n Laparoscopy is established for direct visualization of low-volume peritoneal and hepatic metastasis as well as assessing local spread or operability.

n Around 24% operable patients become inoperable after laparoscopy.

10. ***PET scan***

n The combination of metabolic assessment with 2-[18F] fluoro-2-deoxy-d-glucose (18F-FDG) PET and integrated CT provides both functional and anatomical data.

n The key advantage of the technique is that patient position is unchanged between each procedure and this allows for reliable co-registration of the PET and CT data.

**Staging Conventions**

The guidelines recommended that if >50% of the tumour involved the oesophagus the tumour should be classified as oesophageal, if <50% involved the stomach the tumour as gastric tumour. Tumours exactly at the junction should be classified according to their histology, so squamous cell,

small cell and undifferentiated carcinomas should be oesophageal and adenocarcinomas should be gastric.

**TNM Staging**

Tis : Ca in situ

T1 : Mucosa or submucosa

T2 : Muscularis propria

T3 : Serosa

T4 : Adjacent organ

N0 : No regional lymph nodes metastasis

N1 : Metastasis in 1–2 regional lymph nodes

N2 : Metastasis in 3–6 regional lymph nodes

N3 : Metastasis in 7 or more regional lymph nodes

(N3a, Metastasis in 7–15 regional lymph nodes; N3b, metastasis in >15 regional lymph nodes)

M0 : No metastasis

M1 : Distant metastasis

**Stages 5-yr survival**

**Ia** T1N0M0 95%

**Ib** T1N1M0 82%

T2N0M0

**II** T1N2M0 55%

T2N1M0

**IIIA** T2N2M0 30%

T3N1 M0

**IIIB** T3N2M0 15%

T4N3M0

**IV** Any T any N M1 2%

**Management for Advanced Gastric Cancer**

The management of gastric cancer requires a multi-disciplinary approach. Complete surgical resection is the only therapy, which offers potential cure of gastric cancer. Curative surgery is not possible in the case of more than half of the patients because of the advanced stage of the tumour. Five-year survival in patients with a resectable tumour is around 35–45%, and it is less than 5% in those who undergo palliative resection. The hospital mortality rates in patients after esophagectomy and gastrectomy are 5% and 6–7%, respectively. Gastric cancer is associated with a high tendency of lymph node involvement. The cancer gradually spreads to the lymph nodes from the primary site, and nodal involvement is one of the most important prognostic factors. Thus, extent of the lymphadenectomy is the most important therapeutic aspect.

**Surgery**

1. Curative surgery as well as surgery to palliate dysphagia and gastric outlet obstruction.

2. Important issues in curative surgery for advanced gastric cancer:

n Extent of luminal resection

n Lymph node dissection

**Radical Gastrectomy**

1. Minimum 5 cm proximal margin, resection of greater and lesser omentum – Subtotal gastrectomy is preferred.

2. Lymph node dissection – D2 dissection is better than D1 dissection although it is associated with a little more morbidity.

3. Splenectomy and distal pancreatectomy if nodal involvement or direct infiltration to the splenic hilum.

**Lymph Node Dissection**

1. In gastric adenocarcinoma, mucosal disease is associated with a 0–3% incidence of lymph node metastases, and this increases to 20% for deep submucosal disease.

2. Sixteen different lymph node stations around the stomach have been identified. The lymph node stations along the lesser curvature (stations 1, 3 and 5) and the greater curvature (stations 2, 4 and 6) of the stomach have been grouped as N1. The nodes along the left gastric artery (station 7), the common hepatic artery (station 8), the celiac artery (station 9) and the splenic artery (stations 10 and 11) have been grouped as N2. N3 group encompasses the lymph nodes along the hepatoduodenal ligament (station 12), at the posterior site of the pancreas (station 13), and at the root of the mesentery (station 14). Finally, the lymph nodes around the middle colic artery (station 15) and lower paraesophageal lymph node and diaphragmatic lymph (station 16) are grouped as N4. D1, D2, and D3 are the names given to the procedures that depend on the range of lymphadenectomy.

3. D1 dissection – lymphadenectomy from stations No.1 to 7.

4. D1+ includes D1 stations plus stations No.8a, 9, and 11p.

5. D2 dissection – D1 stations plus stations No.8a, 9, 10, 11p, 11d and 12a.

6. D3 dissection – Nodes in hepatoduodenal ligament.

7. Morbidity is more in D2 dissection Some consider D3 as distant metastasis.

8. Two schools of thought about lymph node dissection: In Eastern countries, D2 lymphadenectomy has been considered the standard procedure since the 60’s, particularly in Japan, whereas in Western countries, D2

lymphadenectomy was not considered a standard procedure in clinical practice.

9. Higher rate of mortality and surgical complications with D2 procedure were mostly related to distal pancreatectomy and/or splenectomy, which previously were included in the standard D2 lymphadenectomy and considered necessary for an adequate nodal dissection.

Results of a Dutch study with 15 years of follow-up showed that the rate of loco-regional recurrence was significantly lower in patients treated with D2 lymph-adenectomy than in those who underwent D1 dissection, which showed a survival benefit with the enlarged dissection.

***Reconstruction Following Curative Surgery***

n For total gastrectomy – Roux-en-Y reconstruction **(Fig. 21.2)**

n For subtotal gastrectomy – Billroth II or Roux-en-Y reconstruction **(Fig. 21.3)**

**Robot-assisted Lymph Node Dissection**

The role of robotics in gastric cancer surgery is increasing. Robotic procedures are more advantageous than laparoscopic

techniques in that they enable use of twisted instruments with 7 degrees of freedom and motion scaling, tremor filtering and 3D visualization of high-resolution images. The ability to view such high-resolution images is especially useful in the infrapyloric, suprapancreatic area and splenic hilum, where an adequate recognition of tiny anatomical structures during lymphadenectomy is of the highest importance. The endowrist instruments might be helpful particularly during lymphadenectomy in the suprapancreatic area, which is difficult to access using linear instruments in a laparoscopic procedure.

**Neoadjuvant and adjuvant chemoradiation**

The results of the INT 0116 trial have shown the effectiveness of adjuvant radiotherapy and chemotherapy compared to those with surgery alone. A 3-year observation showed that the combination therapy showed an 11% improvement in overall survival; the median survival after the combination therapy was 36 months, whereas that after surgery alone was only 27 months. The median recurrence-free survival was 30 months in the chemoradiotherapy group and 19 months in the group receiving surgery alone. Administration of adjuvant chemo-radiotherapy after D1 lymphadenectomy reduced the incidence of local recurrence and improved survival of the patients. Neoadjuvant chemotherapy plus radical surgery has been recommended as a standard treatment for locally advanced tumours. The most commonly used protocols are ECF (epirubicin, cisplatin, 5-FU), ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, 5-FU) and EOX (epirubicin, oxaliplatin, capecitabine).

**Treatment of metastatic gastric cancer**

Palliative radiotherapy is justified in cases of unresectable GC with anaemia, and/or in the cases with pyloric or cardiac obstruction. Palliative chemotherapy improves survival and quality of life. Following the results of the ToGA trial, “trastuzumab” in combination with capecitabine or 5-FU and cisplatin is now the standard of care for HER2-positive GCs.

**Factors Determining Prognosis**

1. Age >50 yrs

2. Tumour size

3. Depth of tumour invasion

4. Intestinal type has better prognosis than diffuse type

5. Undifferentiated histology

6. Lymphatic/vascular invasion

7. Tumour growth pattern (expansile has better prognosis than infiltrative)

8. Nodal metastasis

9. Status of tumour resection margin

**Classification of Gastric Cancer**

1. Main types of gastric cancer:

n Early gastric cancer (EGC)

n Advanced gastric cancer (AGC)

2. Lauren classification

n Diffuse type

- No glandular structure, undifferentiated cells proliferate in sheets.

- Poorly differentiated, diffuse types originate from normal gastric mucosa.

- Worse prognosis

- More common in low-risk population

n Intestinal type

- Epithelial cells that form glandular structure; and is more common in countries where gastric cancer is endemic. It is associated with chronic atrophic gastritis and intestinal metaplasia.

- Environmental and dietary risk factors including *H. pylori*

- Dysplasia-carcinoma hypothesis

- More favorable prognosis

n Unclassified

- Mixed histological features

3. Borrmann’s classification (for AGC)

n Type I polypoid carcinoma

n Type II fungating carcinoma

n Type III ulcerated carcinoma

n Type IV diffusely infiltrative carcinoma

4. WHO classification of stomach tumour

**Epithelial Tumour**

1. Adenoma – Dysplasia

2. Carcinoma

n Adenocarcinoma

n Papillary adenocarcinoma

n Mucinous adenocarcinoma

n Signet ring cell carcinoma

n Tubular adenocarcinoma

n Squamous cell carcinoma

n Small cell carcinoma

n Adenosquamous carcinoma

***Non-Epithelial Tumour***

1. Leiomyoma

2. Schwannoma

3. Glomus tumour

4. Leiomyosarcoma

**Risk Factors of Adenocarcinoma**

1. Definite

n FAP (familial adenomatous polyposis)

n Adenoma

n Dysplasia

n *H. pylori*

n Chronic atrophic gastritis

n HNPCC 1st degree relative

n Intestinal metaplasia

n Post gastrectomy

2. Probable

n Peutz-Jegher syndrome

n Cigarette smoking

n High salt intake

n Low fresh fruit intake

n Pernicious anaemia

n Low ascorbate intake

3. Possible

n Gastric ulcer

n Menetrier’s disease

**Natural History of Gastric Dysplasia**

1. Mild dysplasia regresses in 60% of patients.

2. Moderate dysplasia progresses to severe dysplasia in 20–40%.

3. High grade progresses to cancer in 75–100%.

**Atrophic Gastritis and Gastric Cancer**

1. Atrophic gastritis leads to intestinal type of gastric cancer.

2. Chronic atrophic gastritis leads to hypochlorhydria, which leads to decrease in acid production, colonization of bacteria and endogenous production of N-nitroso compounds lead to the development of cancer.

***H. pylori* and Gastric Carcinogenesis**

1. *H. pylori* infection is a common cause of gastrointestinal problems, but only a few patients with *H. pylori* infection develop a severe disease such as peptic ulcer (10–15%) or GC (1–3%). *H. pylori* contributes to the development of gastric neoplasia by promoting inflammation in the gastric mucosa (gastritis), which leads to sequential histopathologic changes that may result in the development of GC. The exact pathoophysiological

mechanisms and the role of environmental risk factors and host genetic susceptibility in the progression of gastric carcinogenesis have not been completely elucidated thus far.

2. *H. pylori* infection is involved in the early stage of development of chronic atrophic gastritis but not in the progression of atrophic gastritis to gastric cancer.

3. Infection with vacAC1, vacAm-1 and cagA strains of *H. pylori* are associated with an approximate 6-fold increases in the risk of GC.

4. Intestinal type of gastric cancer.

5. Carcinogenesis is the result of chronic inflammation, oxidative stress, DNA damage by free radicals and down-regulation of -catenin.

**Epstein–Barr Virus (EBV) and Gastric Cancer**

1. The prevalence of Epstein-Barr virus (EBV) in 5–16% of gastric carcinomas, which supports its possible role as an aetiologic agent of GC.

2. EBV in carcinoma biopsies indicates that the tumour has been formed by the proliferation of a single infected cell.

**Gastric Polyp and Gastric Cancer**

1. Around 90% of gastric polyps are hyperplastic without any malignant potential.

2. Adenomatous polyp has malignant potential and requires surveillance.

**Post Gastrectomy and Gastric Cancer**

1. Around 5% of all gastric cancers occur in postoperative stomach.

2. Long lag period between the surgery and the development of cancer.

3. At or near surgical anastomosis.

4. Usually advanced.

5. More common with Billroth II than Billroth I operation.

6. May be related to low acid, which leads to bacterial overgrowth or bile and pancreatic juice reflux in the stomach.

**Menetrier’s Disease and Gastric Cancer**

1. Hypertrophy of the surface mucus cells and atrophy of the parietal and chief cells.

2. Relationship between Menetrier’s disease and gastric cancer has not been proved.

**Gastric Ulcer and Gastric Cancer**

Studies failed to confirm an increased incidence of gastric cancer. Less than 10% gastric ulcers progress to cancer.

Biopsy from the edge of ulcer is better to confirm malignant potential of the ulcer.

**Points to Remember**

1. Patients with family history of gastric cancer have 2–3-fold increased chances of gastric cancer and it usually develops in early age and diffuse variety.

2. FAP/HNPCC develop intestinal type of cancer.

3. Cox-2 overexpression is seen in 30% patients with gastric cancer.

4. Chronic atrophic gastritis is defined as the loss of specialized glandular tissue in the stomach mucosa.

**Early gastric cancer (EGC)**

1. EGC is defined as cancer that does not penetrate to muscularis mucosae.

2. Higher prevalence in Japan. Accurate pretreatment staging is critical in identifying EGC patients with disease that is limited to the mucosa and submucosa (stage T1) and who are candidates for endoscopic mucosal resection of most lesions and is the preferred technique (ESD).

3. Around 70% of patients with EGC have symptoms of uncomplicated dyspepsia.

4. Lesser curvature and around the angulus is the most common site.

5. Well-differentiated adenocarcinoma is the most common histology.

6. 5-year survival is greater than 90%.

7. Lymph node metastasis present in 0–7%.

8. 3–13% of EGCs are multifocal and carry a worse prognosis. Studies show that after 30–39 months, two-third of patients with EGC will progress to an invasive cancer.

**Japanese Research Society Classification for EGC**

**Type I** Protruded

**Type II** Superficial

a) Elevated

b) Flat

c) Depressed

**Type III** Excavated

**Management of EGC**

***EMR (Endoscopic Mucosal Resection) and ESD (Endoscopic Submucosal Dissection)***

1. Widely done in Japan

2. Indications

n Cancer involving mucosa without lymph node involvement

n <2 cm for elevated lesion and <1 cm for depressed lesion

n No evidence of multiple gastric cancers

n Intestinal type of tumour

3. ESD permits en-bloc resection of most lesions and is the preferred technique for resecting EGC in Asia, with a complete en-bloc resection rate of 87.7% and low complication rates. ESD has been reported to outperform EMR for en bloc, complete and curative resection with lower recurrence rate.

***Photodynamic Therapy***

Role of phodynamic therapy in EGC is limited.

**Gastroesophageal (GE) Junction Tumour**

GE junction tumours are increasing in under developed countries. There is strong association of *H. pylori* infection and GE junction tumour. The hypochlorhydria associated with *H. pylori* in association with ammonia production from urea by the bacteria may protect the lower oeso-phagus by changing the content of the refluxing gastric juice. In countries with an increase in oesophagogastric junctional cancer, there has been a corresponding decrease in incidence of *H. pylori* infection. Furthermore, com-munity-based approaches to eradicate *H. pylori* infection in the treatment of ulcer and non-ulcer dyspepsia may be inadvertently contributing to the increase in these cancers.

**Siewert Classification**

1. Type I: Cancer associated with Barrett’s oesophagus or true oesophageal cancer.

2. Type II: Tumour at true GE junction (within 2 cm of squamocolumnar junction).

3. Type III: Tumour of proximal stomach.

The guidelines recommended that if >50% of tumour involved the oesophagus the tumour should be classified as oesophageal, if <50% classified as gastric.

**Surgical Management of GE Junction Tumour**

Cardia, subcardia and type II oesophagogastric junctional tumours should be treated by transhiatal extended total gastrectomy or oesophagogastrectomy.

**Chemoradiation in GE Junction Tumour**

1. Preoperative chemoradiation improves the long-term survival over surgery alone.

2. There is no evidence to support the use of preoperative radiotherapy in oesophageal adenocarcinoma.

3. Preoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU) improves long-term survival over surgery alone.

4. Perioperative chemotherapy (combined preoperative and postoperative) conveys a survival benefit and is the preferred option for type II and III oesophagogastric junctional adenocarcinoma.

**Further Reading**

1. Fuchs CS, Mayer RJ. Gastric carcinoma*. N Engl J Med* 1995; 333:32–41.

2. Macdonald JS, Smalley SR, Benedetti J, et al. Chemo-radiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.

3. Uemura N, Okamoto S, Yamamoto S, et al. H*elicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;345:784–89.

4. Hallinan JT, Venkatesh SK. Gastric carcinoma: imaging diagnosis, staging and assessment of treatment response. *Cancer Imaging* 2013;13:212–27.

5. Blakely AM, Miner TJ. Surgical considerations in the treatment of gastric cancer. *Gastroenterol Clin North Am* 2013; 42:337–57.

6. Lordick F, Siewert JR. Recent advances in multimodal treatment for gastric cancer: a review. *Gastric Cancer* 2005; 8:78–85.

7. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial*. Lancet Oncol* 2010;11:439–49.

8. Lawson JD, Sicklick JK, Fanta PT. Gastric cancer. *Curr Probl Cancer* 2011;35:97–127.

9. Yamamoto M, Rashid OM, Wong J. Surgical management of gastric cancer: the East vs West perspective. *J Gastrointest Oncol* 2015;6:79–88.

10. Sasako M, Saka M, Fukagawa T. Modern surgery for gastric cancer—Japanese perspective*. Scand J Surg* 2006;95:232–5.

11. Macdonald JS, Smalley SR, Benedetti J, et al. Chemo-radiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.

12. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;3:CD004064.

13. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2016;27:38–49.

14. Robert Sitarz, Magorzata Skierucha, Jerzy Mielko. Gastric cancer: epidemiology, prevention, classification, and treatment. *Cancer Management and Research* 2018;10:239–48.

**Chapter 22.**

**Postoperative Stomach**

**Introduction**

Previously, postoperative stomach was described as the condition following gastrojejunostomy, partial gastrectomy, including Billroth I and II surgeries. In the era of proton pump inhibitors, surgery for peptic ulcer disease has become very rare. Bariatric surgery is increasingly being accepted as a viable treatment for managing the growing obesity epidemic. Surgery can provide a sustainable long-term option for weight loss. The three most common bariatric surgical procedures are laparoscopic vertical sleeve gastrec-tomy, Roux-en-Y gastric bypass and mini-gastric bypass. Postoperative stomach issues have increased because of an increased prevalence of bariatric surgery. Issues can be short term in relation to decrease in capacity of stomach, increase satiety and related to obstruction as well as long term in the form of nutritional deficiencies due to gastrec-tomies.

**Clinical History**

1. Vomiting

n How soon after meal?

n Content of the vomitus – bile/food/blood stain

n After what interval it started following surgery?

n Does vomiting relieve abdominal pain? – If yes, it may indicates afferent loop obstruction

n Quantity of vomitus – small quantity secondary to reflux while large quantity is secondary to loop obstruction/adhesions/bands/internal hernias.

n Projectile vomiting indicates more of an afferent loop obstruction

n What are the factors aggravating the vomiting

2. Abdominal pain

3. Diarrhoea

n Post vagotomy diarrhoea (see below)

n Bacterial overgrowth syndrome

n Short bowel syndrome

n Malabsoption syndrome

4. Postprandial fullness indicates gastroparesis

5. Postprandial flushing, dizziness indicate early dumping syndrome

6. Postprandial hypoglycemia indicates late dumping syndrome

7. Anorexia

8. Recent onset of marked weight loss should raised the possibility of development of gastric cancer in long standing postoperative stomach.

**Past History**

1. Duration of surgery

2. Type of surgery

3. Preoperative diagnosis if available

4. What was the indication for surgery? – Persistent vomiting, suspected malignant gastric ulcer or gastrointestinal bleeding

5. Was there any immediate postoperative complication?

6. Was dietary modification advised following surgery?

**Physical Examination**

1. Physical examination may be normal in post bariatric patient.

2. Abdominal mass indicates the development of gastric cancer or intussusceptions.

**Investigations**

1. **Biochemistry**

2. **Upper endoscopy**

n Upper endoscopy is the cardinal test to diagnose complications following gastric surgery.

n It can detect perastomal ulceration, gastric cancer developing in the gastric remnants.

3. **Barium study** (rarely done now)

n Barium study is indicated when endoscopy is not available or it cannot be done in view of suspected obstruction.

n Barium delineates exact anatomy in postoperative stomach.

4. **CT scan abdomen**

n Most common modality to evaluate complications following bariatric surgery.

**Management**

Management of complications of postoperative stomach varies according to primary surgery performed (bariatric versus non-bariatric procedures).

**Vagotomy**

1. **Truncal vagotomy**: Denervates entire stomach, pancreas, biliary tree, small intestine and proximal colon. Truncal vagotomy is rarely performed now.

2. **Selective vagotomy**: Denervates motor and acid secreting apparatus of entire stomach.

3. **Highly selective vagotomy**: Denervates acid secretory apparatus, preserving branch to antrum. In highly selective vagotomy, nerve of Latarget is preserved and criminal nerve of Grasi is divided.

Vagotomy and drainage procedure is infrequently performed due to acid suppressant like proton pump inhibitor. As vagus coordinates motor activity of antrum and pylorus, vagotomy leads to pylorospasm. Thus, drainage procedure is required in truncal and selective vagotomy.

**Early Postoperative Complications Following Vagotomy**

1. Gastric atony with delayed gastric emptying in spite of adequate drainage procedure. Size of gastrojejunostomy is not co-related with gastric emptying.

2. Dysphagia

n Suture near oesophageal hiatus

n Haematoma

n Gastric bezoar

n Temporary due to oedema near suture line

n Oesophageal diverticulum

**Late Postoperative Complications Following Vagotomy**

1. Post vagotomy diarrhoea

2. Post vagotomy reflux oesophagitis

3. Development of cholelithiasis

**Post Vagotomy Diarrhoea**

Post vagotomy diarrhoea develops in approximately 25% of patients with truncal vagotomy, 3% with selective vago-tomy and less than 1% with highly selective vagotomy. Symptoms of post vagotomy diarrhoea improve over 6 months to 1 year of surgery. Postvagotomy diarrhoea is commonly not seen in Indian subcontinent; may be due to dietary differences.

***Causes***

1. Gastric alkalinization leads to colonization of bacteria.

2. Alteration in receptive relaxation and gastric emptying.

3. Alteration of emptying of bile in the duodenum.

***Medical Management***

1. Dietary changes like increased fibre content and low lactose content.

2. Codeine sulfate and loperamide to control the frequency of stool.

3. Octreotide also can reduce the frequency of stool.

***Surgical Management***

1. Surgical therapy to decrease intestinal transit time; required only when medical management fails.

2. Conversion to Roux-en-Y gastrojejunostomy.

3. Construction of a 10–15 cm anti-peristaltic jejunal loop, interposed 100 cm to the ligament of Treitz.

**Postvagotomy Cholelithiasis**

1. More with truncal vagotomy.

2. Hepatic branches of anterior vagal trunk play a role in regulating gallbladder motility and preventing stone formation.

3. Management is required only in symptomatic cholelithiasis.

**Drainage Procedure with Truncal Vagotomy**

1. Gastrojejunostomy

2. Heineke–Mikulicz pyloroplasty

3. Finney or Jabouly pyloroplasty

**Vagotomy with Antrectomy (rarely performed in the era of PPI)**

1. Lowest recurrence ratebut highest postoperative complications compared with other procedures.

2. 40% of stomach is removed proximal to 1 cm of duodenum.

3. Reconstruction by either Billroth I or Billroth II surgery.

**Postoperative Complications Following Gastrectomy and Reconstruction**

***Early Complications***

1. Bleeding

n Intraluminal

n Intraperitoneal

2. Gastrointestinal leak – duodenal stump, anastomotic leak

3. Postoperative pancreatitis

4. Obstruction to afferent loop

5. Injury to the bile duct, pancreaticduct or postoperative pancreatitis

***Late Complications***

1. Ulcer recurrence: Stomal & recurrent ulcers

2. Mechanical disorders

n Chronic afferent loop

n Chronic efferent loop

n Internal hernia

n Jejunogastric intussusceptions

3. Physiological disorders

n Blind loop syndrome

n Postvagotomy diarrhoea

n Alkaline reflux

n Dumping syndrome

n Roux stasis syndrome

4. Malabsorption

5. Bezoar formation

6. Carcinoma in gastric remnant

7. Gastrojejunocolic fistula

***Ulcer Recurrence***

1. Rare

2. Secondary due to incomplete vagotomy

3. Retained antrum/G-cell hyperplasia in case of gastrectomy

4. Chronic smoking/NSAID use

5. Hypersecretory state like Zollinger-Ellison syndrome

***Marginal Ulcer***

1. Near gastrointestinal site

2. Jejunal injury due to acid, alkaline reflux

3. Requires revision surgery (conversion to roux loop or Brown’s procedure) if not improved with medical management

***Chronic Afferent Loop Obstruction***

1. After Biliroth II reconstruction

2. Larger afferent loop is predisposed to kinking/twisting/volvulus

3. Also secondary to adhesion or enterolith

4. Bilious vomiting and vomiting relieving abdominal pain

***Chronic Efferent Loop Obstruction***

1. Due to adhesion/internal hernia

2. Roux-en-Y surgery

***Jejunogastric Intussusception***

1. Mass is palpable in epigastrium

2. Patient presents with abdominal pain and vomiting

3. Treated by reconstruction

***Alkaline Reflux Gastritis***

1. Incidence of alkaline reflux gastritis is around 5–15%.

2. This is because detergent activity of bile causes injury to gastric and oesophageal mucosa.

3. It occurs with Billroth II surgery/loop gastrojejunostomy.

4. Medical management usually not very effective.

5. Prokinetic drugs have some role to play.

6. Roux-en-Y reconstruction may be required.

***Early Dumping Syndrome***

1. Around 15% patients develop early dumping syndrome.

2. Symptoms observed within 20 min after meal.

3. Early dumping syndrome is due to rapid emptying of hypertonic gastric contents into the duodenum, which leads to rapid influx of fluid into the intestinal lumen and intravascular volume contractions. It also causes release of vasoactive hormones.

4. Symptoms are exaggerated by consuming high carbohydrate/simple sugar.

*Management of Early Dumping Syndrome*

1. Increased frequency and decreased volume of meals.

2. Avoiding concentrated carbohydrate intake.

3. Taking liquid 30 min after solids.

4. More protein and complex carbohydrate in the diet.

5. Octreotide may be beneficial if taken before each meal.

6. Reconstruction can be performed by Roux-en-Y surgery.

7. Henley loop: Construct 10 cm isoperistaltic jejunal loop between gastric remnant and jejunum to reduce rapidly emptying gastric content in the duodenum.

8. Oral 50 g of glucose is used as provocative test.

***Late Dumping Syndrome***

1. Late dumping syndrome occurs 1–2 hrs after meal.

2. Rapid absorption of glucose and hyperglycaemia lead to robust increase in insulin, which leads to reactive hypoglycaemia.

3. Improved with decreased simple sugar in the diet.

4. Octreotide may be helpful.

***Roux Stasis Syndrome***

1. Delayed transit of food in the Roux limb even after completion of gastrectomy.

2. Treated by adjusting Roux loop to 40 cm.

***Carcinoma of Gastric Remnant***

1. Prevalence of gastric cancer in gastric remnant is 1–15%.

2. Men are more commonly affected than women.

3. Stoma and the lesser curvature are the most common sites.

4. Needs reevaluation from malignancy perspectives and management accordingly.

**Risk Factors for Development of Gastric Cancer**

1. Billroth II surgery

2. Incomplete vagotomy

**Surgery for Duodenal Ulcer**

1. For perforation, Graham patch closure

2. Truncal vagotomy ± drainage procedure

3. Highly selective vagotomy

4. Truncal vagotomy + Antrectomy + Reconstruction

***Surgery for Gastric Ulcer and its Recurrence following surgical intervention* (Table 22.1)**

1. Ulcer excision + Antrectomy (Pouchet procedure)

2. Antrectomy + Vagotomy

3. Subtotal gastrectomy + Roux-en-Y anastomosis

**Surgery Recurrence Morbidity Mortality**

Vagotomy + 10–15% 5% 0.7%

drainage

Vagotomy + 0–2% 5% 1%

antrectomy

HSV 10–17% 1% 0.3%

**Complications following bariatric procedure**

1. The weight loss surgery generally involves restriction, malabsorption, or a combination of these mechanisms. Restrictive procedures decrease the size of the stomach, which result in early satiety and decreased caloric intake. The operations performed include vertical sleeve gastrectomy (VSG -more commonly done) and laparoscopic adjustable gastric banding (LAGB) (less frequently done now).

2. Unlike restrictive procedures, malabsorptive procedures decrease the degree of absorption of nutrients by the small intestine by bypassing a large portion of the small intestine. These procedures include biliopancreatic diversion with or without a duodenal switch. Bariatric surgery involving procedures, malabsorption and restriction, is known as Roux-en-Y gastric bypass (RYGB) and Mini Gastric Bypass (MGB).

3. The perioperative and postoperative mortality rates (0.07% and 0.21%, respectively) associated with LAGB **(Fig. 22.1)** are lower than those associated with other weight loss surgeries. Intractable postoperative vomiting can develop depending on band positioning, gastric prolapse, or excessive incorporation of fat into the band device. Reexploration for the adjustment of the band’s position, removal of the gastric band, or another bariatric operation may be required in the case of some patients. The incidence of late complications is as high as 8–25%. Popularity of LAGB has decreased because of low efficacy and high complications.

4. VSG **(Fig. 22.2)** is primarily a restrictive procedure for weight loss. The perioperative and postoperative mortality rates are 0.29% and 0.34%, respectively, and the rate of complications is 13%. The complications include gastroesophageal reflux (23%), vomiting (18%), gastric tube stricture (2.3%), stenosis (2.4%), leak (2.4%) incisional hernia (2.4%), gastrocutaneous fistula and weight regain. In addition, a neofundus (proximal dilation of the stomach) may form if too much fundus is left at the time of the original operation.

5. RYGB **(Fig. 22.3)** has been one of the most common weight-loss procedure performed. The perioperative and postoperative mortality rates are 0.38% and 0.72%. The most serious complication is an anastomotic leak, which occurs in 0.7% to 5% of patients. GI haemorrhages are observed in 1% of patients; a majority them are staple line hemorrhages. Dumping syndrome develops in the case of 20–25% of patients. Anastomotic stricture and bowel obstruction (adhesion, internal hernia, incisional hernia, and intussusceptions) are the major long-term complications. The incidence of developing gallstones after bariatric surgery ranges from 22 to 71%.

6. MGB is also been one of the most common weight-loss procedure performed especially in eastern part of world. The perioperative and postoperative mortality rates are 0.2% and 0.4%. The most serious complication is an anastomotic leak, which occurs in 0.2–1% of patients. GI haemorrhages are observed in 1% of patients; a majority them are staple line hemorrhages, lately it can develop from stomal ulcers ranging incidence of 2–16%. Dumping syndrome and internal herniation does not develop. Bowel obstruction (adhesion, incisional hernia and intussusceptions) are the major long-term complications along with stomal ulcers. The incidence of developing gallstones after MGB is said to be more than RYGB.

7. Highest amount of weight loss is achieved using biliopancreatic diversion with duodenal switch (BPDDS, **Fig. 22.4**) because of the malabsorptive nature of the operation [79% estimated weight loss (EWL) for BPDDS vs 67% EWL for RNYGBP]. This procedure has the highest postoperative complications. Early complications include anastomotic leak, anastomotic obstruction and GI haemorrhages. Late complications include small bowel obstruction, malnutrition and incisional hernias.

8. Revision procedures are required either because of complications of primary bariatric procedure or regain of weight. A revisional procedure can be defined as a conversion, correction or reversal.

**Further Reading**

1. Csendes A, Burgos AM, Smok G, et al. Latest results (12–21 years) of a prospective randomized study comparing Billroth II and Roux-en-Y anastomosis after a partial gastrectomy plus vagotomy in patients with duodenal ulcers. *Ann Surg* 2009;24:189–94.

2. Mitty WF Jr, Grossi C, Nealon TF. Chronic afferent loop syndrome. *Ann Surg* 1970;172:996–1001.

3. Bult MJ, van Dalen T, Muller AF. Surgical treatment of obesity. *Eur J Endocrinol* 2008;158:135–45.

4. Chang SH, Stoll CR, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA* 2014;149:275–87.

5. Arterburn DE, Olsen MK, Smith VA, et al. Association between bariatric surgery and long-term survival. *JAMA* 2015; 313:62–70.

6. Hamdan K, Somers S, Chand M. Management of late postoperative complications of bariatric surgery. *Br J Surg* 2011;98:1345–55.

**Chapter 23.**

**Ascites**

**Introduction**

Abdominal distension is a common problem in gastro-enterology. It could be due to a sensation of fullness or bloating and is usually associated with functional gastro-intestinal diseases. Obesity may be associated with abdominal prominence. Ascites is an accumulation of fluid in the peritoneal cavity. This section focuses on the approach for the management of patients with ascites. Cirrhosis of the liver leading to portal hypertension is the leading cause of ascites (75%) followed by peritoneal carcinomatosis, cardiac failure and tuberculosis in the developing world. Ascites is the most common complication of cirrhosis and >60% of patients with compensated cirrhosis develop ascites within 10 years during the course of their disease. Development of ascites is associated with a poor prognosis and impaired quality of life in patients with cirrhosis. Thus, patients with ascites should generally be considered for referral for liver transplantation. The mortality rate is approximately 40% at 1 yr and 50% at 2 yrs. The most reliable factors in the prediction of poor prognosis include hyponatremia, low arterial pressure, increased levels of serum creatinine and low levels of urinary sodium. These parameters are not included in the Child-Turcotte-Pugh score (CTP score) and among them, only serum creatinine levels are included in the model for end-stage liver disease (MELD score).

**Clinical History**

1. Abdominal distension

n Progressive increase in the size of abdomen

n Progressive increase in belt or clothing size

n Development of umbilical or inguinal hernias

n Sensation of “stretching” of the flanks

2. Onset

n *Sudden onset*

- Acute Budd-Chiari syndrome

- Acute right heart failure

- Sudden decompensation of previously compensated cirrhosis

- Pancreatic ascites

n *Insidious onset*

- Decompensated cirrhosis of liver

- Chronic Budd-Chiari syndrome

- Tuberculosis

- Neoplasm

- Hypoalbuminemia

- Nephrotic syndrome

- Hypothyroidism

- Right heart failure

- Constrictive pericarditis

3. Associated pedal oedema

n In congestive heart failure, oedema precedes ascites, while in cirrhosis liver, usually abdominal distension precedes pedal oedema

4. Jaundice

n Budd-Chiari syndrome

n Cirrhosis liver – Jaundice is mild in cirrhosis liver

n Severe jaundice indicates associated biliary obstruction, alcoholic hepatitis or development of hepatocellular carcinoma

n Congestive heart failure

5. Haemetemesis or melena

n History of haemetemesis or melena indicates portal hypertension

6. Low-grade fever, anorexia suggest tuberculosis, neoplasm

7. Abdominal pain

n Diffuse abdominal pain indicates development of bacterial peritonitis.

n Mild, diffuse abdominal ache is also present in tuberculous ascites.

n Right hypochondriac pain is due to stretching of Glisson’s capsule secondary to hepatomegaly in case of acute Budd-Chiari syndrome, heart failure and hepatocellular carcinoma.

8. Facial puffiness, constipation, oligomenorrhea and cold intolerance indicate myxedema.

9. Early morning periorbital puffiness suggests nephrotic syndrome.

10.Breathlessness and orthopnea suggest congestive heart failure or tense ascites, pushing diaphragm upward.

11.Cough with or without expectoration suggests congestive heart failure or tuberculous focus in the lungs.

12.Easy fatigability, generalized weakness and shortness of breath secondary to anaemia and hypoproteinaemia.

**Past History**

1. Past history of pulmonary tuberculosis

2. Past history of cardiac illness like rheumatic heart disease and coronary artery disease

3. Past history of hepatitis B infection

4. Personal/Social history

5. Alcohol intake: Development of alcoholic liver disease or cardiomyopathy

6. Smoking

**General Examination**

1. Abdominal distension with generalized wasting indicates neoplasm, cirrhosis liver or disseminated tuberculosis

2. Pallor – Anaemia

3. Icterus – Cirrhosis liver, Budd-Chiari syndrome, congestive heart failure

4. Increased jugular venous pressure – Congestive heart failure, absent in Budd-Chiari syndrome

5. Clubbing – Biliary cirrhosis, protein losing enteropathy

6. Pedal oedema – Pitting oedema, non-pitting oedema (myxedema)

7. Supraclavicular adenopathy (Virchow’s node) suggests underlying gastrointestinal malignancy

8. Stigmata of chronic liver disease (Ch. 12)

9. Periorbital puffiness secondary to nephrotic syndrome

10. Cutaneous markers of internal malignancy (Ch. 12)

**Abdominal Examination (Ch. 12)**

**Inspection**

1. Tensely distended abdomen with tightly stretched skin, bulging flanks and everted umbilicus is characteristic of ascites.

2. Distance from lower sternum to umbilicus is more than from umbilicus to pubic symphysis (reverse is for ovarian tumours).

3. Umbilical nodule (sister Mary Joseph’s nodule) suggests metastatic disease from gastrointestinal primary tumour.

4. Umbilical hernia

5. Dilated venous collaterals near umbilicus (caput medusa) suggest portal hypertension, whereas dilated veins over anterior abdominal wall and flanks with blood flow from below upwards suggests inferior vena cava obstruction.

6. Bulging hernia sites.

7. Visible epigastric mass with evident peristalsis from left to right suggests gastric malignancy with pyloric obstruction.

8. Nodular right upper quadrant mass suggests metastatic deposits in the liver.

**Palpation**

1. Fluid thrill

2. Firm, nodular hepatomegaly suggests cirrhosis liver, whereas hard liver suggests malignancy

3. Soft hepatomegaly suggests congestive hepatomegaly

4. Pulsatile liver indicates tricuspid regurgitation

5. Splenomegaly suggests the presence of portal hypertension

6. Palpable primary gastrointestinal or pelvic tumour

**Percussion**

1. Shifting dullness

2. Horse-shoe dullness

3. Puddle’s sign to demonstrate minimal fluid

4. Percussion over palpable mass

**Auscultation**

1. Auscultation over the enlarged liver for arterial bruit

2. Venous hum over umbilicus

**Digital Rectal Examination**

1. Palpable mass

2. Pelvic deposit (Blumer’s shelf)

**Respiratory System Examination**

1. Features of right/bilateral pleural effusion (hepatic hydrothorax)

2. Bibasilar crepitations indicates congestive heart failure

**Cardiovascular Examination**

1. Cardiomegaly

2. Murmur of tricuspid regurgitation or tricuspid stenosis

**Investigations**

1. Biochemistry/serology

2. Ultrasonography abdomen

n Confirmation of ascites.

n Ultrasound abdomen can detect as little as 100 mL fluid.

n Detection of cirrhosis liver by coarse shrunken liver, dilated portal vein (>10 mm), hepatopetal flow in portal vein, venous collaterals near splenic hilum and splenomegaly.

n Septation and internal echoes in the ascites indicate tuberculous ascites or neoplasm.

n Detection of primary or secondary hepatic neoplasm.

n Enlarged liver with dilated hepatic veins and IVC suggests congestive hepatomegaly.

n Diagnosis of Budd-Chiari syndrome using hepatic venous Doppler study.

n Identification of bowel or pelvic mass.

3. CT scan abdomen

n Spiral CT scan abdomen is better than ultrasound of abdomen.

n Can detect primary tumour in case of peritoneal carcinomatosis.

n Better detection of liver lesion, primary or secondary, than ultrasound abdomen.

4. Endoscopy

n Upper endoscopy demonstrates features of portal hypertension in the form of oesophageal and gastric varices and portal gastropathy.

n Upper endoscopy evaluation in suspected gastric malignancy with peritoneal metastasis.

n Colonoscopy evaluation in suspected colonic malignancy with peritoneal metastasis.

5.Role of diagnostic laparoscopy

n It is the gold standard test to diagnose peritoneal carcinomatosis and tuberculous peritonitis.

n Care should be taken while performing diagnostic laparoscopy in patients with suspected “mixed” ascites in cirrhosis, in view of coagulopathy and periumbilical collaterals.

**Ascitic Fluid Analysis**

Ascitic fluid analysis is the most important investigation to evaluate aetiology of ascites.

1. **Appearance of ascitic fluid**

n Clear: Suggests low protein, no pigmentation.

n Cloudy: Suggests infection.

n Red: Haemorrhagic ascites or traumatic blood-tinged ascites.

n Blood usually clots in the traumatic ascites while blood does not clot in non-traumatic ascites.

n Increased haemorrhagic ascites occurs in around 10% of patients with peritoneal carcinomatosis.

n Opaque milky: Chylous ascites (ascitic fluid triglyceride content >200 mg/dL is called chylous ascites).

n Dark brown: Biliary ascites

n Black colour: Malignant melanoma

n Straw colour: Tuberculosis

2. **Serum–ascites albumin gradient**

n Routine exudates/transudate system of pleural fluid is no more used in ascites.

n It is always advisable to calculate SAAG (serum–ascites albumin gradient, see below) rather than protein alone.

n Serum–ascites albumin gradient (SAAG) calculation is better than protein estimation to diagnose and classify ascites.

**SAAG = Serum albumin – ascites albumin**

n If SAAG is >1.1 g/dL, it indicates portal hypertensive ascites, whereas SAAG <1.1 g/dL suggests non-portal hypertensive ascites.

n Specificity and sensitivity of SAAG to detect portal hypertension is around 97%.

**SAAG >1.1 g/dL (high gradient)**

n Cirrhosis liver

n Cardiac ascites

n Budd-Chiari syndrome

n Veno-occlusive disease

n Portal vein thrombosis

n “Mixed” ascites

n Fulminant hepatic failure

**SAAG <1.1 g/dL (low gradient)**

n Tuberculosis

n Peritoneal carcinomatosis

n Nephrotic syndrome

n Pancreatic ascites

n Biliary ascites

3. **Protein**

n Ascitic fluid protein estimation has distinct value after calculating SAAG.

n Protein content >3.0 g/dL is called high protein ascites. Total ascitic fluid protein concentration should be measured to assess the risk of SBP as patients with protein concentration lower than 15 g/L have an increased risk of infection (spontaneous bacterial peritonitis, SBP).

*High protein, high SAAG ascites*

n Cardiac ascites

n Acute Budd-Chiari syndrome

*Low protein, high SAAG ascites*

n Cirrhosis liver

*Low protein, low SAAG ascites*

n Nephrotic syndrome

*High protein, low SAAG ascites*

n Tuberculosis

n Peritoneal carcinomatosis

4. **Cell count**

n Cell count in ascitic fluid helps to diagnose bacterial peritonitis or tuberculous peritonitis.

n The white blood cell (WBC) count in uncomplicated cirrhotic ascites is usually less than 500 cells/mm3, and absolute polymorphonuclear leukocyte (PMN) count is less than 250 cells/mm3.

n Any inflammatory process can result in an elevated ascitic fluid WBC count.

n The WBC count >500 cells/mm3 and PMN count >250 cells/mm3 indicate spontaneous bacterial peritonitis (SBP) in cirrhotic patients.

n Elevated WBC count with lymphocytic predominance suggests possible tuberculous ascites.

5. **Culture**

n Bed side inoculation of ascitic fluid (10 mL) in blood culture bottles is far superior to detect bacterial growth in comparison to delayed laboratory inoculation.

6. **Gram stain**

n SBP is monomicrobial infection with a low bacterial concentration (median colony count of <1 organism/mL), thus Gram stain has no value in SBP.

n It has got value in the diagnosis of free perforation of the gut, where sheets of multiple different bacteria are found.

n Direct smear to detect acid-fast bacilli in tuberculous peritonitis is never positive.

7. **Glucose**

n Ascitic fluid glucose is similar to that in serum unless glucose is being consumed by bacteria in the ascitic fluid.

n Low ascitic fluid glucose indicates infection.

8. **Lactate dehydrogenase (LDH)**

n Ascitic fluid LDH is less than half of the serum in uncomplicated ascites.

n Raised LDH suggests SBP or secondary peritonitis.

9. **Amylase**

n Markedly elevated ascitic fluid amylase (>2000 U/L) indicates pancreatic ascites or gut perforation.

10.**Bilirubin**

n Ascitic fluid bilirubin greater than serum bilirubin suggests biliary ascites or upper gut perforation.

11. **Triglyceride**

n Triglyceride level >200 mg/dL in ascitic fluid suggests chylous ascites.

12.**Cytology**

n Cytology has sensitivity of 60% in detecting malignant ascites.

n As hepatocellular carcinoma rarely metastasizes to peritoneum, cytology has no role in suspected hepatocellular carcinoma.

13.**Adenosine deaminase**

n Insensitive test to diagnose tuberculous ascites.

**Type of ascites**

**Grade I ascites**  Mild ascites only detected by

ultrasound

**Grade II ascites** Moderate symmetrical abdominal

distension

**Grade III ascites**  Ascites with marked abdominal

distension

**Ascites and Portal Hypertension**

Portal hypertension is defined by a pathological increase in portal pressure in which portal pressure gradient (PPG, pressure gradient between the portal vein and inferior vena cava) is increased above the upper normal limit of 5 mmHg.

**PPG Sequelae**

6–10 mmHg Subclinical portal hypertension

>10 mmHg Formation of oesophageal varices

(CSPH, clinically significant portal

hypertension)

>12 mmHg Ascites, variceal bleeding

1–5 mmHg Normal

***Causes of Portal Hypertension***

1. **Prehepatic**

n Portal vein thrombosis

n Splenic vein thrombosis

n Extrinsic compression of the portal vein

n Arteriovenous fistula

2. **Intrahepatic**

n Nodular regenerative hyperplasia

n Non-cirrhotic portal fibrosis (NCPF)

n Schistosomiasis

n Primary biliary cirrhosis

n Chronic hepatitis

n Haemochromatosis

n Wilson’s disease

n Alcoholic cirrhosis

3. **Posthepatic**

n Budd-Chiari syndrome

n IVC thrombosis

n Constrictive pericarditis

n Tricuspid valve disease

n Ascites in cirrhosis is derived mainly from both hepatic and splanchnic microcirculation. Ascites usually does not develop in patients with prehepatic portal hypertension.

***Starling’s Force***

Intravascular volume is maintained by hydrostatic pressure (“pushing” force) and oncotic pressure (“pulling” force). At the arterial end of the capillaries, the hydrostatic pressure is more than the oncotic pressure, while at venous end; the oncotic pressure is more than the hydrostatic pressure. Because of the difference in hydrostatic and oncotic pressure, fluids do not accumulate in the interstitial space.

Intravascular oncotic pressure is maintained by plasma proteins. Any change in the hydrostatic or oncotic pressure leads to accumulation of fluid in the interstitial space (ascites and pedal oedema). In patients with postsinusoidal portal hypertension, ascites occurs because of an increase in the hydrostatic pressure in the hepatic sinusoids. Hepatocytes have a porous sinusoidal wall. The concentration of protein in the hepatic lymph is almost the same as that in the plasma. Thus, an acute increase in hydrostatic pressure leads to increased permeability of protein. Thus, patients with postsinusoidal portal hypertension have high protein content in ascitic fluid. Patients with cirrhosis of the liver and long-standing post sinusoidal hypertension (chronic Budd-Chiari syndrome and cardiac cirrhosis) show capillarization of the sinusoidal wall. So, the sinusoidal wall becomes less porous and is impermeable to proteins. Thus, these patients have low levels of protein in the ascitic fluid.

***Why ascites does not develop in Prehepatic Portal Hypertension?***

1. Autoregulation of splanchnic circulation, thus, increase in portal pressure is not transmitted to splanchnic microcirculation.

2. Normal oncotic pressure inside the splanchnic vasculature.

3. Efficient lymphatic drainage system in intestine.

***Theories of Ascites in Portal Hypertension***

1. **Backward theory**

n Portal hypertension and low albumin lead to rupture of Starling’s equilibrium, so increases intestinal lymph formation.

2. **Forward theory**

n Peripheral vasodilatation in splanchnic bed leads to forward increase in capillary pressure and filtration coefficient, leads to increased lymph formation.

3. **Overflow theory**

n Increased plasma volume and cardiac output due to salt retention (which is the initial event) lead to more and more increase in plasma volume, so increase hepatic lymph production.

4. **Underfilling theory**

n Splanchnic vasodilatation leads to arterial underfilling, which leads to activation of RAAS and sympathetic system leading to salt and water reabsorption.

Second and fourth theories are acceptable for ascites development.

**Types of Ascites**

1. Monomicrobial non-neutrocytic bacteriascites

n Culture positive for one organism

n PMN <250 cells/dL

n No evidence of intra-abdominal cause

2. Polymicrobial non-neutrocytic bacteriascites

n Multiple organisms on culture

n PMN <250 cells/dL

n Traumatic paracentesis

3. Culture-negative neutrocytic ascites (CNNA)

n Culture sterile

n PMN >250 cells/dL

n No antibiotics given

n No explanation for increased PMN

4. Spontaneous bacterial peritonitis (SBP)

n PMN >250 cells/dL

n Culture positive with single organisms

n No evidence of surgical abdomen

n Underlying liver disease

5. Secondary bacterial peritonitis

n Culture positive for multiple organisms

n PMN >250 cells/dL

n Surgical abdomen

**Treatment of Ascites in Cirrhosis**

1. Low sodium intake – sodium intake should be around 60–90 mEq/day

2. Diuretics

3. Therapeutic paracentesis

4. Liver transplantation

***Bed Rest and Sodium Restriction***

To date, sufficient evidence indicating bed rest as part of the treatment of ascites is not available. No data are available to support the use of fluid restriction in patients with ascites with normal serum sodium levels. Moderate restriction of salt intake is an important component in the management of ascites (intake of sodium of 80–120 mmol/day, which corresponds to 4.6–6.9 g of salt/day). This is generally equivalent to a no added salt diet with avoidance of pre-prepared meals. Mobilization of ascites occurs in 10% patients with sodium restriction with normal blood levels of aldosterone and renine. Sodium restriction will decrease the requirement of diuretics. Increasing the dose of diuretics is better than decreasing the salt intake in diuretic-responsive ascites. Although there are no comparative trials to support bed rest in the management of ascites, theoretically an upright posture increases renal sodium retention. Always ensure and confirm compliance with sodium restricted diet and dose of diuretics. Spontaneous natriuresis occurs in 10–15% of patients who are only on sodium restriction.

***Diuretic Therapy***

1. **Loop diuretics**

n Furosemide, pyratinide, bumetanide, ethacrynic acid, torsemide.

n Furosemide and torsemide are the most commonly used.

Pharmacological action:

n Inhibits Na+2Cl-K+ contransporter system in thick ascending limb of loop of Henle.

n Increases synthesis of PGE2 leading to natriuresis (increases sodium excretion up to 30%).

Pharmacokinetics:

n Starts at a dose of 30 min, peak 1–2 hrs and action persists 3–4 hrs.

Dose:

n Start with 20–40 mg/day. Increase every 2 days and maximum 160 mg/day.

2. **Spironolactone**

Pharmacological action:

n Active metabolite is canrenone

n Competitive inhibition of aldosterone in distal nephron

Dose:

n Initial dose is 100 mg/day and increases to maximum 400 mg/day

***How to start diuretic therapy***

Aldosterone antagonists are more effective than loop diuretics in the management of ascites and are the diuretics of choice. Aldosterone stimulates reabsorption of renal sodium by increasing both the permeability of the luminal membrane of principal cells to sodium and the activity of the Na/K ATPase pump in the basolateral membrane. As the effect of aldosterone is slow, it involves interaction with a cytosolic receptor and then a nuclear receptor, the dosage of aldosterone antagonists should be increased every 7 days. Amiloride, a diuretic acting in the collecting duct, is less effective than the aldosterone antagonists and should be used only in those patients who develop severe side effects (gynecomastia) with aldosterone antagonists. Diuretic therapy with a single agent such as spironolactone requires several days to induce weight loss. Thus, it is advisable to begin spironolactone (100 mg) + furosemide (40 mg) in patients with cirrhosis on the first hospital day for rapid natriuresis. Spironolactone + furosemide (torsemide) are given as a single dose once daily and the dose is gradually

increased as required (e.g., spironolactone 200 mg + furosemide 80 mg). The dosage is adjusted according to weight loss and natriuresis. The ratio/dosage of both the diuretic agents can be adjusted to correct abnormal serum potassium levels. Maximum dosage of furosemide is 160 mg/day and spironolactone is 400 mg/day.

In all patients, dosage of the diuretic should be adjusted to achieve a rate of weight loss of not greater than 0.5 kg/day in patients without peripheral oedema and 1 kg/day in those with peripheral oedema to prevent diuretic-induced renal failure and/or hyponatremia. Following mobilization of ascites, the dose of diuretics should be reduced to maintain patients with minimal or no ascites to avoid diuretic-induced complications. Alcohol abstinence is the most important for the control of ascites in patients with alcohol-related cirrhosis.

**Complications of Diuretic Therapy**

The use of diuretics may be associated with several compli-cations such as renal failure, hepatic encephalopathy, electrolyte disorders, gynecomastia and muscle cramps. Although diuretic therapy has been classically considered as a precipitating factor of hepatic encephalopathy, the mechanism underlying its development remains to be clarified. Hyponatremia is another frequent complication of diuretic therapy. To date, the level of hyponatremia at which diuretics should be discontinued has not been established. However, most experts agree that diuretics should be stopped temporarily in patients whose serum sodium levels decrease to less than 120–125 mmol/L. Diuretics may cause muscle cramps. If cramps are severe, the dose of the diuretic should be decreased or stopped and albumin infusion may be administered to relieve symptoms. Furosemide should be discontinued if there is severe hypokalaemia (serum potassium levels <3 mmol/L). Aldosterone antagonists should be discontinued if patients develop severe hyper-kalaemia (serum potassium levels>6 mmol/L).

**Refractory Ascites**

Refractory ascites is defined as ascites that cannot be mobilized or early recurrence (i.e., after therapeutic paracentesis) that cannot be prevented with medical therapy.

***Subtypes of Refractory Ascites***

1. Diuretic-resistant ascites is that which cannot be mobilized (loss of body weight less than 200 g/day after 4 days) or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction (approximately 50 mEq/day) and aggressive diuretic therapy (spironolactone 400 mg/day plus furosemide 160 mg/day).

2. Diuretic-intractable ascites is that which cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage (hepatic encephalopathy, hyponatremia and hypo- or hyperkalaemia).

**Recidivant Ascites**

Recidivant ascites is ascites that recurs frequently (on three or more occasions within a 12-month period) despite dietary sodium restriction and adequate diuretic dosage.

***Large-volume Paracentesis***

*Indications*

1. Tense ascites

2. Refractory ascites

*Contraindications*

1. Clinically evident fibrinolysis

2. Clinically evident disseminating intravascular coagulation

*Replacement Fluid*

1. The removal of large volumes of ascitic fluid is associated with circulatory dysfunction characterized by a reduction of effective blood volume, a condition known as post-paracentesis circulatory dysfunction (PPCD).

2. The most effective method to prevent circulatory dysfunction after LVP is the administration of albumin. Albumin is more effective than other plasma expanders (dextran-70, polygeline) for the prevention of PPCD. When less than 5 L of ascites are removed, dextran-70 (8 g/L of ascites removed) or polygeline (150 ml/L of ascites removed) show efficacy similar to that of albumin. Polygeline is no longer used in many countries because of the potential risk of transmission of prions.

**Drugs Contraindicated in Patients with Grades 2 and 3 Ascites**

1. Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with ascites because of the high risk of developing further sodium retention, hyponatremia and renal failure.

2. Drugs that decrease arterial pressure or renal blood flow such as ACE-inhibitors, angiotensin II antagonists or 1-adrenergic receptor blockers should generally not be used in patients with ascites because of increased risk of renal impairment.

3. The use of aminoglycosides is associated with an increased risk of renal failure.

4. Non-selective beta blocker (NSBB) should be discontinued once patient develop moderate-to-severe ascites as it reduces preload and thus worsening ascites.

**Surgical Management of Ascites**

***Surgical Methods***

1. Side-to-side shunt (Ch. 26)

2. TIPS (transjugular intrahepatic porto-systemic shunt)

3. Peritoneovenous shunt

4. Automated low-flow ascites pump or ALFA pump system

5. Liver transplantation (Ch. 26)

Reduction of sinusoidal hypertension is the main goal in surgical management of ascites. End-to-side portocaval shunt and distal splenorenal shunt do not decompress sinusoidal hypertension, so these procedures have no role in the management of ascites.

***Peritoneovenous Shunt***

Shunting of ascitic fluid from high-pressure peritoneal cavity to low-pressure superior vena cava **(Fig. 23.1)**.

1. Le Veen shunt

2. Denver shunt

3. Minnesota shunt

Essentially, a peritoneovenous shunt is a device designed to transfer ascitic fluid from the abdominal cavity to systemic circulation through a tube ending in the superior vena cava connected through a one-way valve. This device was used extensively in the 1970s and 1980s for the treatment of refractory ascites in cirrhosis. Although the system was pathophysiologically sound, its use progressively declined during the 1990s because of a high incidence of severe adverse events, high rates of obstruction, lack of survival benefits and development of new procedures such as transjugular intrahepatic portosystemic shunt (TIPS). Therefore, this procedure is rarely used these days. Placement of a peritoneovenous shunt may hinder the placement of a TIPS in the future and may complicate liver transplant surgery given its ability to produce peritoneal adhesions, which has limited its use in today’s practice. A peritoneovenous shunt can only be considered in the rare case of patients who frequently require large volume paracentesis (LVP) and in those who are not candidates for TIPS or transplant.

*Complications of Peritoneovenous Shunt*

1. Late

n Malfunction

n Sepsis

n Central vein thrombosis

n Pulmonary embolism

2. Early

n Shunt occlusion

n Malfunction

n DIC

n Sepsis

n CCF

n Variceal haemorrhage

n Air embolism

**Automated Low-flow Ascites Pump or ALFA Pump System**

The ALFA pump system is a subcutaneously implanted battery powered pump that is connected to a catheter placed in the abdominal cavity and another catheter connected to the bladder. It removes ascites as it forms by transferring it to the bladder where it is eliminated through normal urination. Implantation can be performed under local or general anaesthesia, which takes about 45 min. It is indicated for the management of refractory and recurrent ascites due to liver

cirrhosis, in which massive and uncontrolled fluid accumulation occurs in the abdominal cavity. The ALFA pump is recharged wirelessly through the skin, moves 5 L of ascites per charge and can be wirelessly programmed by the physician.

**Approach for Patients with Refractory Ascites**

1. Onset of refractory ascites denotes further progression of cirrhosis, and therefore, is associated with a worse prognosis than that of patients with cirrhosis and uncomplicated ascites.

2. LVP + albumin and the transjugular intrahepatic porto- systemic shunt (TIPS) improve the quality of life of patients and delay or prevent the recurrence of ascites, but neither of the procedures them have been shown to improve patient survival.

3. The median survival of patients with refractory ascites is approximately 6 months. Therefore, patients with refractory ascites who have not been evaluated for liver transplant candidacy should be evaluated without delay.

***The following approach is recommended in patients with refractory ascites***

1. LVP is the standard treatment for patients with refractory ascites; albumin is added if more than 5 L of fluid is removed at once. If 5 L of fluid is removed, a plasma volume expander can be utilized. To reduce the frequency of repeated paracentesis, patients may continue with the maximally tolerated dose of the diuretic provided that the urinary sodium level is >30 mEq/L. Because paracentesis does not affect renal sodium retention, all patients should be given diuretics if renal function is acceptable.

2. Recent studies have shown a very low prevalence (0–3.5%) of spontaneous bacterial peritonitis (SBP) in patients undergoing therapeutic paracentesis in an outpatient

setting. Therefore, routine cell count and culture analysis is not warranted in asymptomatic patients with cirrhosis undergoing paracentesis for refractory ascites in an outpatient setting.

3. However, if a patient with refractory ascites is hospitalized or if the patient develops symptoms suggestive of SBP and/or worsening of renal function, a diagnostic paracentesis should be performed to investigate SBP. The presence of a PMN count >250/mm3 in the ascitic fluid is diagnostic of SBP.

4. If a patient is diagnosed with SBP, evidence supports the use of either a third-generation cephalosporin (cefo-taxime 1g IV every 12 hrs or ceftriaxone 2 g IV every 24 hrs) or amoxicillin/clavulanate for initial therapy of SBP. Therapy should be administered for at least 5 days (preferably 8 days) and when feasible, paracentesis should be repeated within 48 hrs to document >25% decrease in PMN counts.

5. Patients with elevated bilirubin levels >4 mg/dL and evidence of acute renal dysfunction [defined as a blood urea nitrogen (BUN) level >30 mg/dL and creatinine level >1.0 mg/dL] should receive adjunctive albumin at days 1 and 3 of acute SBP therapy as this will prevent further renal deterioration and improve survival. Albumin 1.5 g/kg should be intravenously administered at the time of

diagnosis of infection and 1 g/kg should be administered after 48 hrs.

6. Long-term prophylaxis with oral norfloxacin (400 mg QD) is indicated in patients with an increased risk of SBP, which includes patients:

n With a previous history of SBP.

n Without a previous history of SBP but who have a low protein concentration (<1 g/dL) plus renal failure (creatinine levels >1.2 mg/L or BUN levels >25 mg/dL) or serum sodium levels <130 mEq/L or severe liver disease (Child score >9 points with serum bilirubin levels >3 mg/dL). Most patients with refractory ascites complicated by hepatorenal syndrome with advanced liver failure meet the above criteria.

7. TIPS should be considered in patients requiring LVP more than 2–3 times per month or in those with loculated ascites that cannot be entirely removed with a single LVP. Patients with a Child–Pugh score >11 have a high mortality post TIPS; moreover, a high bilirubin level is the main predictor of death after the placement of TIPS in patients with refractory ascites. Therefore, placement of TIPS is not recommended in patients older than 70 years with serum bilirubin levels >3 mg/dL or Child–Pugh score >11. TIPS is not recommended in patients with heart failure (ejection fraction <55%), because with high right-sided pressures an adequate pressure gradient may not be present between

the portal and the systemic venous systems for functioning of the TIPS; moreover, placement of TIPS in this setting may exacerbate heart failure. TIPS is more effective than LVP in the prevention of recurrences of ascites. However, normalization of sodium homeostasis is not completely achieved and most patients treated with TIPS have an increased risk of hepatic encephalopathy and does not significantly reduce the risk of complications of cirrhosis such as SBP. TIPS is associated with a high rate of shunt stenosis or obstruction that requires frequent intervention to maintain shunt patency. Despite better control of ascites and a reduction in the number of hospitalizations for ascites, compared to LVP, TIPS does not improve the overall quality of life of patients. The cost of TIPS is higher than that of conventional therapy with LVP and IV albumin. Compared to repeated LVP, TIPS does not improve the overall rate of transplant-free survival. High-quality meta-analysis of randomized controlled trials (RCTs) showed that compared to paracentesis, TIPS is better at controlling ascites but does not improve survival. Thus, because of the higher frequency of hepatic encephalopathy and the higher cost of TIPS than LVP and albumin, until sufficient data are obtained, TIPS will continue to be a second line of therapy in the management of refractory ascites. The first line of treatment is repeated LVP with albumin. TIPS may be an option for patients with preserved liver function (bilirubin levels <3 mg/dL, Na levels >130, Child score <7, MELD <18, age <70 yrs without encephalopathy or cardiopulmonary disease).

Resolution of ascites after TIPS is slow and most patients require continued administration of diuretics and restriction of salt intake.

8. A liver transplant in patients with cirrhosis is associated with a 5-year survival of 80%, which is markedly greater than that in patients with cirrhosis and ascites not receiving a liver transplant (20%). The median survival is less than 1 year for patients with refractory ascites and those recovering from SBP and is even shorter in patients with the factors indicating poor prognosis include:

n Spontaneous dilutional hyponatraemia (serum Na levels <130 mEq/L).

n Arterial hypotension (mean arterial pressure <80 mmHg in the absence of diuretic therapy).

n Reduced glomerular filtration rate (even moderate reduction as indicated by serum creatinine levels between 1.2 and 1.5 mg/dL in the absence of diuretic therapy).

n Marked sodium retention (urine sodium levels<10 mmol/L) under a moderate sodium restricted diet and absence of diuretic therapy. Interestingly, in patients

with ascites, these parameters are better than liver function tests as predictors of poor prognosis. Therefore, in addition to patients with refractory ascites and complications like SBP and hepatorenal syndrome, patients with ascites and those meeting the above-mentioned criteria should be referred to a transplant centre for evaluation.

**HYPONATRaEMIA IN PATEINTS WITH CIRRHOSIS**

**Definitions and Prevalence of Hyponatraemia**

Patients with cirrhosis may develop two types of hypo-natraemia. In some patients, hyponatraemia is due to an excessive loss of extracellular fluid, most commonly from the kidneys or from the gastrointestinal tract. This condi-tion, known as *hypovolaemic hyponatraemia,* is charac-terized by low serum sodium levels associated with contraction of plasma volume, lack of oedema and ascites and prerenal renal failure. But, in most patients with cirrhosis, hyponatraemia develops because of expanded extracellular fluid volume and plasma volume with ascites and oedema. This condition is known as *hypervolaemic* or *dilutional hyponatraemia* and is due to a marked impairment

in the excretion of renal solute-free water, which results in a disproportionate retention of water and sodium in the kidneys. A serum sodium level 130 mmol/L is considered as clinically significant hyponatraemia; patients with hypo-natraemia have a more severe liver disease.

**Pathogenesis of Hyponatraemia**

The pathogenesis of water retention in cirrhosis is complex and involves several factors, including increased plasma levels of vasopressin (AVP), reduced renal synthesis of prostaglandins and reduced delivery of filtrate to the

ascending limb of the loop of Henle, the diluting segment of the nephron.

**Clinical Significance of Hyponatraemia**

1. From a clinical point of view, hyponatraemia was associated with greater likelihood of hepatic encephalopathy, hepatorenal syndrome (HRS) and SBP. Results of previous studies showed that in patients with cirrhosis treated with TIPS, hyponatraemia is a major risk factor for the development of hepatic encephalopathy. Finally, the presence of hyponatraemia is a major risk factor for the development of overt encephalopathy in all patients with cirrhosis and ascites, particularly, in those with refractory ascites. In addition, hyponatraemia is a significant risk factor for the development of HRS in patients with cirrhosis. Recent studies have shown that hyponatraemia impairs survival in patients with cirrhosis and ascites as well as in patients with acute-on chronic liver failure.

Hyponatraemia, uncontrolled ascites and type 1 HRS are predictors of short-term mortality independent of the MELD score.

2. Patients with cirrhosis and hyponatraemia are at an increased risk of developing neurological complications, including central pontine myelinolysis, after liver transplantation. Further, these patients have an increased risk of renal failure and infectious complications, require a longer duration of hospital stay, and more importantly, have a higher incidence of short-term mortality after transplantation.

**Management**

1. The first step to determine the right approach for the management of hyponatraemia in cirrhosis is to identify whether the hyponatraemia is hypovolaemic or hyper-volaemic. An important step in the management of hypovolaemic hyponatremia is the administration of sodium with an aim of normalizing the depleted sodium stores in the body.

The key of the management of hypervolaemic hyponatremia is to increase the renal excretion of solute-free water with an aim of normalizing the increased total body water, which would result in an improvement of serum sodium concentration. The administration of hypertonic sodium chloride is not recommended for the management of hypervolaemic hyponatraemia in patients with cirrhosis as it has a partial and short-lived effect in increasing serum sodium concentration, and it increases ascites and oedema in these patients. New families of drugs, known as vaptans, increase the excretion of renal solute-free water through the inhibition of the V2 receptors located in the renal tubules. Fluid restriction has been the standard of care for the management of hypervolaemic hyponatremia in cirrhosis for many years, particularly because of the lack of alternative effective therapies.

2. Tolvaptan has been recently approved in the USA for the management of severe hypervolaemic hyponatraemia (<125 mmol/L) associated with cirrhosis, ascites, heart failure and syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH). In Europe, the drug is currently only licensed for the treatment of SIADH. Conivaptan is also approved in the USA for the short-term (5-day) intravenous treatment of hypervolaemic hyponatraemia associated with different conditions. Treatment with tolvaptan is started at 15 mg/day, and the dose is titrated progressively to 30 and 60 mg/day, if needed, according to the changes in serum sodium concentration. Rapid increases in serum sodium concentration (>8–10 mmol/day) should be avoided to prevent the occurrence of osmotic demyelination syndrome. Results from

previous RCTs have shown that vaptans, including lixivaptan, tolvaptan and satavaptan, are effective in improving the serum sodium concentration in patients with hyponatraemia. The most frequent side effect of vaptans, related to their pharmacodynamic effects, in patients with cirrhosis is thirst, which was reported in up to 29% of patients. Central pontine myelinolyis has never been reported thus far in any of the studies with vaptans. Similarly, compared to the placebo group, the vaptan-treated groups showed no significant impairment of renal function.

Concomitant treatment with potent inhibitors (keto-conazole, clarithromycin and grape juice) or inducers (rifampicin, barbiturates and phenytoin) of the CYP3A should be avoided. The duration of treatment with vaptans remains to be established. Further, safety has only been established for short-term treatment (1 month).

**Further Reading**

1. Gines P, Arroyo V, Rodes J. Pathophysiology, complications, and treatment of ascites. *Clin Liver Dis* 1997;1:129–55.

2. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. *N Engl J Med* 2004 15;350:1646–54.

3. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164–76.

4. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving

MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 1992; 117:215–20.

5. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the treatment of refractory ascites. *Gastroenterology* 2003;124:634–41.

6. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerna F, Angeli P, Porayko M, Moreau R, Garcia–Tsao G, Jimenez W, Planas P, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258–66.

7. Angeli KL. European Association for the study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepato-renal syndrome in cirrhosis. *J Hepato*l 2010;53:397–417.

8. Runyon BA; AAASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49:2087–107.

9. Fernandez J, Navasa N, Planas R, et al. primary prophylaxis of spontaneous bacterial peritonitis delays hepato-renal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007;133:188–24.

10. Moore KP, Wong F, Ginès P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258–66.

11. Gines P. The vaptans: a promising therapy in the management of advanced cirrhosis. *J Hepatol* 2007;46:1150–2.

12. Biecker E. Diagnosis and therapy of ascites in liver cirrhosis. *World J Gastroenterol* 2011;17:1237–48.

**Chapter 24.**

**Budd-Chiari Syndrome**

**Introduction**

Budd-Chiari syndrome (BCS) is defined as an obstruction of the hepatic venous outflow track in the absence of cardiac or pericardial diseases **(Fig. 24.1)**. It is also known as hepatic venous outflow track obstruction (HVOTO). Involvement of large hepatic veins is called classic BCS, whereas involvement of intra/suprahepatic portion of the inferior vena cava is known as obliterative hepato-cavopathy (HVC-BCS). Small-vessel BCS is very rare, in which the hepatic outflow obstruction is limited to the small intrahepatic veins. The syndrome comprises abdominal pain, hepatomegaly, ascites and zone 3 sinusoidal distension on hepatic histology.

Hepatic veno-occlusive disease (VOD) is characterized by hepatic venous outflow obstruction at the level of the central or sublobular hepatic veins.

**Clinical History**

1. Clinical history depends on the site and rapidity of obstruction as well as development of collateral circulation to decompress the liver sinusoids. The classic triad of abdominal pain, ascites and hepatomegaly is observed in the vast majority of patients with acute or subacute BCS but not chronic BCS, which presents with ascites and portal hypertension (PHT). A high index of suspicion is needed to make the diagnosis of chronic BCS.

2. Obstruction of one major hepatic vein is silent.

3. Rapid obstruction of 2 or 3 major hepatic veins gives rise to an acute or fulminant presentation. Rapid accumulating ascites, jaundice and often hepatic encephalopathy, resistance to diuretics and therapeutic paracentesis suggest acute presentation.

4. Slow obstruction of 2 or 3 major veins produces a chronic presentation or, when accompanied by extensive collaterals, may be asymptomatic or ascites and PHT.

5. Obstruction to the suprahepatic segment of the IVC would manifest with venous congestion of the lower limbs as evidenced by pitting oedema of the lower extremities, varicosity of the veins, hyperpigmentation of the skin and stasis ulcers. Infertility in women and poor fetal outcomes in pregnancy, secondary to pelvic venous congestion is not uncommon.

6. Combination of obstruction to the HV and IVC would present with ascites, hepatomegaly, prominent anterior abdominal veins and chronic venous congestion of the lower limbs.

n Acute Budd-Chiari syndrome (7%)

- Abdominal pain

- Abdominal distension

- Encephalopathy

- Development of jaundice (mild)

- Nausea and vomiting

n Subacute Budd-Chiari syndrome (28%) – more insidious onset

- Abdominal pain

- Abdominal distension

- No encephalopathy

n Chronic Budd-Chiari syndrome (65%)

- Symptoms of portal hypertension – ascites and varices

**General Examination**

1. Jaundice

2. Pallor – secondary to gastrointestinal blood loss

3. Absence of hepatojugular reflux (usually cardiac cause of ascites like constrictive pericarditis and tricuspid regurgitation is associated with positive hepatojugular reflux)

4. Stigma of chronic liver disease is seen mainly in chronic Budd-Chiari syndrome.

5. Signs of constrictive pericarditis to be excluded.

6. Signs of venous congestion in the lower limbs such as non-pitting oedema, varicose veins, hyperpigmentation of the skin and stasis ulcers.

**Abdominal Examination**

1. Dilated venous collaterals in the flanks and over the back indicates IVC obstruction.

2. Tender smooth hepatomegaly in acute and subacute form of Budd-Chiari syndrome.

3. Mild splenomegaly

4. Ascites

**Investigations**

1. ***Haematological investigations***

n To evaluate hypercoagulable state

2. ***Biochemistry***

n AST/ALT level > 5 x ULN in acute BCS

n AST/ALT minimal elevation in chronic BCS

3. ***Ascitic fluid analysis***

n Serum–ascitic fluid albumin gradient (SAAG) is high (>1.1) in chronic form of BCS

n Total ascitic fluid protein >2.5 g/dL

n Low cell count

4. ***USG abdomen with Doppler study***

n Initial investigation of choice with specificity and sensitivity more than 85%.

n Echogenicity of the liver, caudate lobe hypertrophy, IVC thrombosis or compression.

n No flow signals or reversal of flow in hepatic veins.

n Large intrahepatic collateral vessels, ‘comma-shaped collaterals.’

n Hyperechoic cord replacing a normal vein

n Absent hepatic vein waves

n Splenomegaly

n Ascites

n Associated portal vein thrombosis (20%)

n In suprahepatic obstruction of the IVC: the site, length of obstruction, presence of stasis thrombus, flow velocity across the stenotic segment.

5. ***Dynamic CT abdomen***

n Intraluminal defects of the IVC and hepatic veins

n Hepatomegaly, especially caudate lobe

n Assessment of collaterals

n Ascites

6. ***MRI***

n Non-invasive tool, which provides both static and functional information without the need for iodinated

contrast material. MRI is the most reliable investigation to confirm the diagnosis and plan radiological intervention.

7. ***99m-Technetium liver scan***

n Not useful but can demonstrate caudate lobe hypertrophy

8. ***Hepatic venography and inferior vena cavogram***

n “Spider web” appearance near hepatic vein ostia **(Fig. 24.2)**

n No longer considered necessary for establishing the diagnosis

n Bi-directional, transatrial and transfemoral inferior vena cavogram can be performed preoperatively.

n Done in the same sitting as the intervention or rarely done when there is ambiguity in diagnosis.

9. ***Liver biopsy***

n Liver biopsy is usually not required except in the case of suspecting small vessels BCS. Can be performed at the time of TIPS.

n Centrilobular congestion, necrosis and sinusoidal dilation.

n BCS-related hepatic fibrosis is predominantly in the central part of the lobule, with central central bridging and maintenance of vascular relationships, unlike other forms of cirrhosis.

10. ***Genetic marker testing***

n Myeloproliferative neoplasms (MPNs) are the most common aetiology of classical BCS and account for 35–50% of cases in western world. Janus kinase 2 (JAK2) V617F mutation is detected in more than half of the patients with MPNs. JAK2 V617F positive MPNs are more frequent in BCS than in portal vein thrombosis.

n Somatic mutations of the Calreticulin (CALR) gene have been identified in MPN patients lacking the JAK2 V617F mutation.

n It is recommended to screen all BCS patients for underlying MPN mutations even if blood counts are normal, as many have masked polycythaemia. JAK2 V617F mutation should be evaluated first, followed by targeted CALR mutation testing.

**Management**

Management of patients with Budd-Chiari includes medical management and the relief of hepatic venous outflow tract obstruction. Stepwise management strategy includes anticoagulation, treatment of identified prothrom-botic risk factors, percutaneous revascularization and transjugular intrahepatic portosystemic stent shunt to re-establish hepatic venous drainage and last liver trans-plantation. This strategy provides a 5-year survival rate of nearly 90%. Long-term outcome is influenced by any underlying haematological condition and development of hepatocellular carcinoma.

**Medical Management**

1. Medical management is not impressive.

2. Control of ascites by sodium restriction, diuretics, with or without large-volume paracentesis.

3. Role of diuretics alone is questionable.

4. Anticoagulant therapy to prevent further extension of the venous thrombosis in acute case.

5. Treating underlying hypercoagulable cause.

**Management of Hepatic Venous Outflow Tract**

**Obstruction**

1. **Pharmacotherapy**

n Long-term anticoagulation therapy should be promptly initiated in all BCS patients in the absence of contra-indications. Upper endoscopy should be performed to assess the gastroesophageal varices prior to the initiation of anticoagulant treatment.

n Low molecular weight heparin followed by vitamin K antagonists (target INR between 2 and 3) is an ideal treatment regime. Medical management alone can be appropriate for early classical BCS patients without evidence of significant portal hypertension (ascites, varices), in which 33–54% of the patients treated with medical management alone showed good outcomes.

n Limited data supporting role of new oral anticoagulants (NOACs) in patients with BCS.

n Role of thrombolytic therapy is limited except in fulminant BCS or acute BCS.

2. **Angioplasty**

n Percutaneous or transhepatic angioplasty of narrowed hepatic vein or IVC web with or without stent placement.

n Success rate of percutaneous recanalization is 90% of the patients.

n 50% re-stenosis occurs within 6 months without anticoagulant, so anticoagulant is must following percutaneous recanalization.

n With wall stent, 5-year patency is around 80–90%.

n Long term efficacy is more for IVC obstruction than hepatic vein obstruction.

3. **Surgical portosystemic shunts**

n Surgical portosystemic shunting had been traditionally preferred decompressive strategy in BCS patients. Favourable outcome was only noted with side-to-side porto caval shunt in patients with HV occlusion alone.

n Surgical portosystemic shunting did not show survival benefit in BCS patients.

n Surgical shunts were associated with high periop-erative mortality, low late shunt patency and technical difficulties.

n This modality is largely replaced by TIPSS.

4. **TIPSS (Transjugular Intrahepatic Portosystemic Shunt)**

n TIPSS should also be promptly considered in patients with acute liver failure, and in cases with diffuse thrombosis of hepatic veins, as it is technically difficult to maintain the long-term HV patency with percutaneous angioplasty±stenting.

n TIPSS in BCS patients demonstrated high technical success rates and excellent short- and long-term prognosis of BCS TIPSS patients.

n *TIPSS-related complications* are liver capsule perforation, IVC and portal vein leak; contrast-induced nephropathy and stent migration.

n *Shunt dysfunction* appeared to be more frequent in BCS TIPSS patients due to their prothrombotic states. It is more with bare stent than PTFE-coated stent.

n Hepatic encephalopathy is observed in around 20% of patients but often transient and well responsive to medical treatment.

n 1- and 5-year pooled survival rates in TIPSS patients were 87.3% and 72.1%.

n A new prognostic score BCS TIPSS PI was proposed to predict post TIPSS outcome and it emerged as an effective clinical score at predicting 1 yr survival rate after TIPSS. BCS TIPSS PI >7 was associated with worse outcome for death or need liver transplantation 1 yr after TIPSS; and such patients should be considered for early transplantation.

5. **Liver transplantation**

n About 10–20% of the BCS patients shows progressive liver deterioration despite medical management, percutaneous revascularization and TIPSS. LT is the only remaining treatment option in these patients.

n Transplantation will correct some underlying hypercoagulable states like protein C, S and anti-thrombin III deficiencies.

n 5-year survival is around 70–95%.

n Recurrent BCS after transplantation has been reported, lifelong anticoagulation is recommended.

**Causes of Budd-Chiari syndrome**

There are various causes of Budd-Chiari syndrome listed below **(Table 24.1)**.

**Non-membranous Membranous**

**Hypercoagulable state** Web

n Antithrombin III deficiency Membrane

n Protein C/S deficiency

n Factor V leiden mutation

n Prothrombin mutation

n Myeloproliferative disorders (50%)

n PNH

n Oral contraceptives

n Pregnancy

Tumour invasion

n Hepatocellular carcinoma

n Renal cell carcinoma

n Adrenal carcinoma

Inflammatory bowel disease

Behcet’s syndrome

Idiopathic

**Classification of Hepatic Venous Outflow Tract Obstruction (HVOFT)**

***Primary***

1. Hepatic vein thrombosis (classic Budd-Chiari type)

n Subtype – Main hepatic vein thrombosis with IVC involvement

2. IVC thrombosis

n Subtype – IVC thrombosis with venous ostia involvement

***Secondary***

1. Compression

2. Tumour invasion

**Pathophysiology**

Severity of liver dysfunction depends on the speed of onset and extent of the obstruction. Obstructions are generally caused by thrombosis (primary BCS). With time, thrombi reorganize to form a fibrous tissue that leads either to localised stenosis of the thrombotic vein or to diffuse obliteration resulting in its transformation into fibrous cords. Localized stenosis may present as the appearance of a membrane-like structure. Secondary BCS results from tumour invasion into the lumen or compression of the vein by an expansive lesion. Obstruction of intrahepatic veins leads to congestive hepatopathy. This results from obstruction of large- or small-caliber veins, which leads to hepatic congestion as blood flows into, but not out of, the liver. Hepatocellular injury results from microvascular ischaemia due to congestion.

**Prognosis**

1. The natural history is not well known. The following factors have been associated with a good prognosis:

n Younger age at diagnosis

n Low Child-Pugh score

n Absence of ascites or easily controlled ascites

n Low serum creatinine level

2. A formula to calculate the prognostic index has been proposed. A score of less than 5.4 is associated with a good prognosis. The formula to calculate the prognostic index is as follows:

Prognostic index = (Ascites score x 0.75) + (Pugh score x 0.28) + (Age x 0.037) + (Creatinine level x 0.0036)

3. The prognosis is poor in patients with Budd-Chiari syndrome who remain untreated. Death results from progressive liver failure in 3 months to 3 yrs from the time of diagnosis.

4. The 5-yr survival rate is 38–87% following porto-systemic shunting. The actuarial 5-yr survival rate following liver transplantation is 70%.

**Salient Points about Budd-Chiari Syndrome**

1. Budd-Chiari leads to increased sinusoidal pressure and decreased sinusoidal blood flow.

2. Outflow obstruction leads to decreased portal blood flow, which may lead to portal vein thrombosis (10–20%).

3. Collateral circulation is found in 80% of patients.

4. IVC block is more common than hepatic vein block in patients with HCC.

5. IVC obstruction

n Membranous

n Segmental stenosis

n IVC occlusion

6. IVC block can occur in BCS either due to thrombosis itself or due to caudate lobe hypertrophy.

7. Hepatic portion of IVC is the most common site of IVC block because respiratory movement of diaphragm and coughing cause microscopic damage to the endothelial lining of IVC and turbulence in blood flow from hepatic vein enhances thrombus formation.

8. In patients with IVC and hepatic veins obstruction, first stenting of IVC followed by either hepatic vein stenting or mesoatrial shunt.

**Small Vessels BCS**

1. It is characterized by hepatic outflow obstruction limited to small intrahepatic veins, with normal appearances of the large hepatic veins on imaging.

2. Sinusoidal obstruction syndrome (veno-occlusive disease) and congestive cardiac disease are excluded from the definition of small-vessel BCS.

3. Sinusoidal obstruction syndrome (SOS, also known as veno-occlusive disease) is a distinct entity characterized

by sinusoidal endothelial injury to the “terminal” small hepatic veins (endophlebitis) as a result of a radiation induced or chemical toxic (oxaliplatin, gemtuzumab, alkaloids) insult.

**Further Reading**

1. Menon KVN, Shah V, Kamath PS. Current concepts: the Budd-Chiari syndrome. *N Eng J Med* 2004;350:578–85.

2. Janssen HL, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC. Budd-Chiari syndrome: a review by an expert panel. *J Hepatol* 2003;38:364–71.

3. Dominique-Charles Valla. The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. *Hepatology* 2003;38:793–803.

4. EASL Clinical Practice Guidelines. Vascular disease of the liver*. J Hepatol* 2016;64:179–202.

5. Valla DC. Hepatic vein thrombosis (Budd-Chiari syndrome). *Semin Liver Dis* 2002;22:5–14.

6. Valla D. Hepatic venous outflow tract obstruction etiopathogenesis: Asia versus the West. *J Gastroenterol Hepatol* 2004;19:S204–11.

7. Valla DC. Budd-Chiari syndrome/hepatic venous outflow tract obstruction. *Hepatol Int* 2018;12:168–80.

8. Darwish MS, Plessier A, Hernandez-Guerra M, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med* 2009;151:167–75.

**Chapter 25.**

**Portal Vein Thrombosis**

**Introduction**

This topic is divided into two different clinical challenges; one would be chronic portal vein thrombosis (portal cavernoma) affects younger population in developing world and other is acute portal vein thrombosis in cirrhosis liver.

**EXTRAHEPATIC PORTAL VEIN THROMBOSIS**

Extrahepatic portal vein obstruction (EHPVO, portal cavernoma) is an important cause of presinusoidal portal hypertension. The spectrum of portal vein thrombosis that is seen in Indian sub-continent is different from that seen in western populations, where the disease is seen in adults and portal vein thrombosis is secondary to a haematologic disease, intra-abdominal malignancy, etc.

**Clinical History**

1. Age of onset of symptoms – 3–15 yrs.

2. Children who develop EHPVO following neonatal umbilical sepsis usually present early (around 3 yrs), as compared to those who develop it after intra-abdominal infection or have idiopathic EHPVO (around 5–15 yrs).

3. *Haematemesis and melena*: Variceal bleeding is well tolerated in EHPVO, unlike patients with cirrhosis liver, who tolerate the bleeding poorly with deterioration in liver function, development of ascites and encephalopathy. Severity and frequency of haematemesis is reduced after onset of puberty.

4. Left upper quadrant pain and fullness secondary to splenomegaly. Post prandial abdominal pain may be due to mesenteric ischaemia.

5. *Abdominal distension*: Transient ascites is well known in EHPVO following bleeding or surgery.

**Past History**

1. Recurrent, well-tolerated variceal bleeding in the past.

2. History of umbilical vein catheterization (9%) and umbilical sepsis (9%).

3. History of home delivery.

**General Examination**

1. Growth retardation (50%): Weight, height, BMI, height/weight for age according to percentile.

n Deprivation of hepatotrophic growth factor

n Resistance to the action of growth hormone

n Early satiety and secondary decrease intake due to splenomegaly

2. Icterus – secondary to portal biliopathy

3. Pallor – secondary to variceal bleeding

4. Bruising; petechiae – secondary to hypersplenism

5. Normal hepatojugular reflux

6. Absence of other signs of liver disease (e.g., spiders, oedema, encephalopathy)

**Abdominal Examination**

1. Splenomegaly

2. Ascites – Usually transient and immediately after the episode of bleeding

3. Absence of dilated abdominal veins suggesting extrahepatic portal vein obstruction

4. Absence of back veins

**Investigations**

1. ***Biochemistry/Serology***

n Hematology

- Anemia – secondary to blood loss

- Pancytopenia – secondary to hypersplenism (40–80%)

- Coagulation profile: Protein C, protein S, factor V Leiden etc.

n Liver biochemistry

- Albumin may be low in undernourished patients or after a bleed.

- Increase in bilirubin and enzymes may occur after a bleed.

- Increase in bilirubin with high alkaline phosphatase may suggest portal biliopathy.

n Serology

- HIV

- In multi-transfused children – HBV and HCV serology

2. ***USG abdomen with Doppler study***

n Sensitivity and specificity is more than 92%.

n Portal vein is transformed into cavernoma, produces a distinctive tangle of tortuous vessels near porta with hepatopetal flow.

n Extensive collaterals in paracholecystic, parachole-dochal and pancreaticoduodenal areas

n Normal liver size and echotexture

n Splenomegaly

n Absence of significant ascites

3. ***Splenoportography***

n Safe, simple and easy to perform in experienced hands. Risk of bleeding from SPG puncture site is 5% and splenic tear <1%.

n Identify the site of obstruction, extent of obstruction, location and extent of collateral circulation.

n Allows to assess splenic pulp pressure

n At present, its use is limited in view of alternative non-invasive imaging.

4. ***Upper endoscopy***

n Oesophageal varices are seen in 90–95% and gastric varices in 35–40%.

n Used as diagnostic as well as therapeutic purpose.

n Portal gastropathy is relatively rare.

5. ***Sigmoidoscopy***

n Frequency of anorectal varices is more in EHPVO in comparison with cirrhosis.

n Rectal varices: Dilated veins on the distal rectum usually caused by portal hypertension. The varices are located just proximal to internal haemorrhoids.

n Classification of rectal varices

- Grade I : <3 mm

- Grade II : 3–6 mm

- Grade III : >6 mm

n Colonoscopy to identify colopathy and in case of bleeding from ectopic varices

6. ***Other investigations***

n Intravenous CT portography

n MR angiography (venous phase)

n CT transplenic portography

**Management**

In the era of therapeutic endoscopy, endoscopic treatment is the most suitable management approach with 90–95% success compared with emergency surgery, which has 10–30% mortality. Role of non-selective beta-blocker in primary prophylaxis has not been proven.

1. **Endoscopic variceal obliteration**

n Endoscopic sclerotherapy (EST)

n Endovariceal ligation (EVL): EVL preferred over EST due to lower risk of complications and earlier obliteration of varices. EVL combined with EST found to have Better results in children.

n Endotherapy has more than 90% efficacy in both control of bleeding as well as eradication of varices.

n Gastric variceal bleeding can be controlled by cyanoacrylate injection.

n Indications of upper endoscopy in EHPVO.

n Active bleeding.

n Assessment of size of varices (gastric and esophageal) and identify PHG.

n As many of these patients may require blood transfusion, vaccinate against hepatitis B.

2. **Surgery** (see details in Chapter 26)

***Surgical procedures are of two types***

n Portosystemic shunt

n Ablative procedure

***Indications for surgery***

n Failed to respond to endoscopic management

n Bleeding from ectopic varices or portal hypertensive gastropathy

n Portal biliopathy which has failed to respond with endoscopic therapy

n Symptomatic hypersplenism

***Efficacy of total (non-selective) shunts***

n Rate of re-bleeding and shunt thrombosis 2–10%

n Mortality 0–2%

Incidence of hepatic encephalopathy is low

***Efficacy of selective shunts***

n 5-yr patency of shunt is 92%

n Re-bleeding rate is 12%

n Shunt dysfunction – 25%

n Concurrent splenic vein thrombosis is the contraindication to perform selective shunt

3. **Pharmacotherapy**

Efficacy of non-selective beta-blockers in EHPVO has been evaluated in animals as well as in humans, but the beneficial effect of beta-blockers on gastrointestinal bleeding has not been evaluated much in clinical trials.

***Management of Hypersplenism***

n Rarely require specific treatment.

n Splenectomy is required only in symptomatic hypersplenism.

n Splenomegaly is not required in end-to-side DSRS.

n Shunt surgery reduces spleen volume.

n Can be treated by partial splenic embolization or splenic irradiation.

**Causes of Portal Vein Thrombosis**

1. Direct portal vein injury with subsequent obstruction

n Omphalitis

n Umbilical vein catheterization

n Neonatal peritonitis

n Trauma

n Iatrogenic during surgery

n Cyst or tumour encasing the portal vein

2. Developmental anomalies

n Stenosis

n Atresia

n Agenesis

3. Indirectly associated with portal vein thrombosis

n Neonatal sepsis

n Hypercoagulable state (generally found in adults)

***Site of Portal Vein Obstruction***

1. Portal vein formation (90%)

2. Splenorenal axis (10%)

3. Entire length of portal vein with extension into splenic vein and superior mesenteric vein (1%)

***Causes of Portal Vein Thrombosis in Cirrhosis (20–30%)***

1. Due to decreased portal blood flow

2. Periportal lymphangitic fibrosis

3. Cavernoma – hepatopetal flow

4. Hypercoagulopathy

5. Tumour thrombus – in HCC

**Mechanisms of Transient Ascites (10%)**

1. Transient derangement in liver function

2. Low albumin

3. Splanchnic hyperemia

4. Autoimmune dysfunction

**Portal Biliopathy**

1. Portal biliopathy is changes occurring in biliary system secondary to mechanical compression of biliary tree from portal cavernoma.

2. Prevalence is as high as 80% in some studies.

3. Venous drainage of common bile duct is via:

n Epicholedochal venous plexus of Saint

n Paracholedochal plexus of Petren

4. Pathogenesis is either mechanical or ischaemic injury to bile duct leading to stricture, dilatation, angulations or stone formation.

5. Only 14% are symptomatic and choledocholithiasis in 17%.

6. Abnormal cholangiogram in portal hypertension:

n Extrahepatic portal vein obstruction - 87%

n Non-cirrhotic portal fibrosis - 40%

n Cirrhosis - 30%

7. Abnormality on cholangiogram in portal biliopathy

n Left ductal systems is the most commonly involved.

n Stricture or dilatation.

- Irregular walls

- Angulations

- Displacement

- Stone

***Classification of Portal Biliopathy***

1. Involvement of extrahepatic bile duct

2. Involvement of intrahepatic bile duct

3. a) Extrahepatic with right intrahepatic

b) Extrahepatic with left intrahepatic

4. Both extra- and intrahepatic

***Management of Portal Biliopathy***

1. Asymptomatic patients do not require any treatment.

2. Removal of biliary stones are reported in the literature; however, there is danger in doing ERCP with sphincterotomy in view of para-choledochal varices. Risk of bleed during ERCP can be reduced by preceding with decompressive shunt surgery. TIPS is an alternative in case of refractory bleeding.

3. Treatment of portal biliopathy includes decompressive shunt followed by hepaticojejunostomy.

**Anticoagulants**

Current EASL guidelines and Baveno VI consensus state-ment both support indefinite anticoagulation in patients with chronic PVT after prophylaxis of gastrointestinal bleeding and according to underlying prothrombotic risks and history of thrombotic events.

**PORTAL VEIN THROMBOSIS IN LIVER CIRRHOSIS**

Cirrhosis is the underlying cause in 22–32% of all cases of PVT. The reported prevalence of PVT in patients with cirrhosis is highly variable and ranges from 0.6 to 44%. The prevalence increased with the severity of the disease (1% in compensated cirrhosis vs 8–25% in transplant candidate). Development of portal vein thrombosis (PVT) is a significant event in the natural history of cirrhosis. It may be associated with a deterioration of liver function or occurrence of variceal bleeding, but most frequently it is an incidental finding during routine use of ultrasonography

(US).

**Risk Factors**

In relation to local factors, a recent prospective study has suggested a major role is reduced portal blood flow velocity (<15 cm/sec), as a consequence of portal hypertension, in the development of PVT in cirrhosis.

Other factors that have been found to be associated with an increased risk of PVT in cirrhosis are male gender, NASH, previous spontaneous bacterial peritonitis, previous

variceal bleeding, encephalopathy, ascites low platelet count and advanced liver failure.

**Diagnosis**

The diagnosis of PVT in cirrhosis may be an incidental finding of Doppler US performed for HCC screening. The benign or malignant nature of PVT may not be easily distinguishable by conventional imaging studies. Presence of intrathrombus signals with arterial waveforms on US Doppler examination or the presence of neovascularity within PVT at contrast sonography may raise a high suspicion of malignant PVT. It has also been suggested, as suspicious of malignant PVT, the finding of a portal vein diameter greater or equal as 23 mm. Contrast-enhanced cross-sectional images plays very important role to identify bland thrombus or malignant thrombus.

**Yerdel Classification of Portal Vein Thrombosis**

1. Grade 1 : <50% of lumen thrombosis of portal vein

2. Grade 2 : >50% of lumen thrombosis of portal vein

3. Grade 3 : Complete thrombosis of both PV and proximal superior mesenteric vein (SMV)

4. Grade 4 : Complete thrombosis of PV and proximal and distal SMV, respectively

In new classification of PVT by Dr Sarin, not only anato-mical location and extension but also functional issues of liver are also considered.

**Management**

The aim of treatment should be to achieve recanalization or to prevent thrombosis progression. Therefore, early detection of PVT is essential. If patients are candidates for liver transplantation (LT), the aim is to prevent the extension of thrombosis to the splenomesenteric confluence and superior mesenteric vein, because this may preclude LT.

**Role of anticoagulant in portal vein thrombosis**

Low-molecular weight heparin (LMWH) or oral vitamin K antagonists (VKA, warfarin) are safe in patients with cirrhosis and acute PVT. Anticoagulant treatment did not lead to more bleeding events or a need of more blood transfusion. Anti-coagulant prevents extension of thrombosis as well as

improves chances of recanalization. Recurrence of PVT after anticoagulation withdrawal has been documented in 38% of the patients that achieved previous recanalization. That means that once started, anticoagulation treatment shall be maintained till liver transplantation.

**New Oral anticoagulants**

New class of anticoagulants, (DOAC, direct oral anti-coagulants) either directly inhibits thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) are currently advised in patients with acute PVT. There is no discomfort of daily injection of LMWH or INR monitoring of VKA. Studies comparing conventional anticoagulation with DOAC are still pending.

**Liver transplantation (LT)**

Literature showed that overall actuarial survival after liver transplantation in PVT patients was lower compared to patients without (65 vs 76%). However, patients with minimal or partial thrombosis of the portal vein have similar 5-yr survival as patients without PVT. Literature showed that presence of PVT at LT was associated with more postoperative complications, renal failure, primary graft non-function and PV rethrombosis.

**Further Reading**

1. Shah SR, Mathur SK. Presentation and natural history of variceal bleeding in patients with portal hypertension due to extrahepatic portal venous obstruction. *Indian J Gastroenterol* 2003;22:217–20.

2. Sarin SK, Agarwal SR. Extrahepatic portal vein obstruction. *Semin Liver Dis* 2002;22:43–58.

3. Chandra R, Kapoor D, Tharakan A, et al. Portal biliopathy. *J Gastroenterol Hepatol* 2001;16:1086–92.

4. Zargar SA, Yattoo GN, Javid G, et al. Fifteen-year follow up of endoscopic injection sclerotherapy in children with extrahepatic portal venous obstruction. *J Gastroenterol Hepatol* 2004;19:139–45.

5. Alam MS, Bin Khalid QS, et al. Portal biliopathy. *J Pak Med Assoc* 2012;62:177–80.

6. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis*. Clin Gastroenterol Hepatol* 2012;10:776–83.

7. Chen H, Turon F, Hernandez-Gea V, Fuster J, et al. Nontumoral portal vein thrombosis in patients awaiting liver transplantation. *Liver Transpl* 2016;22:352–65.

8. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. *Hepatology* 2009;49:1729–64.

**Chapter 26.**

**Liver Transplantation**

**Introduction**

Liver transplantation (LT) is currently the only therapeutic curative procedure for patients with end-stage liver failure due to chronic and acute liver failure (ALF). As Thomas Starzl performed the first human deceased donor (DDLT) at the University of Colorado in 1963, significant development occurred in all aspects of LT, including recipient and donor selection, operative technique, anaesthetic and critical care management and immunosuppressive medications. The overall 1-year survival for adult and paediatric DDLT is now expected to be in excess of 90%, whereas 5 and 10-yr survival approach almost 70%. The indisputable success of LT became its own victim when the number of deceased donors were too few to meet the ever-increasing demand of prospective recipients with liver disease. The first successful living donor liver trans-plantation (LDLT) was performed for paediatric recipient using lateral segment of liver from the mother (Couinaud’s segment 2 and 3) by Strong RW in 1989.

**Indications of LT** fall into 4 major categories:

1. Chronic liver disease (Cirrhosis)

2. Acute liver failure

3. Hepatocellular carcinoma

4. Inherited metabolic liver diseases

Before discussing indication, it may be prudent to consider first, the contraindication for LT.

**Contraindications for LT**

**Absolute**

1. Severe cardiac and/or pulmonary diseases and severe pulmonary hypertension (mPAP >45 mmHg).

2. Active substance abuse (e.g., alcohol) without motivation for abstinence and untreated or ongoing substance abuse. By and large an abstinence period of 6 months is usually obligatory before considering transplant.

3. Incurable extrahepatic malignancy.

4. Uncontrolled sepsis.

6. Active HIV not responsive to anti-retroviral therapy. HIV-positive patients with non-detectable viral load and appropriate hepatologic indication should, however, be assessed for LT.

**Relative**

1. Chongiocarcinoma (unless as part of a protocolized study)

2. Hepatic metastatic neuroendocrine tumours (NET), metastatic haemangioendothelioma

3. Morbid obesity

4. Extreme psychosocial dysfunction

5. Advanced age: Patient’s age more than 80 yrs have extended ICU stay, prolonged hospitalization and less survival compared to age less than 70 yrs. However, it must be stressed, it is the physiologic age and not the chronologic age that matters.

**Indications for LT**

a. **Cirrhosis**

Cirrhosis of liver accounts for more than 80% of LT performed in adults.

Causes of cirrhosis include:

1. Alcoholic liver cirrhosis

2. Nonalcoholic steatohepatitis (NASH)

3. Hepatitis C and B infection

4. Primary biliary cholangitis (Primary biliary cirrhosis)

5. Primary sclerosing cholangitis

6. Autoimmune hepatitis

The usual causes for cirrhosis in **children** necessitating LT include:

1. Extrahepatic biliary atresia

2. Caroli’s disease

3. Metabolic conditions such as Wilson’s disease, alpha-1 antitrypsin deficiency, hereditary tyrosinemia

4. Progressive familial intrahepatic cholestasis

***Minimal Listing Criteria***

The goal of LT is to prolong and improve the quality of life. For this, patients with chronic liver failure must be chosen independent of aetiology and their natural prognosis balanced with the possible morbidity and mortality following LT, both in the immediate postoperative as well as the long-term course. Thus, the diagnosis of liver cirrhosis per se does not automatically mean that LT is a necessity. It is now agreed

that a 1-year survival prognosis of less than 90% is the minimum criterion for listing for LT. Numerous analyses have shown that “decompensation” is accompanied by a marked deterioration in prognosis, with 1-year survival dropping below 50%. Decompensation for the purpose of transplant listing include:

1. Recurrent variceal bleeding

2. Refractory ascites

3. Spontaneous bacterial peritonitis (SBP)

4. Hepatorenal syndrome

5. Hepato-pulmonary syndrome

6. Hepatocellular carcinoma (HCC)

Decompensation is usually associated with a worsening of the Child–Pugh Score from A (5-yr survival of 90%) to B (5-yr survival of 70%) or C (1-yr survival of 50%). It is recommended that patients should be considered for liver transplant evaluation once CTP score goes above 7. Because of subjective parameters (ascites, encephalopathy) and the so-called plateau effect of CTP score, particularly for bilirubin and prothrombin time, this score has been replaced with the MELD (Model for End-stage Liver Disease) score.

***Model for End-stage Liver Disease (MELD Score)***

MELD was studied initially to predict mortality after trans-jugular intrahepatic portosystemic shunt (TIPS).

1. The initial MELD included the four clinical parameters: serum creatinine, bilirubin, international normalized ratio (INR) and underlying diagnosis. However, UNOS chose to omit diagnosis as a parameter in the MELD formula. Following modification, UNOS proposed that a modified version of the same model could be applied as a prognostic indicator to allocate donor allograft to cirrhotic adults.

2. Similar score was also developed in pediatric patients (age <12 yrs) termed as paediatric end-stage liver disease (PELD) score. The calculation of both MELD and PELD scores are given below.

3. Neither the complications of portal hypertension nor the aetiology of liver disease influenced the accuracy of the MELD model.

4. MELD score varies from 6 to 40 with 90% and 7%, 3-month survival, respectively. It has been recommended that patients begin the transplant evaluation process at a MELD >10 but will only receive benefit from transplant when MELD >15 in most cases.

5. Limitations of the MELD: MELD does not take account for complications of portal hypertension such as recurrent bleeding, refractory ascites, hepatic encephalopathy, hepatopulmonary syndrome or onset of HCC.

6. In 2016, MELD allocation system was further modified to MELD-sodium, where sodium was incorporated in MELD score. Sodium is incorporated only if MELD more than 11.

MELD Risk Score = 10 × [0.957 × Loge (creatinine mg/dL) + 0.378 × Loge (Bilirubin mg/dL) + 1.120 × Loge (INR)]

PELD Risk Score = -0.436 age (<1)-0.687 Loge (albumin g/dL) + 0.480 Loge (bilirubin mg/dL) + 1.867 Loge (growth failure <2SD)

b. **Acute Liver Failure**

Acute liver failure (ALF) is defined as coagulopathy (INR>1.5) of hepatic onset associated with hepatic encephalopathy in the absence of pre-existing liver disease. In adults, in the absence of HE, the condition is termed as acute liver injury. In paediatric ALF, however, HE is not mandatory and INR of >2 of hepatic onset without evidence of chronic liver disease qualifies for the definition of ALF. If left untreated, mortality in ALF is usually due to cerebral oedema or multi-organ failure. The survival of ALF has improved drastically from approximately 17% about 4 decades ago to almost 90% as reported in 2017. This can be attributed to better understanding of the disease and consequent evolution of management options ranging from good intensive care to timely LT.

***Usual causes of ALF include***

1. Viral hepatitis; A, B, E and seronegative.

2. Drug-induced acute liver failure (paracetamol, anti-tubercular).

3. Fulminant Wilson’s disease, autoimmune disease, vertically transmitted Hep B although chronic liver diseases can have their index presentation as ALF.

4. Acute Budd-Chiari syndrome

The limited therapeutic options for ALF include steroids for autoimmune hepatitis, N-acetylcysteine for paracetamol overdose and silibinin for Amanita mushroom poisoning. The crucial decision in the management of ALF revolves around the possibility of spontaneous resolution with medical management. In approximately 10–20% of patients, the liver damage is extensive and salvage is possible solely by LT. The decision to proceed with LT is usually based on prognostic markers, which vary from country to country. These include King’s College Hospital criteria (KCH), Clichy, MELD, Indian criteria and among these, ever since its introduction in 1989, the KCH criteria has been widely used world over.

***King’s College Criteria to list ALF patients for LT***

*For Acetaminophen Toxicity (common in UK)*

Acidosis (pH < 7.3) or

PT INR > 6.5 + S. creatinine >3.4 mg/dL

*For Other Causes of Acute Liver Failure*

PT INR >6.5

or

Any three of the following:

n Age <10 yrs or >40 yrs

n Non-A, non-B hepatitis or drug-induced disease

n Duration of jaundice before encephalopathy more than 7 days

n INR >3.5

n Bilirubin >17.5 mg/dL

c. **Hepatocellular Carcinoma**

Hepatocellular carcinoma (HCC) is most often secondary to liver cirrhosis, a pre-cancerous state. In every patient with HCC and liver cirrhosis an indication for LT should be assessed if resection cannot be performed because of the cirrhosis stage or other factors. To minimize the danger of an HCC relapse following LT and achieve a 5-year survival rate of more than 70%, patients with favourable prognosis must be selected. The Milan criteria, since their publication in 1996, set the standard for the selection of patients with HCC. Numerous studies have shown that patients fulfilling Milan criteria have a <20% risk for relapse and a survival rate comparable to that for benign indications following LT. Nevertheless, if LT is restricted to patients who meet the Milan criteria, only relatively few patients with HCC will qualify for LT. Although the relapse risk following LT increases with the increase in tumour size, even those with more advanced tumour stages (so-called **expanded criteria**), can have a survival advantage.

The most popular criteria are:

Milan criteria Single HCC nodule 5 cm

3 lesions each 3 cm

UCSF criteria Solitary HCC lesion 6.5 cm

3 nodules each 4.5 cm with total diameter of 8 cm

Up to 7 criteria Sum of the size of the largest

tumour (in cm) and the number

of tumours <7

Asian Medical Largest tumour diameter 5 cm,

Centre criteria number 6 and no gross

vascular invasion

Macrovascular invasion, generally demonstrable by contrast CT or MRI is a contraindication for LT. Sadly, histological tumour grading, (namely the degree of differentiation and the presence of microscopic vessel invasion), the best predictors of tumour recurrence, can be determined only by the explant liver histology after LT.

Patients who initially present in a tumour stage outside the accepted transplant criteria can be brought into a tumour stage inside the Milan or expanded criteria by means of local ablative procedures such as radiofrequency ablation (RFA) or transarterial chemo embolization (TACE). This is referred to as “**down staging**.”

Other than number and size of tumour, surrogate para-meters that reflect the tumour biology include alpha-fetoprotein level, PIVKA (protein induced by vitamin K absence) concentration, avidity on PET scan, peripheral blood neutrophilic-lymphocytic ratio (NLR) more than 5, radiological response to loco-regional ablative therapies and histologically proven lack of microvascular invasion.

d. **Inherited Metabolic Liver Disease**

Metabolic liver diseases are a heterogeneous group of diseases that in adults include hemochromatosis, Wilson’s disease and alpha 1-antitrypsin deficiency as the most frequent metabolic causes of liver cirrhosis. The general indications for LT are same as in other causes of cirrhosis. For patients with Wilson’s disease presenting with acute liver failure, the indications for acute liver failure apply, irrespective of the stage of the chronic liver disease. In addition, in the case of progressive neurological symptoms of Wilson’s disease despite medical therapy, LT is to be given consideration.

Few other metabolic disease states leading to hepatic dysfunction in the paediatric population include Crigler-Najjar syndrome, glycogenosis, metabolic respiratory chain deficiencies, familial hypercholesterolemia, methylmalonyl aciduria.

Rare indications for LT are primary hyperoxaluria, inherited amyloidosis, the hepatic manifestation of cystic fibrosis, polycystic liver–kidney disease and Osler-Weber-Rendu disease.

**Types of LT**

Mainly two types of LT:

1. **Deceased donor liver transplant (DDLT)**: Liver is harvested from a deceased donor. Deceased donation maybe following brain death (donation after brain death or DBD) or cardiac death (donation after cardiac death or DCD). DCD causes a period of hypoperfusion starting from the time of circulatory arrest to time of cold perfusion - the warm ischaemia time. DCD recipients

are therefore likely to have higher incidence of biliary complications, ischaemic cholangiopathy and primary graft non-function. In DCD donation, machine perfusion is often performed prior to implant to assess the quality of liver as well as to correct the ischaemic damage sustained during warm ischaemia.

Whole liver graft from a deceased donor can be split into a left lateral segment (paediatric patient) and a right extended graft (adult patient) or right and left half (for 2 adult donors). This procedure termed “**split liver transplant**” is performed to increase the supply of donor organs.

2. **Living donor liver transplant (LDLT**): Transplant is done using a part of the liver from a living donor (LDLT).

Auxiliary LT is a variety of LT where the recipient’s own liver is not completely removed. Its purpose is to retain the native liver in case where spontaneous recovery maybe possible as in cases of ALF or if there is a potential for future gene therapy in cases of hereditary or metabolic liver diseases.

Domino LT in which a select group of liver transplants recipients can donate their explanted native livers for use as liver grafts in other patients. Several hereditary metabolic diseases (such as familial amyloid polyneuropathy, maple syrup urine disease and familial hypercholesterolemia) are caused by aberrant or deficient protein production in the liver, and these conditions can be cured with an orthotopic liver transplant. Although their native livers eventually caused severe systemic disease in these patients, these livers are otherwise structurally and functionally normal.

**Post-transplant Complications**

1. First 3 days following transplantation

n Primary non-function graft (PNF)

n Hyperacute rejection (extremely uncommon except in transplants across ABO incompatible barrier)

n Hepatic artery thrombosis

n Portal vein thrombosis

n Hepatic vein thrombosis (particularly in patients transplanted for Budd-Chiari syndrome)

2. 3–14 days

n Acute rejection

n Hepatic artery and portal vein thrombosis

n Biliary leak

n Cholangitis

n Drug toxicity

3. >14 days

n Graft dysfunction and chronic rejection

n Cytomegalovirus (CMV) infection

n Drug toxicity

n Disease recurrence (especially HCV)

***Primary Non-function Graft (PNF)***

PNF represents the failure of the allograft soon after revascularization with no discernible technical or immunologic cause, leading to either death or retransplantation. This injury is characterized in the first week after LT by a marked increase in aminotransferases (over 5000 s), prolonged prothrombin time, high lactates (>4) and acidosis (arterial Ph <7.3 or venous Ph <7.25). The risk of PNF is donor age more than 60 yrs, more than 60% macro-vesicular steatosis in donor liver, donor hypernatraemia of more than 170 mEq/L, prolonged cold ischaemia time and reduced-size grafts. Early re-transplant is the only treatment for PNF.

***Rejection***

1. Around 30% of patients develop rejection within the first 6 weeks of LT. It is suspected by elevated transaminases and confirmed by liver biopsy.

2. The histologic hallmark is portal inflammation, bile duct damage and endothelitis (attachment of inflammatory cells to the endothelial surface of portal or terminal hepatic veins).

3. More than 2/3 of patients respond to steroid pulse therapy; and augmented immunosuppression; nevertheless 10% may require antilymphocyte therapy (ATG; OKT3).

***Small-for-size Syndrome (SFS)***

1. This is a form of liver dysfunction described predominantly in live donor liver transplant here the quantity of donor graft volume is inadequate to meet the demands of the recipient. It typically occurs when the Graft to recipient weight ratio (GRWR) is less than 0.7.

2. There is no uniform consensus on the definition of SFS; its diagnosis is generally based on persistent hyperbilirubinemia (>5.85), coagulopathy (INR >2), grade 3 or 4 encephalopathy and massive ascites during the first week without evidence of vasculo-biliary, infective or immunological problem.

3. Higher incidence of septic complications and renal or pulmonary insufficiency are seen in SFSS, leading to higher mortality.

***Hepatic Artery Thrombosis (HAT)***

1. More common in paediatric transplantation.

2. May present as allograft dysfunction if occurring within 4 weeks. If tolerated, early HAT leads to bile duct strictures. Late HAT is better tolerated due to collateral blood

flow, but can still lead to biliary strictures, recurrent

bacterial cholangitis, hepatic abscesses and delayed bile leak.

3. Diagnosed by Doppler ultrasonography and confirmed by angiography.

4. Treated by urgent re-vascularization or re-transplantation. HAT has a mortality of 30%.

***Portal Vein Thrombosis***

1. Portal vein thrombosis occurs in 1–3% of patients following transplantation.

2. Acute portal vein thrombosis typically leads to liver failure.

3. It is treated by urgent re-vascularization or re-transplantation.

***Biliary Complications***

1. Bile leaks and biliary stricture occur in around 10–30% of patients.

2. More frequent with living donor liver transplantation (LDLT), especially when there are multiple ducts in the donor. Routine bilary stenting has not reduced the rate of this complication. However, careful harvesting of the bile ducts along with the Glisson’s plate, thus maintaining its blood supply, does appear to reduce the rate of bile leak. Stricture can be treated by either ERCP or surgical revision.

***Post-transplant Steatosis***

1. Post transplant steatosis affects 18–40% of LT recipients and even 39–70% of those transplanted for NAFLD-related cirrhosis.

2. Risk factors of post transplant NAFLD include pre-transplant and posttransplant obesity, alcoholic cirrhosis as an indication for LT, posttransplant DM, hyperlipidemia, hypertension, tacrolimus administration and pretrans-plant graft steatosis.

3. Post transplant significant steatosis (grades 2 and 3) was not associated with worse patient survival.

***Chronic Rejection***

1. This currently occurs in less than 5% of grafts at 5 yrs. Chronic rejection can occur as early as 2–5 weeks after transplantation, with a peak incidence of graft failure occurring at 3 months after transplantation and more than 85% of cases falling within 6 months.

2. Most cases occur either after an episode of acute rejection unresponsive to corticosteroids with persistent aminotransferase elevation and progressive rise in alkaline phosphatase and bilirubin levels.

3. Histologic features of chronic rejection include bile duct loss (disappearance in at least 50% of portal tracts) and

obliterative vasculopathy in medium- and large-sized arterioles (previously termed “ductopaenic rejection” or vanishing bile duct syndrome”).

***Recurrent Hepatitis B***

1. Recurrent HBV infection is associated with poor graft survival. The factors associated with high rates of HBV reactivation are high viral load prior to the transplant, HBV e antigen (HBeAg) reactivity, co-infection with human immunodeficiency virus type 1 (HIV), non-compliance with drug therapy, HCC at the time of LT and anti-viral drug resistance.

2. Tenofovir and immunoglobulin (HBIG) are effective in preventing recurrence of HBV. Recent evidences showed high-dose HBIG-LAM combination, low-dose HBIG and potent NAs (TDF or ETV) demonstrated significantly lesser HBV recurrence. HBIG free treatment is also recommended in view of potent nucleoside analouge (NAs) like tenofovir or entecavir.

***Recurrent Hepatitis C***

1. Recurrent infection of the transplanted liver used to be universal in patients with detectable HCV viremia at the time of transplant, and infection of the allograft was seen to occur within hours of organ transplantation. The course of chronic recurrent HCV in the immuno-compromised transplant recipient is more aggressive than in immunocompetent patients, with 5 yr rates of chronic hepatitis and cirrhosis reaching 80–95% and 10–28%, respectively.

2. However, the current effective treatment for HCV before or after transplant has entirely changed the scenario now.

***Post-transplant De-novo Diabetes Mellitus***

The prevalence of post transplant de-novo diabetes mellitus (PTDM) was reportedly 27%, 9% and 7% at 1, 2 and 3 yrs post-transplant, respectively. The decrease in the prevalence over time is likely related to reducing steroid use, which is a major risk factor in de novo PTDM.

***Post-transplant Metabolic Bone Disease***

Osteopenia and osteoporosis are prevalent in 10–40% of patients with end-stage liver diseases pre-transplant, and these conditions likely persist in the post-transplant period. Patient-specific risk factors of post-transplant metabolic bone diseases are female gender, older age, post menopause and a pre-transplant history of vertebral fracture.

Transplantation for cholestatic liver disease (PBC, PSC), post-transplant cholestasis, prolonged bed rest and immobility are other predisposing factors of metabolic bone disease.

***Post-transplant de-novo Malignancy***

The overall incidence of de-novo cancer post-transplant is about 2.5 times of the general population. Risk factors in developing post-transplant lymphoproliferative neoplasm are Epstein-Barr virus (EBV) infection, age >50, transplantation for HCV or alcohol cirrhosis, use of anti-lymphocyte antibody, and rejection therapy with high-dose steroids. Stepwise approach to PTLD treatment should begin with the reduction or complete withdrawal of immunosuppression, followed by various chemotherapies, radiation therapy or surgery.

**Donor Complications in LDLT**

1. Donor morbidity is around 16% & mortality about 0.2%.

2. Common donor complications reported include biliary leaks beyond postoperative day 7 (9%), bacterial infections (12%), incisional hernia (6%), pleural effusion requiring intervention (5%), neuropraxia (4%), re-exploration (3%) and wound infection (3%).

**Post Transplant Immunosuppression**

LT does not require human leukocyte antigen (HLA) matching between donor and the recipient. Immune responses in the liver are skewed towards tolerance, making the liver a privileged organ. LT recipients need less intense immuno-suppression than those of other solid organ transplants. The goal of immunosuppression after LT is to reduce allogeneic T-cell responses. Induction of immuno-suppression is to prevent acute cellular rejection. Intra-venous corticosteroid is the main stay of the treatment. Polyclonal antibodies like antithymocyte globulin (ATG) and interleukin receptor 2 antibodies like basiliximab and daclizumab also can be used. Calcineurin inhibitors (CNIs) are the backbone for the maintance of immunosuppression **(Table 26.1)**. Calcineurin inhibitor-related nephrotoxicity is the most frequent cause of renal dysfunction after LT and is associated with a 4.55-fold increased risk of death. Strategies of CNI reduction and withdrawal have recently been introduced in clinical practice in view of preventing or limiting its toxicities. Various medications are like antimetabolites (azathioprine and

mycophenolic acid derivatives), the anti-interleukin-2 receptor antibody basiliximab and the mammalian target of rapamycin inhibitors (mTORi) like everolimus (EVR), and sirolimus (SIR), alone or in different combination can be used.

Mammalian target of rapamycin inhibitors and CNI act on different sites of the T cell activation pathway. EVR is an mTOR inhibitor and has antiproliferative properties. It reduces protein synthesis and cell proliferation by binding to FK-binding proten-12 to form a complex that inhibits activation of the mTOR serine threonine kinase activity. EVR has a shorter terminal half-life and quicker steady state vs SIR. Late introduction of EVR is better than early introduction of EVR to reduce wound healing compli-cations. Adverse effects of proteinuria and hyperlipidemia are significantly higher compared to CNI and long-term effect on graft and patient survival in LT is still unclear.

**Surgery in Portal Hypertension**

1. Most common site of variceal bleeding is distal 2 cm of oesophagus.

2. Submucosal and periesophageal veins communicate around the gastroesophageal junction through perforating vessels and align in a consistent pattern with palisades zone that run in the submucosa.

3. In the era of therapeutic endoscopy, indications of surgery in patients with portal hypertension are few. Shunt surgery is discussed initially followed by role of LT in present section.

**Surgical Methods of Treating Portal Hypertension**

1. Decompressive shunt

2. Devascularization – mainly for the treatment of gastroesophageal varices

3. LT

**Decompressive shunts**

Decompressive shunts are of two types: surgical and non-surgical shunts.

**Surgical Shunts**

1. **Total portosystemic shunts**: Decompress all portal venous pressure; however, this will impair hepatic perfusion.

2. **Partial portosystemic shunts**: Decrease portal pressure <12 mmHg to reduce risk of complications and at the same time preserving hepatic perfusion.

3. **Selective shunt**: Decompress gastroesophageal varices only, but maintain portal hypertension.

***Total Portosystemic Shunt***

1. **End-to-side portocaval shunt (Eck fistula)**

n End-to-side portocaval shunt is no more used now.

n It is not useful in patient with ascites due to persistent hepatic sinusoidal pressure.

2. **Side-to-side portocaval/mesocaval shunt/central spleno-renal shunt**

n Side-to-side vein-to-vein anastomosis **(Fig. 26.1)** or incorporate prosthetic material (diameter 10 mm).

n It may cause hepatic arterial steal.

n High frequency of hepatic encephalopathy or hepatic

decompensation following total portosystemic shunt due to impaired hepatic perfusion.

n The advantage of mesocaval shunt is that it avoids hepatic hilum dissection, so future transplantation will not be technically difficult.

**Indications of Total Shunt**

1. Massive GI bleed with ascites.

2. Acute Budd-Chiari syndrome; to decompress obstructed sinusoids. Herein side-to-side portocaval shunt is preferred, where the portal vein acts both as the inflow to and outflow from the liver.

***Partial Portosystemic Shunt***

1. Shunt diameter is reducing to 8 mm rather than 10 mm.

2. It maintains portal flow in 80% and decreases portal hypertension <12 mmHg.

3. As this shunt maintains portal blood flow, there is significantly low frequency of encephalopathy.

***Selective Shunt***

1. Decompress gastroesophageal variceal blood flow and maintain portal blood flow. In fact it is strictly not a portocaval shunt! Herein the main intend is to reduce the risk of gastrooesophageal variceal bleed only.

2. Distal splenorenal shunt (DSRS, Warren shunt) is the most commonly used selective shunt. The splenic vein is disconnected from the portal vein and anastomosed to the top of the left renal vein. The left gastric vein is disconnected from the portal vein and tied off. Thus, the blood flows from the varices through the splenic vein, to the left renal vein and empties into the inferior vena cava. The blood flow to the liver is maintained through the portal vein **(Fig. 26.2)**. The highest time for re-bleeding following DSRS is first month to 6 weeks.

**Devascularization**

**Sugiura Surgery**

The most effective non-shunt operation for preventing recurrent variceal haemorrhage is esophagogastric devascu-larization with oesophageal transection and splenectomy, as advocated by Sugiura and associates. This procedure

involves ligation of venous branches entering the distal oesophagus and the proximal stomach from the level of the inferior pulmonary vein, combined with selective vagotomy and pyloroplasty. The most important is that the left gastric (coronary) vein and the paraesophageal collateral veins are preserved to permit portoazygous collateralization, which inhibits future varix formation. Initial success of these procedures cannot be replicated subsequently, as postoperative mortality has exceeded 20%, with bleeding recurring in 35–55% of patients.

**Hasabb Modification**

Except splenectomy, surgical procedure is reaming the same as Sugiura surgery.

1. Used in acute refractory bleeding.

2. TIPS is better than devascularization.

**Further Reading**

1. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunt. *Hepatology* 2000;33:464–70.

2. Wiesner RH, McDiarmid SV, Kamath P, et al. MELD and PELD. Application of survival models to liver allocation. *Liver Transplantation* 2001;7:567–80.

3. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from Child to MELD. *Hepatology* 2001;33:473–5.

4. Keeffe EB. Liver transplantation: Current status and novel approaches to liver replacement. *Gastroenterology* 2001; 120:749–62.

5. Jenkins RL. Defining the role of transjugular intrahepatic portosystemic shunts in the management of portal hypertension. *Liver Transpl Surg* 1999;1:225.

6. Rosen HR. Disease recurrence following liver transplantation. *Clin Liver Dis* 2000;4:675–89.

7. Feng S, Lai JC. Expanded criteria donors. *Clin Liver Dis* 2014; 18:633–49.

8. Moini M, Schilsky ML, Tichy EM. Review on immunosuppression in liver transplantation. *World J Hepatol* 2015; 7:1355–68.

9. Mei-Ling Yee and Hui-Hui Tan. Use of everolimus in liver transplantation. *World J Hepatol* 2017;9:990–1000.

10. Julie H Zhu, Trana Hussaini, Siegfried R Erb, et al. Medical complications of liver transplantation. *AME Med J* 2018;3:11–5.

11. Clara Tan-Tam, Maja Segedi, Andrzej Buczkowski. Surgical complications of liver transplantation. *AME Med J* 2018;3:107–13.

**Chapter 27.**

**Hepatocellular Carcinoma**

**Introduction**

Hepatocellular carcinoma (HCC) is the sixth most common cancer and fourth leading cause of cancer-related death. Early diagnosis of HCC can be achieved by surveillance of at-risk population. Candidates for resection must be carefully selected to minimize the risk of postoperative liver failure and improve long-term results. Access to liver transplantation is granted after balancing survival probability and organ availability. When surgical options are not feasible, image-guided tumour ablation is recommended as the most appropriate therapeutic choice. Despite the widespread implementation of surveillance programs, more than half of the patients with HCC are diagnosed late, when curative treatments are not applicable.

**Clinical History**

1. Often presents as nodule/nodules in a cirrhotic liver on radiological surveillance.

2. Abdominal pain (60–90%)

n Dull, continuous, dragging type of pain situated in the right hypochondrium and epigastrium secondary to stretching of Glisson’s capsule.

3. Weight loss: 34–70%

4. Weakness: 20–50%

5. Abdominal swelling: 28–43%

6. Jaundice: 5–25%

7. Rarely acute presentation with hemoperitoneum

8. Fever: 10–60%

9. Paraneoplastic symptoms

n Hypoglycaemia (type A occurs at terminal stage due to inadequate handling of glucose by liver and type B is due to secretion of insulin-like growth factor, IGF -II)

n Muscle weakness

n Tingling, numbness

10. Recent onset of hepatic decompensation in previously compensated cirrhosis liver

**Past History**

1. Past history of jaundice indicates acute hepatitis B infection leading to chronic liver disease.

2. Past history of blood transfusion, surgery, tattooing, homosexuality and sexual promiscuity – high risk for hepatitis B and C.

**Family History**

1. Family history of HBV infection – Intra-familial transmission of HBV infection.

2. Family history of liver disease in the family – Hemochromatosis, autoimmune liver disease and Wilson’s disease.

**Personal History**

1. Alcohol – Alcoholic cirrhosis, associated hepatitis C increase chances of HCC.

2. Smoking – Population studies showed that cigarette smoking is a causal risk factor for HCC.

**General Examination**

1. Pallor

2. Icterus

3. Stigma of chronic liver disease (Ch. 12)

4. Clubbing

5. Polycythemia

6. Skin lesions – Pityriasis, dermatomyositis, pemphigus (paraneoplastic manifestation)

**Abdominal Examination**

1. Inspection

n Abdominal distension secondary to ascites

n Fullness of flanks secondary to ascites

n Body hair – Sparse body hairs indicate cirrhosis liver

n Umbilicus – Bulging umbilicus secondary to ascites

n Dilated veins due to portal hypertension

n Fullness in right hypochondrium secondary to hepatomegaly

2. Palpation

n Tenderness in right hypochondrium

n Hepatomegaly (50–90%): Liver span, surface, edge, movement, consistency, tenderness

n Splenomegaly secondary to portal hypertension

3. Percussion

n Liver dullness

n Ascites

4. Auscultation

n Systolic arterial bruit (6–25%)

Other causes of bruit – alcoholic hepatitis, AV malformation.

**Neurological Examination**

1. Look for myopathy or neuropathy as paraneoplastic manifestation.

2. Asterixis suggestive of hepatic encephalopathy.

**Investigations**

Investigations of HCC include detection of the index lesion, staging of the lesion within the liver, assessment for extrahepatic metastasis and presence of underlying cirrhosis. Diagnosis of small HCC (<2 cm) is difficult in cirrhotic patients because of distortion of liver parenchyma, and the inability of portal venous phase contrast imaging to be effective in cirrhotic patients.

1. **Biochemistry**

**Haematology**

n Anaemia – secondary to blood loss

n Pancytopenia – secondary to hypersplenism (40–80%)

n Coagulation profile like prothrombin time

**Liver biochemistry**

n Low albumin secondary to poor liver synthetic function.

n Increase in bilirubin and enzymes may occur occasionally.

n Increased alkaline phosphatase.

**Serology**

n Serology for HIV, HBV and HCV infection.

2. **Ultrasound abdomen**

n Tumour is usually hyperechoic.

n Location and size of tumour.

n Associated portal vein thrombosis.

n Evidence of underlying cirrhosis and portal hypertension.

n Dilation of biliary radicles in case of porta nodes.

n Dynamic contrast ultrasound with intra-arterial infusion of CO2 micro bubbles increases sensitivity.

3. **Spiral CT abdomen with contrast (triple-phase multislice CT)**

n Tumour hypervascularization in the arterial phase is the biological hallmark of HCC.

n HCC receives virtually all its functional blood supply from the hepatic arterial flow, thus enhances vividly in arterial phase (begins 20–35 sec after initiation of the contrast infusion). Liver parenchyma, which receives major blood supply from the portal vein, will not enhance until portal venous phase dominates (55–75 sec). Thus, arterial enhancement profile of HCC is the most important diagnostic value.

n Site and size of the tumour.

n Associated arteriography to evaluate vascular invasion

n Evidence of underlying cirrhosis liver with portal hypertension

n Portal vein and hepatic vein thrombosis

n Extrahepatic metastasis

4. **MRI**

n MRI with dynamic gadolinium enhancement appears to be superior to helical CT for diagnosis of HCC.

n Tumour less than 2 cm size is difficult to diagnose in underlying cirrhotic liver because of considerable overlap on imaging between benign (regenerative), borderline (dysplastic) and malignant (HCC) nodules.

n In MRI, HCC looks like a focal lesion with high signal intensity on T2-weighted images, variable signal intensity on T1-weighted images, arterial enhancement after gadolinium and hypointense in portal venous phase.

n MR angiogram (MRA) is useful to evaluate vascular invasion.

5. **Angiography**

n Angiography or lipiodol CT should be used to determine the number of the nodules before definitive therapy is planned.

n Angiography is more useful to look at the number of lesions rather than size, position and arterial anatomy and vascular invasion.

6. **Tumour markers**

**Alfa fetoprotein (AFP)**

n Serum AFP level >400 ng/mL is a complementary method for the diagnosis of HCC.

n Serum AFP levels often are normal in small HCC < 2 cm size. Thus, serum AFP has a poor sensitivity for detecting HCC.

n 50–70% sensitive in low endemic area.

n False-positive results seen in teratocarcinoma of testis or embryonal cell carcinoma of ovaries and testis.

**Des--carboxyprothrombin**

n Sensitivity 50–90% and specificity 84%.

n Used when AFP level is not elevated in suspected case of HCC.

**Immunomarkers**

n Glypican-3, heatshock protein 70 and glutamine synthetase increase the diagnostic accuracy.

7. **Histopathology**

n Percutaneous biopsy for histological confirmation is not mandatory in patients with cirrhosis liver, hypervascular lesion of more than 2 cm in diameter

(**Table 27.1**, EASL criteria). Preoperative diagnostic accuracy without histology is around 98%.

n For nodules between 1 and 2 cm in size, the use of fine-needle aspiration with biopsy is recommended for the diagnosis.

n Nodule <1 cm in diameter needs serial follow-up with abdominal ultrasound every 3 months until the lesion exceeds 1 cm in size.

n FNA leads to haemoperitoneum (< 0.5%) and needle tract tumour dissemination in (3–5%) patient.

**Cytohistologic criteria**

**Non-invasive criteria (for cirrhotic patients)**

n Focal lesions of >2 cm with arterial hypervasculariza-

tion by two coincidental image (spiral CT scan, MRI,

angiography or contrast USG).

n Combined criteria including one imaging technique

with arterial hypervascularization and serum APF >400

ng/mL.

*(Bruix J, et al. J Hepatol 2001;35:421–30.)*

**Classification of HCC**

**Gross**

1. Nodular

2. Massive

3. Diffuse

**Microscopic**

1. Well-differentiated

2. Moderately differentiated (solid/scirrhous/clear cell)

3. Undifferentiated

**Natural History**

1. 40% of tumours <2 cm exhibit microscopic venous invasion.

2. Median doubling time is 200 days.

**Staging of HCC**

1. TNM staging

2. Okuda staging system

3. BCLC (Barcelona Cancer Liver Clinic) system

4. CLIP (Cancer of the Liver Italian Programme) system

**TNM**

T1 Solitary; <2 cm without vascular invasion

T2 Solitary; <2 cm with vascular invasion

Multiple; one lobe: <2 cm without vascular invasion

Solitary; >2 cm without vascular invasion

T3 Solitary >2 cm; with vascular invasion

Multiple; one lobe; <2 cm with vascular invasion

Multiple; one lobe: >2 cm with/without vascular

invasion

T4 Multiple; both the lobes with vascular invasion

N0 No regional node

N1 Regional nodes

M0 No metastasis

M1 Distant metastasis

**BCLC System**

In BCLC staging classification, the functional status of the patient and the liver status are measured by the performance status and Child-Pugh class, respectively **(Fig. 27.1)**.

**CLIP (Cancer of the Liver Italian Programme)**

In CLIP system, tumour size, Child-Pugh score, AFP level and portal vein invasion are taken as variables.

**Survival Following 5-Year Treatment According to the TNM Stage**

**Stage TNM class 5 yrs after treatment**

I T1N0M0 75%

II T2N0M0 68%

III T3N0M0 32%

T2N1M0

IVA T4N1M0 < 10%

IVB Any T, any N; M1 < 10%

**Okuda Staging Variables**

Includes tumour volume and hepatic involvement

**Criteria Positive Negative**

Size

(% of liver volume) >50% <50%

Ascites + –

Albumin <3 g% >3 g%

Bilirubin >3 mg% <3 mg%

**Stages Survival without treatment**

I No positive 8 mo

II 1 or 2 positive 2 mo

III 3 or 4 positive 0.7 mo

**Surgical Management of HCC**

There is no consensus on a common treatment strategy for patients with HCC worldwide. Treatment is largely based on number and size of tumours, presence or absence of cirrhosis and degree of hepatic deterioration. Majority of patients with HCC are not candidates for surgery due to large tumour size, extrahepatic metastasis and presence of underlying cirrhosis or vascular invasion. Surgical management is either resection or liver transplantation. **(Fig. 27.1)**

**Surgical Resection**

Patients with a solitary tumour at an early stage (BCLC, stage 0 or A) regardless of tumour size in whom the performance status is good, liver function is well preserved and there is no significant portal hypertension are ideal for surgical resection. Presence of oesophageal varices or ascites, platelet count of less than 100,000/cmm and indocyanine green retention of more than 14% are poor prognostic factors precluding surgical resection. Patients having the ideal criteria have a survival of 60% at 5 yrs with a postoperative mortality of less than 3% although 70% will have a tumour recurrence at 5 yrs.

**Large HCCs**

Several studies have reported the short and long-term outcomes of resection of extremely large (>10 cm in diameter) HCCs. The mortality and 5-yr overall survival rates were 2–3.3% and 28–33%, respectively. Multiple tumours, vascular invasion and impaired liver function were found to be predictors of poor survival. Large HCCs should be treated by surgical resection as long as the liver function is maintained within a satisfactory range.

**HCCs with Macroscopic Vascular Invasion**

Presence/absence of macroscopic vascular invasion is one of the strongest predictors of the prognosis in patients with HCC.

HCCs tend to invade adjacent venous branches, which process is associated with an increased risk of intrahepatic or extrahepatic metastases. The prognosis of HCCs with vascular invasion is even more dismal if they are left

untreated. The median survival of untreated HCC patients with portal venous invasion is only 2.7 months. Surgical resection leads to better survival outcomes than nonsurgical treatment strategies. Portal venous invasion by the tumour is typed as Vp1 once peripheral venous branches are involved, Vp2 for secondary branches, Vp3 for right or left main trunk and Vp4 for invasion of main trunk. The resection for HCCs with Vp3 or Vp4 is not recommended. As compared to portal venous invasion, HCC invasion of the bile duct or inferior vena cava is quite rare.

**Resection of Extrahepatic Metastases**

Several studies reported limited benefit of aggressive resection of extrahepatic metastases when the extrahepatic lesion was solitary and/or the intrahepatic recurrence was well controlled. The lungs are the most common site of extrahepatic metastasis from HCC, with pulmonary metastases accounting for 50–60% of all extrahepatic metastases. The outcomes of surgical resection of lung metastases have been increasingly reported recently, with the reported 5-year survival rate after pulmonary resection being in the range of 27–33%; however, the number of patients included in each of these studies was small (8–61 patients), because, in most cases of pulmonary metastases, the lesions are multiple and surgical resection is contraindicated.

**Resection of Recurrent HCCs**

The most common site of recurrence is the remnant liver, which accounts for 85–90% of the initial recurrences. The reported incidence of intrahepatic recurrence within 2 yrs after primary hepatic resection is 70%. The effectiveness of systemic chemotherapy for HCCs has not yet been established; therefore, in the absence of extrahepatic metastases, locoregional treatment is currently the only approach that can yield long-term survival in patients with recurrent HCC. Locoregional treatment such as ethanol injection (PEI), radiofrequency ablation (RFA) or TACE, for an intrahepatic recurrence may be repeated as long as there are no extrahepatic recurrences and the remnant liver function is reasonably adequate.

**Preoperative and Adjuvant Treatments**

Several other studies report that preoperative TACE may improve the disease-free and overall survivals in selected cases such as HCC patients with macroscopic portal venous invasion, advanced-stage tumours, severe liver dysfunction (ICG-R15 >17%) or centrally located large tumours.

One study showed that TACE converted initially unresectable HCCs to resectable tumours, yielding a 5-year survival rate of 56%. Sorafenib has not yet been validated as a preoperative or adjuvant treatment.

**Laparoscopic Hepatectomy**

Several specialized centers have expanded the indications of laparoscopic hepatectomy from benign tumours to malignant tumours, including HCCs. The consensus conference by 45 experts held in October 2008 proposed that the most suitable candidates among HCC patients for laparoscopic hepatectomy are, in general, those with solitary lesions measuring 5 cm or less in diameter, located in the peripheral segments.

**Liver Transplantation for HCCs**

The Milan criteria (solitary HCC <5 cm or up to 3 tumours with none >3 cm), which were published in 1996, are appropriate for patients with HCC who are potential candidates for liver transplantation. In those patients who meet the Milan criteria, survival is 60–80% at 5 yrs and 50% at 10 yrs with tumour recurrence of less than 15%. The Milan criteria are rather restrictive, permitting liver trans-plantation in only a limited proportion of patients with HCC, and therefore, expansion of the criteria has been proposed. The most representative example of such expanded criteria is the University of San Francisco (UCSF) criteria, which include solitary tumour 6.5 cm, or two or three nodules with the largest lesion 4.5 cm and total tumour diameter 8 cm. These criteria were also validated by subsequent studies from high-volume transplantation centres, which reported overall 5-year survival rates of 52–64%. In the University of Tokyo, patients with HCC having up to 5 nodules with a maximal diameter of 5 cm (the 5–5 rule) have been treated by transplantation, and the 5-yr survival rate according to this 5–5 rule was reported to be 75%.

Other ways by which ineligible candidates are made eligible (downstaged) or waiting list patients are treated are by the techniques of portal branch embolization to increase regeneration of healthy liver, transarterial chemo-embolization (TACE) or ablation by radiofrequency (RFA) or ethanol injection (PEI).

**Systemic therapies**

Sorafenib exerts an anti-tumour effect by blocking different signalling pathways mainly related to proliferation (e.g., RAS/MAPK) and angiogenesis (e.g., VEGFR and PDGFR). The SHARP trial proved its effectiveness and led to development of other drugs. Unfortunately, newer drugs like erlotinib, brivanib, sunitinib, linifunib and others have not shown any superiority over sorafenib. Lenvatinib has been

approved by FDA after demonstration of non-inferiority. Regorafenib, an inhibitor of multiple kinases increased survival in those not responding to sorafenib. Cabozantinib and Ramucirumab have also given good results.

Research in treatment of cancers by immune system modification is a promising new pathway. In HCC, treme-limumab showed a response rate of 17.6% in those not benefiting by sorafenib. Nivolumab and pembrolizumab have also been trialled.

**Management of Inoperable Tumour**

Majority of HCC are inoperable at the time of presentation. There are various treatment modalities available using imaging guidance to destroy tumour without significantly affecting cirrhotic liver tissue around the tumour. Image-guided loco-regional therapies – including direct tumour ablation techniques and transcatheter treatments – play a major role in the clinical management of HCC.

**Image-guided tumour ablation**

The term “image-guided tumour ablation” is defined as the direct application of chemical or thermal therapies to a specific focal tumour (or tumours) in an attempt to achieve eradication or substantial tumour destruction.

**Percutaneous Ethanol Injection (PEI)**

The aim of PEI is to substantially kill tumour cells by injecting alcohol into the tumour. Encapsulated hepatoma responds well to PEI. Lesion site is very important, for lesion smaller than 3 cm has good outcome, equal to that from surgery or other ablation techniques. Larger lesion PEI acts as bride to transplantation. The major limitation of PEI is the high local recurrence rate that may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm. The injected ethanol does not always accomplish complete tumour ablation because of its inhomogeneous distribution within the lesion, especially in the presence of intratumoral septa and diffuse infiltrative tumour.

The recent introduction of a specific device for single-sessions PEI, a multi-pronged needle with three retractable prongs, each with four terminal side holes, has been shown to overcome some of these limitations, by ensuring a more homogeneous ethanol perfusion throughout the whole tumour mass.

**Method of PEI**

1. Nil per orally for at least 6 hrs.

2. Procedure should be done under sedation and analgesia.

3. The tumour is punctured with a 21- or 22- gauge, 1.5 cm needle under US guidance.

4. Absolute ethanol is injected into the tumour at one or more locations under US guidance. Tumour becomes hyperechoic following ethanol injection.

5. Around 2–4 mL of ethanol is injected in one session to reduce complications.

6. Around 3–6 sessions are needed for HCC <2 cm in diameter whereas 7–9 sessions for HCC diameter >3 cm.

7. Total volume of ethanol required to destroy tumour is calculated by the following equation:

V = 4/3  (r + 0.5)3

Where V is volume of ethanol (mL), r is radius of the tumour (cm) and addition of 0.5 is provided as a safety margin.

**Radiofrequency ablation (RFA)**

In RFA, radiofrequency waves are used to create heat to destroy tumour cells. The important factor that affects the success of RFA is the ability to ablate all viable tumour tissue and create an adequate tumour-free margin. Ideally, a 360o, 0.5–1 cm thick-ablative margin should be produced around the tumour. This cuff will ensure that the peripheral portion of the tumour as well as any microscopic invasion located in its close proximity has been eradicated. Three independent meta-analyses including all RCTs have confirmed that treatment with RFA offers a survival benefit comparable to PEI, particularly for tumours larger than 2 cm, thus establishing RFA as the standard percutaneous technique.

Recent reports on long-term outcomes of RFA-treated patients have shown that in patients with Child-Pugh class A and early stage HCC, 5-yr survival rates are as high as 51–64%, and may reach 76% in patient who meet the BCLC criteria for surgical resection.

The ability of RFA to achieve complete tumour eradi-cation appears to be dependent on tumour size and location. Tumour size above 3 cm or the presence of large (3 cm) abutting vessels result in a drop of the rate of complete tumour necrosis to 50% or less. HCC tumours in subcap-sular location or adjacent to the gall bladder are associated with an increased risk of incomplete ablation and local tumour progression.

**New methods for local Ablation**

**Microwave Ablation**

Microwave ablation (MWA) is the term used for all electromagnetic methods of inducing tumour destruction by using devices with frequencies greater than or equal to 900 kHz.

MWA is emerging as a valuable alternative to RFA for thermal ablation of HCC. An important advantage of MWA over RFA is that treatment outcome is less affected by vessels located in the proximity of the tumour.

**Laser Ablation**

The term laser ablation should be used for ablation with light energy applied via directly inserted into the tissue. To date, few data are available concerning the clinical efficacy of laser ablation.

**Cryoablation**

Cryoablation is a technique in which a liquid nitrogen cooled cryo probe is placed into the tumour and an ice ball is created in the target tissue. The complication rate is not negligible, particularly because of the risk for “cryoshock,” a life-threatening condition resulting in mutiorgan failure, severe coagulopathy and disseminated intravascular coagulation following cryoablation.

**Irreversible Electroporation**

Irreversible electroporation (IRE) or electropermeabilization is a new, non-thermal ablation technique. Electroporation is a technique that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupting the lipid bilayer integrity to allow transportation of molecules across the cell membrane via nano-size pore. IRE is a method to induce irreversible disruption of cell membrane integrity resulting in cell death without the need for additional pharmacological injury. IRE is administered under general anaesthesia with administration of a neuro-muscular blocking agent to prevent undesirable muscle contraction. IRE creates a sharp boundary between the treated and untreated area *in vivo*. Because IRE is a non-thermal technique, there appears to be complete ablation to the margin of blood vessels without compromising the functionality of

the blood vessels.

**Image-guided Transcatheter Tumour Therapy**

The term “image-guided transcatheter tumour therapy” is defined as the intravascular delivery of therapeutic agents via selective catheter placement with imaging guidance. The term “Transcatheter” aims to distinguish these therapies from direct ablative therapies. The most common methods of image-guided transcatheter tumour therapy used in HCC treatment are chemoembolization and radioembolization.

**Conventional TACE**

TACE has been established as the standard of care for patients who meet the criteria for the intermediate stage if the BCLC staging system, i.e., those with multinodular HCC, relatively preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread.

**TACE with Drug-Eluting Beads**

The ideal TACE scheme should allow maximum and sustained concentration of chemotherapeutic drug within the tumour with minimal systemic exposure combined with calibrated tumour vessel obstruction. The recent introduction of embolic microspheres that have the ability to actively sequester doxorubicin hydrochloride from solution and release it in a controlled and sustained manner, has been shown to substantially diminish the amount of chemotherapy that reaches the systemic circulation compared with lipiodol-based regiments, thus significantly increased the local concentration of the drug and the antitumour efficacy. Use of doxorubicin-eluting beads resulted in a marked and statistically significant reduction in liver toxicity and drug-related adverse events compared with conven-tional TACE with doxorubicin. TACE with drug-eluting beads achieved complete necrosis in 77% of lesions, whereas bland embolization achieved complete necrosis in only 27% of lesions.

**Radioembolization**

The use of conventional external-beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the cirrhotic liver that often resulted in radiation-induced liver disease, previously known as radiation-included hepatitis. Radioembolization is defined as

the infusion of radioactive substances including microspheres containing yttrium-90 (Y90), iodine 131 iodized oil or similar agents into the hepatic artery. Given the hypervascularity of HCC intra-arterial-injected microspheres will be preferentially delivered to the tumour-bearing area and selectively emit high-energy, low-penetration radiation to the tumour. These are currently two commercially available Y90 microsphere devices: one is made of glass and the second is made of resin.

Due to the minimally embolic effect of Y90 micro-spheres, treatment can be safely used in patients with portal vein thrombosis. Toxicities included fatigue (57%), pain (23%) and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%.

Despite the amount of data, no RCTs have been published so far to prove the clinical benefit to radioembolization with respect to the established treatment options for the patient populations that are targeted by radioembolization, i.e., TACE for noninvasive multinodular tumours at the intermediate stage of the BCLC classification and Sorafenib for advanced HCC showing vascular invasion.

**Synergies and Combination Strategies**

An accepted indication is the use of interventional treatment in patients awaiting transplantation to prevent tumour progression when the waiting time exceeds 6 months. The combined use of transcatheter treatments and tumour ablation techniques is very popular in the treatment of HCC tumours of intermediate (3–7 cm) size. A combination of TACE followed by RFA has been used to minimize heat loss due to perfusion-mediate tissue cooling and increase the therapeutic effect of RFA.

An important limitation of any loco-regional treatment is the high rate of tumour recurrence. After local ablation of early stage HCC, tumour recurrence rate exceed 80% at 5 yrs, similar to post-resection figures. Molecular studies have shown that early recurrences – occurring within the first 2 yrs after curative treatment – are mainly due to the spread of the original tumour, whereas late recurrences are more frequently due to the development of meta-chronous tumours independent of the previous cancer. On the other hand, in patients with large or multinodular tumour at the intermediate-stage HCC who received TACE, tumour recurrence or progression is almost inevitable.

Tumour recurrence following TACE, in particular, is characterized by increased vascular endothelial growth factor (VEGF) production and subsequent angiogenesis. Based on these finding, combinations of TACE with agents with anti-angiogenic properties (Sorafenib) would appear as a rational approach. Summary of various modalities of management according to BCLC staging systems is described in **Fig. 27.1**.

**Risk Factors for HCC**

**Major Risk Factors**

1. Cirrhosis

2. Hepatitis B

3. Hepatitis C

4. Alcohol

5. Non-alcoholic fatty liver disease (NAFLD)

6. Aflatoxin B1 – *Aspergillus flavus*

7. Contaminated food stuffs, mainly grains and legumes

8. Autoimmune liver disease

9. Smoking – role of smoking in the development of HCC is controversial

10. Chemical compounds – Thorotrast

**HCC without Background Cirrhosis**

1. Hepatitis B

2. Hepatitis C

3. Aflatoxin B1

4. Thorotrast

5. Alfa-1 antitrypsin deficiency

**HBV Infection and HCC**

1. Chronic hepatitis B virus (HBV) infection is a major risk factor for development of HCC.

2. As infection early in life often becomes persistent, HBV infection at young age is an important risk factor for HBV-related tumours.

3. 0.3% per year in carriers.

4. 1.5–6.6% per year in compensated cirrhosis.

5. Risk factors for developing HCC in patients with HBV infection:

n Male sex

n Family history of HCC

n Underlying cirrhosis

n HBV DNA positivity

n Co-infection with HCV

6. Possible mechanism of carcinogenesis related to HBV infection:

n Activation of oncogenes

n Inactivation of tumour suppressor gene

n Integration of HBV DNA into DNA of the host cells

n Interactions of HBV specific protein with hepatic gene

n Chronic inflammation and effect of cytokines in the development of fibrosis and hepatocyte proliferation

n Transactivation of Hbx-gene

**HCV Infection and HCC**

1. Estimated risk for the development of HCC in HCV infection is 17.5-fold.

2. Development of HCC is 0.4% per year in carrier and 1.7–2.4% per year in cirrhotic.

3. HCC usually arises after 2–4 decades of infection, typically in the context of underlying cirrhosis.

4. Risk factors for developing HCC in patients with HCV infection:

n Late acquisition of HCV virus

n Severity of HCV infection

n Co-infection with HBV infection/alcohol

5. Possible mechanism of carcinogenesis related to HCV infection

n Core protein of HCV is possibly oncogenic

n Downregulation of p53

n Incorporated with k-ras

n Free radical production

n Truncated NS3 protease leads to mitosis

**Alcohol and HCC**

1. Chronic alcohol use of greater than 80 g/day for more than 10 yrs increases the risk for HCC approximately 5-fold.

2. Alcohol use in chronic hepatitis C doubles the risk for HCC compared with the risk in HCV infection.

3. Alcohol is not a mutagenic.

4. Cirrhosis is the basis for ethanol-related HCC; however, HCC can occur in a noncirrhotic liver.

5. Possible mechanism of carcinogenesis related to alcohol ingestion:

n Chromosomal loss

n Oxidative stress

n Genetic susceptibility

n Altered DNA methylation

**Non-alcoholic Fatty Liver Disease (NAFLD) and HCC**

1. Incidence of NAFLD has gone up dramatically in USA because of exponential increase in obesity and is estimated to be as high as 30%.

2. In 10–20% of cases, there is development of cirrhosis predisposing to HCC. HCC can occur without cirrhosis also in NAFLD.

3. Risk of HCC in NAFLD is considerably higher although the absolute risk is low. The 5- and 10- year HCC risk is 0.8 and 1.7 per 1000 patients, respectively. Older Hispanics have the highest risk.

**Liver Cirrhosis and HCC**

1. Cirrhosis from any cause is the most common risk factor for HCC. Majority of patients with HCC have underlying cirrhosis.

2. Annual incidence of cirrhosis is 3%.

3. Risk factors for developing HCC in liver cirrhosis:

n Male sex

n Elevated AFP

n Severity of cirrhosis

n Increased rate of liver cell proliferation

n Macroregenerative nodules

**Haemochromatosis and HCC**

1. The risk for development of HCC in patients with hereditary haemochromatosis (HH) is around 200-fold.

2. Excess iron in the liver leads to cellular proliferation, direct damage to DNA, inactivation of tumour suppressor gene like p53.

3. Excess iron also leads to lipid peroxidation and acceleration of fibrogenesis.

**Fibrolamellar HCC**

1. Fibrolamellar HCC comprises around 1% of all HCCs.

2. Fibrolamellar HCC occurs in young patients with equal frequency in male and female in the noncirrhotic liver.

3. Imaging shows well-defined solitary lesion in non-cirrhotic liver with minute calcification.

4. Elevated serum APF is seen in only 20% of patients.

5. Histology shows fibrous stroma with lamellar stranding.

6. More suitable for liver resection because it is sharply demarcated and arises in noncirrhotic liver.

7. 5-yr survival of fibrolamellar HCC is 25–35%.

**Screening for HCC**

Majority of HCC are inoperable at the time of presentation and there are only few therapeutic options left for the patients. Thus, screening and surveillance for HCC would appear to be very important. But the optimal method for surveillance and its impact on survival is not known.

**Target Population**

1. Patients with cirrhotic liver

2. Chronic HBV and HCV infection

3. Hereditary hemochromatosis

**Surveillance Tests**

1. Ultrasound examination of abdomen

2. Measurement of -fetoprotein (AFP) levels

**Surveillance intervals**

Optimal surveillance interval for HCC is not known. But clinical trials have shown a surveillance interval of 6 months is cost effective.

During surveillance, identification of nodule less than 1 cm in size indicates aggressive surveillance once in 3 months till the nodule increases to 1 cm. If nodule size is between 1 and 2 cm in diameter, FNA from the nodule is advocated to see whether it is a dysplastic nodule or an HCC. However, this can be technically very challenging. If nodule size >2 cm, it needs further imaging in the form of CT/MRI/angiography to confirm HCC (see EASL Criteria). There are no recommendations for surveillance in NAFLD at present.

**Summary**

HCC develops commonly in cirrhotic. Nodules are often first discovered during ultrasound surveillance of cirrhotic livers. It is imperative that cirrhotics are followed up regularly in specialist units where such surveillance can be carried out in conjunction with radiologists with an interest in liver diseases. Distinguishing a regenerative nodule from a HCC

can be challenging and requires a combination of US, multislice CT, MRI and angiography +/- biopsy.

The diagnosis should be made in the clinical context within a multidisciplinary setting (hepatologist, HPB/transplant surgeons, liver radiologists, oncologists and liver patholo-gists).

Liver transplantation appears to give the best results in terms of long-term recurrence-free survival. However, not all patients are liver transplant candidates and strict criteria

such as the Milan criteria should be followed to get the best results. Patients who are not transplant candidates should be considered for liver resection; however, this is only possible in those with preserved liver function. Majority of the patients are neither resectable nor transplantable and may benefit from one of the ablation procedures.

All cirrhotic should be offered 6-monthly surveillance and policies should be targeted towards prevention of cirrhosis and hepatitis, if we are to make any headway in the eradication of HCC.

**Further Reading**

1. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-200 EASL conference. European Association for the study of the Liver. *J Hepatol* 2001;35:421–30.

2. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma. The BCLC staging classification. *Semin Liver Dis* 1999;19:329–38.

3. Llovet JM, Fuster J, Bruix J, et al. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma; resection versus transplantation. *Hepatology* 1999; 20:1434–40.

4. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334: 693–99.

5. SD Ryder. Guideline for the diagnosis and treatment of Hepatocellular carcinoma (HCC) in adults. *Gut* May 2003; 52:1–8.

6. Pandey DK, Lee H, CT Wai G, et al. Long term outcome and prognostic factors for large hepatocellular carcinoma (10 cm or more) after surgical resection. *Annals of Surgical Oncology* 2007;14:2817–23.

7. Bolondi L, Sofia S, Siringo S, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001;48:251–9.

8. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *The Annals of Surgery* 2007;246:502–9.

9. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–9.

10. Orlando A, Leardro G, OlivO M, ANdriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trail. *Am J Gastroenterol* 2009;105:514–24.

11. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systemic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology* 2009; 49:453–9.

12. Germani G, Pleguezuelo M, Gurusamy K, et al. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta analysis. *J Hepatol* 2010; 52:380–8.

13. Belghiti J, Carr BI, Greig PD, et al. Treatment before liver transplantation for HCC. *Ann Surg Oncol* 2008;21:224–30.

14. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2010;53:1020–2.

15. Llivot JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359:378–90.

16. Villaneuva A. Hepatocellular carcinoma. *N Engl J Med* 2019;380:1450–62.

17. Chedid MF, Kruel CRP, Pinto MA, et al. Hepatocellular carcinoma: diagnosis and operative management. *Arq Bras Cir Dig* 2017;30;272–8.

18. Gray JB. Ablation with absolute ethanol, In: Interventional Radiology by Wilfrido R. Third edition, 1997, Williams and Wilkins, pp. 175–91.

**Chapter 28.**

**Liver Abscess**

**Introduction**

Liver abscess can be defined as an encapsulated collection of suppurative material within the liver parenchyma, which may be infected by bacterial, fungal and/or parasitic micro-organisms. Liver abscesses can be divided into three main categories based on the underlying conditions: infectious, malignant and iatrogenic. Infectious abscesses include those secondary to direct extension from local infection, systemic bacteraemia and intra-abdominal infections that infect the portal venous system. Amebic liver abscess is very common in tropical countries. This section describes the clinical manifestation, investigations and management of amebic and pyogenic liver abscess.

**Amebic Liver Abscess**

**Introduction**

Amebic liver abscess is an inflammatory space-occupying lesion of the liver caused by *Entamoeba histolytica*. It is the most common form of extraintestinal amebiasis. Amebic liver abscesses are usually single and mostly found in the right lobe of the liver. The incidence of amebic abscess in the left lobe of the liver ranges from 5 to 21%. The liver abscess has a thin capsular wall with a necrotic centre that consists of a thick fluid. Typically, abscess fluid is odorless and resembles “chocolate syrup or anchovy paste” in half. Bacteriologically it is sterile, however, secondary bacterial infection may occur (in 15–20%). The mortality rate has been estimated to be around 0.2–2.0% in adults and up to 26% in children. Alcoholism, malignancy, HIV infection, corticosteroid usage or other immunosuppressive conditions are the common risk factors for amebic liver abscess.

**Clinical History**

1. Usually occurs in young adults.

2. Amebic liver abscess is 10 times as common in men as in women.

3. Presentation may be either acute or chronic indolent.

4. Abdominal pain – localized in right hypochondrium and epigastrium (in case of left lobe abscess), moderately severe, continuous and radiating to right shoulder.

5. Moderate degree of fever.

6. Jaundice (30%) – Due to large or multiple abscess or an abscess situated at the porta.

7. Diarrhoea is a presenting complaint in around one-third of patients.

8. Cough with expectoration and pleuritic chest pain

**Physical Examination**

1. Moderate degree of fever

2. Jaundice

3. Tender, soft, smooth hepatomegaly

4. Shifting of liver dullness by one or two spaces above

**Investigations**

1. ***Microscopy***

n Fresh fecal sample may detect trophozoites containing erythrocytes, preferably within 30 min of the passage of stool. Wet mount preparation should be made in saline solution, in saline plus iodine, and in saline plus methylene blue. Presence of erythrophagocytic trophozoites is strongly suggestive of invasive disease.

n Sensitivity of stool microscopy to detect *E. histolytica* is 10–40%.

n False-positive results in the presence of *E. dispar* infection.

n Sensitivity of abscess fluid microscopy is less than 20%.

2. ***Chest X-ray PA view***

n Elevated right hemidiaphragm

n Minimal right pleural effusion

3. ***USG abdomen***

n Usually amebic liver abscess is solitary abscess situated in right lobe.

n Size and number of abscess.

n May identify complication of abscess like rupture.

n Can identify feasibility of percutaneous aspiration in case of inadequate response to medical management.

4. ***CT scan abdomen***

n Complimentary to USG abdomen, better delineation of size, number and location of the abscess.

n Indicated only when USG findings are equivocal or suspicion of additional pathology.

5. ***Serology***

n Antiamebic antibody is positive in more than 90% of patients. Antibody titer peaks in 2–3 months and persists till 9 months. Antibody remains positive for years in endemic area.

n Indirect hemagglutination test (IHA) has sensitivity and specificity more than 85%. Antibody may be negative in early infection and should be repeated 7 days later. IHA may remain positive for up to 20 yrs and represent a previous infection. EIA (Enzyme-linked immunosorbent assays) is the most commonly employed test and it usually become negative within 6–12 months.

n Detection in stool of *E. histolytica*-specific antigen or DNA.

n PCR technique to detect *E. histolytica* cysteine proteinase gene product.

**Management**

1. Medical management

2. Aspiration or drainage of abscess

3. Surgical intervention

***Medical Management***

Medical therapy is effective in more than 90% of patients with amebic liver abscess. Nitroimidazoles group (metro-nidazole, ornidazole, satronidazole, tinidazole, etc) is the main stay of treatment. Therapy should continue for at least 10 days. Relapses have been reported with this duration and the drug may be administered for up to 3 weeks. Single agent therapy with metronidazole yields excellent results and the alternative toxic drugs are indicated rarely and used probably in seriously ill patients where the risk of failure of therapy is unacceptable. The response to anti-amoebic drug is usually evident within 48–72 hrs with the subsidence of toxemia.

***Aspiration or Drainage of Abscess***

Routine aspiration or drainage of liver abscess is not indicated for therapeutic purposes. Anti-amebic therapy is equally effective as aspiration for uncomplicated abscess.

*Indications of Aspiration*

1. Lack of improvement after 48–72 hrs of treatment with anti-amebic drugs

2. Left lobe abscess (because it can lead to pyopericardium)

3. Abscess rim less than 10 mm

4. Seronegative abscess

5. Abscess with impending rupture

6. Abscess size more than 10 cm

***Surgical Intervention***

Surgical intervention is rarely indicated. It is indicated in large abscess with poor response to aspiration.

The only clear indication of surgery is rupture of abscess into the adjacent viscera or pericardium.

**Long-term Follow-up of Patients with Amebic Liver Abscess**

After clinical cure, the mean time for the disappearance of the abnormality on the sonography is 6–9 months. Relapses are very uncommon and the sonographic abnormality does not warrant continued therapy. The patterns of resolution seen on sonographic follow-up include the following: Type I: where complete disappearance of the cavity occurs within 3 months (29.8%) and Type II: a rapid reduction up to 25% of the original cavity size and then a delayed resolution (5.9%). Factors influencing healing time include the size of abscess cavity at admission, hypoalbuminemia and anaemia. Multiple liver abscesses are similar to a solitary abscess in terms of the type of clinical presentation, nature of therapy, number of location of the abscesses and time for clinical resolution. The total volume of abscess in all the cavities is the most important factor that influences the resolution time in multiple abscesses. Ultrasonographic resolution does not always indicate clinical resolution; therefore, clinical criteria rather than USG should be used to confirm the outcome of the therapy.

**Prognostic Markers**

Poor prognostic criteria in patients with amebic liver abscess:

1. Serum bilirubin more than 3.5 mg/dL

2. Encephalopathy

3. Volume of abscess cavity

4. Hypoalbuminemia

***Variant of Amebic Liver Abscess***

1. Left lobe abscess 35%

2. Multiple abscesses 15%

3. Posteriorly located abscess compresses hepatic veins or inferior vena cava

4. Abscess rupture into adjacent viscera

***Unusual Manifestations of Amebic Colitis***

1. Acute necrotizing colitis

2. Toxic megacolon

3. Ameboma

4. Perianal ulceration with formation of a fistula

***WHO Clinical Classification of Amebiasis (modified)***

1. Asymptomatic infection

2. Symptomatic infection

n Intestinal amebiasis

- Amebic dysentery

- Nondysentery gastroenteritis

- Ameboma

- Complicated intestinal amebiasis

- Postamebic colitis

n Extaintestinal amebiasis

- Nonspecific hepatomegaly

- Acute nonspecific infection

- Amebic abscess

- Amebic abscess, complicated

- Amebiasis cutis

- Visceral amebiasis

**Pyogenic Liver Abscess**

**Introduction**

Pyogenic liver abscesses result from bacterial infection of the liver parenchyma and subsequent infiltration of the area with neurtophils and other phagocytes to form a collection of pus.

**Clinical History**

1. Clinical history is usually non-specific.

2. Insidious onset right upper quadrant pain – dull, continuous, radiating to the tip of the shoulder.

3. Moderate degree fever.

4. Loss of appetite and weight loss.

5. History of interventions like endoscopic stenting of biliary duct and transarterial chemoembolization.

6. Right-sided pleuritic chest pain, an abscess adjacent to the diaphragm may cause pleuritic type pain, cough and dyspnea.

**Physical Examination**

1. Clinical features of septic shock when liver abscess is associated with cholangitis

2. Right upper quadrant tenderness

3. Soft, smooth, tender hepatomegaly

**Investigations**

1. ***Biochemistry***

n Neutrophilic leukocytosis

n Elevated C-reactive protein and erythrocyte sedimentation rate

n Mild anaemia

n Hyperglycaemia may be the first indication that the patient is diabetic or there is loss of control because of septic process

2. ***Chest X-ray***

n Elevated right hemidiaphragm

n Right-sided pleural effusion or basal infiltrates

3. ***USG abdomen***

n Ultrasonography is the most useful screening test and highly sensitive (85–95%).

n Can detect site and number of liver abscess.

n Evaluation of biliary tree.

n Distinguishing solid from cystic lesion. Initially the abscess is hyperechoic and indistinct, but with maturation and pus formation, it becomes hypoechoic with a distinct margin.

n Cluster sign: Aggregation of multiple small abscesses suggests the beginning of coalescence into single large abscess.

4. ***CT scan abdomen***

n CT scan of abdomen is more accurate than USG in the differentiation of pyogenic liver abscess from other liver lesions has a sensitivity of approximately 95%. The portal venous phase using intravenous contrast material gives the best differentiation between the liver and the abscess, with the periphery of the abscess having contrast enhancement as opposed to non-enhancement of the central portion.

5. ***Microbiology***

n Gram stain of aspirated pus has poor sensitivity.

n Blood and pus both should be sent for aerobic and anaerobic cultures.

n Blood culture is positive in 60% of patients while pus culture is positive in 70–88%.

**Microbiology**

1. Aerobes

n *Escherichia coli*

n *Klebsiella pneumoniae*

n *Enterobacter* Spp.

n *Pseudomonas* Spp.

n *Staphylococcus aureus*

n *Streptococci*

2. Anaerobes

n *Bacteroides fragilis*

n *Fusobacterium* Spp.

n *Clostridium perfringens*

3. Yeast

**Management**

1. Medical management

2. Aspiration or drainage of abscess

3. Surgical intervention

***Medical Management***

1. Antimicrobial therapy should be started immediately after obtaining specimen for culture.

2. Initial empiric antibiotics should cover aerobic and anaerobic bacteria. Management with antibiotics alone

has been shown to be effective for multiple small abscesses, <5 cm in diameter.

3. Patients are typically treated initially with IV antibiotics, followed by a course of oral (PO) antibiotics recommendations for duration range from 3 weeks IV plus 1–2 months PO to 2–3 weeks IV plus 1–2 weeks PO. Treatment duration depends on both response to treatment, as determined by repeat US imaging, and resolution of fever and leukocytosis. Empiric coverage for gram-negative bacilli, gram-positive cocci, as well as anaerobic bacteria has been recommended.

Combination of third-generation cephalosporin plus metronidazole or broad-spectrum penicillin with aminoglycosides. Imipenem has activity against almost all aerobic and anaerobic bacteria.

***Aspiration or Drainage of Abscess***

Liver abscess can be drained either with needle aspiration or by insertion of a pigtail catheter drain (PCD) under US or CT guidance. With percutaneous needle aspiration, a 16–18-G needle is inserted into the abscess cavity, and the contents are aspirated until the abscess is completely evacuated. Similarly, during percutaneous catheter drainage, an 8-14 F pigtail catheter is inserted into the lesion and left in place. The abscess is then drained by gravity until empty. Ascites is a contraindication for percutaneous drainage because of risk of septic peritonitis. Around 15–36% of the liver abscess fails to improve following percutaneous drainage because of the multiloculated nature or the contents of the liver abscess, which leads to blockade of the pigtail catheter.

Antibiotics and drainage are unlikely to cure pyogenic liver abscess in two situations:

1. Secondary infection of hepatic malignancy.

2. Hepatic abscess associated with chronic graulomatous disease of childhood.

***Surgery***

Surgical approach could be either laparotomy or laparoscopy.

*Indications for Surgery in Pyogenic Liver Abscess*

1. Failed percutaneous drainage

2. Evidence of clinical deterioration despite adequate antimicrobial agents and drainage

3. Multiloculated left lobe abscess

4. Rupture of an abscess in peritoneal cavity

**Aetiology of Pyogenic Liver Abscess**

1. Biliary tract infection

n Blocked biliary stent

n Cholecystitis

n Benign and malignant biliary obstruction

n Caroli’s disease

n Sclerosing cholangitis

2. Haematogenous infection

n Appendicitis

n Diverticulitis

n Infected haemorrhoids

n Portal thrombophlebitis

n Intra-abdominal abscess

3. Extension of contagious infection

4. Iatrogenic

n Transarterial chemoembolization (TACE), radio-frequency ablation (RF).

n The incidence of HA has been reported to range from 0 to 1.4% following TACE, and 0.1 to 0.7% following RFA. The incidence increases in patients who have a pre-existing bilioenteric anastomosis.

**Further Reading**

1. Sharma MP, Dasarathy S, Verma N, et al. Prognostic markers in amebic liver abscess: a prospective study. *Am J Gastroenterol* 1996;91:2584–8.

2. Sharma MP, Dasarathy S, Shushma S, Verma N. Long term follow up of amoebic liver abscess: clinical and ultrasound patterns of resolution. *Trop Gastroenterol* 1995;16: 24–8.

3. Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr. Current concepts: amebiasis. *N Engl J Med* 2003;348:1565–73.

4. Chu KM, Fan St, Lai EC, Lo CM, Wong J. Pyogenic liver abscess. An audit of experience over the past decade. *Arch Sur* 1996;131:148–52.

5. Lardière-Deguelte S, Ragot E, Armoun K, et al. Hepatic abscess: diagnosis and management. *J Visc Surg* 2015;152:231–43.

6. Shin JU, Kim KM, Shin SW, et al. A prediction model for liver abscess developing after transarterial chemoembolization in patients with hepatocellular carcinoma. *Dig Liver Dis* 2014;46:813–7.

7. Pang TC, Fung T, Samra J, et al. Pyogenic liver abscess: an audit of 10 years’ experience. *World J Gastroenterol* 2011;17:1622–30.

8. Ferraioli G, Garlaschelli A, Zanaboni D, et al. Percutaneous and surgical treatment of pyogenic liver abscesses: observation over a 21-year period in 148 patients*. Dig Liver Dis* 2008;40:690–6.

9. Biskup E, Yang XY. Pyogenic hepatic abscess - less is more. A review for general internists. *Praxis* (Bern 1994) 2015; 104:1091–5.

10. Stanley SL Jr. Amoebiasis. *Lancet* 2003;361:1025–34.

Chapter 29.

**Hydatid Disease**

**Introduction**

Cystic echinococcosis (CE) or hydatidosis is a zoonotic infection caused by larval form of tapeworms (metacestodes) of genus echinococus.

**Clinical History**

1. Infections are usually acquired during childhood, but most of the patients present during 3rd to 5th decade of life.

2. There is no sex predilection.

3. Majority of cysts produce no symptoms and are detected as incidental findings on routine imaging.

4. Symptoms may be produced by mechanical effect or by rupture.

5. Common symptom is dull pain or self-diagnosed mass in right upper quadrant.

6. Cyst may rupture into the peritoneal, pleural or pericardial cavity, into the biliary tree (5–20%) or the gastrointestinal tract. Biliary rupture presents as cholangitis, pancreatitis or cholestasis mimicking choledocholithiasis or malignant cholestasis.

7. Cyst rupture or leakage can cause immunologic symptoms from the initiation of an immunoglobulin (Ig)E response, leading to allergic reactions most frequently characterized by hives, flushing and mucous membrane swelling. Major rupture into peritoneum leads to life-threatening anaphylaxis. Ruptured cysts can release viable cystic contents and protoscolices into the peritoneum, resulting in secondary hyatidosis.

8. Fever suggests infected cyst.

9. Hydatid cyst in the lung causes cough, haemoptysis and chest pain.

10. History of contact with dog.

11. Similar illness in other family members or neighbour.

**Physical Examination**

n Physical examination may be normal.

n Hepatomegaly with one or more rounded soft-to-firm masses felt on its surface. Hepatomegaly when tender and associated with fever and chills suggest secondary infection of the cyst.

n Splenomegaly, if present, may suggest co-existing splenic echinococcosis or portal hypertension.

n Jaundice may indicate biliary rupture or pressure effect on bile duct.

n Hydatid thrill

**Investigations**

1. ***Biochemistry***

n Eosinophilia in about 25%.

n Elevation of bilirubin or cholestatic liver enzymes may suggest biliary rupture.

2. ***Plain radiograph abdomen***

n Calcification in the cyst wall

3. ***USG abdomen***

n Sonographic appearances of liver hydatid cysts are of five types (Gharbi’s classification was revised by the WHO-Informal Working Group Classification on Echinococcus-IWGE).

- Type I (CE1): Univesicular fluid collection/simple cyst – active stage of the disease.

- Type II (CE3A): Fluid collection with detached membrane (water lily sign) – stage of the disease is transitional.

- Type III (CE2, CE3B): Fluid collection with daughter cysts and multiple septa giving honeycomb appearance – active or transitional stage of the disease.

- Type IV (CE4): Hypoechoic with heterogeneous matrix, no daughter cyst – inactive stage.

- Type V (CE5): Cyst with calcified thick walls – inactive or degenerative cyst.

n Assess the size, number and location of hydatid cyst.

n Sonographic features of types II, III and V are pathognomonic of hydatid disease, whereas type I can be confused with simple cyst and type IV with malignancy or granuloma **(Fig. 29.1 A-D)**.

n Dilated bile ducts with or without non-shadowing filling defects and loss of continuity of the cyst wall adjacent to the bile duct representing biliary communication.

4. ***CT and MRI scan abdomen***

n CT has a sensitivity rate approaching 94% and plays a crucial role during the perioperative period for detection of complications, such as biliary and vascular involvement, cyst ruptures and underlying infection.

n To identify hydatid cyst in other organ.

n MRI has no advantage over CT scan.

5. ***Serology***

n IgG anti-echinococcus antibody.

n 80–100% sensitive and 88–96% specific but unable to differentiate active or past infection.

n Less sensitive and specific for pulmonary hydatid.

n Evaluation of two recombinant antigen assays B2t and 2B2t by ELISA method may enhanced performance in the diagnosis and follow-up of patients with CE.

n Measurement of IL-4 response to the native antigen B (AgB) of *Echinococcus granulosus* is under evaluation.

6. ***Diagnostic puncture***

n Only justified when imaging and serological tests do not permit differentiation between hydatid cyst and neoplasm or simple cyst.

n It carries risk of anaphylaxis.

7. ***ERCP***

n Both diagnostic as well as therapeutic for biliary rupture.

n Has both palliative and curative role in selected cases.

n Has curative role for biliary fistula following surgery on hydatid.

**Complicated Hydatid Cyst**

1. Age (>40 yrs)

2. Cyst size (>10 cm)

3. Number of cysts (>3)

**Treatment**

1. Medical management by anthelminths

2. Percutaneous aspiration

3. Surgery

**Medical Management**

1. Indications:

n Unfit (because of location or concomitant medical diseases) for surgery.

n Cysts located in more than two organs. To reduce cyst pressure, secondary seeding and risk of recurrence in presurgical and prepuncture cases.

n Peritoneal cysts

n Recurrent cysts

2. Contraindications

n Pregnancy

n Bone marrow suppression or liver disease

3. Drugs

n Bezoimidazoles (mebendazole and albendazole)

n Praziquentel

n Mebendazole 40–50 mg/kg divided dose or albendazole 10–15 mg/kg daily or praziquentel, 40 mg/kg per week.

n Albendazole is the best drug available; efficacy of praziquentel yet undetermined.

n Imidazoles are administered for 3–6 months.

n Most (50–75%) of the cysts staged as CE1 (active) were determined to be inactive after initiation of benzimidazole treatment (monitored after 1–2 yrs), compared to 30–50% of CE2 and CE3 cysts that were staged as inactive. In addition, 50–60% of smaller cysts (<6 cm at baseline) responded better to treatment after 1–2 yrs compared to 25–50% of larger cysts.

n Praziquentel 40 mg/kg per week for 3 months can be used. This is alone not sufficient as therapy for CE and is recommended in combination with albendazole, particularly as a preoperative regimen.

4. Response

n 30% complete response

n 30% partial response

5. Predictors of good response

n Young patient

n Thin wall

n Size less than 4 cm

**Percutaneous Aspiration**

1. PAIR (Puncture, Aspiration, Installation of scollicidal agents, Re-aspiration)

2. PEVAC (Percutaneous Evacuation)

***Indications***

1. WHO-IWGE classification CE1 and CE3a cysts (single compartment cysts) <5 cm that have not responded well to medical therapy, and in combination with medical therapy for cysts >5 cm.

2. Patient who is poor surgical candidate.

3. Recurrence after surgery or chemotherapy.

4. Percutaneous treatment along with albendazole is a safe and effective treatment for uncomplicated CE and is associated with a shorter hospital stay.

***Contraindications***

1. Pedunculated cyst and lung cyst

2. Cysts located superficially (risk of spillage)

3. Type III cysts with numerous daughter cysts and non-drainable material

4. Types IV and V cysts

5. Cyst with biliary communication

***Procedure***

1. Cysto-biliary communication should be excluded prior to PAIR by CT scan or ERCP in selected cases.

2. The scoliocidal agent that is injected is left for approximately 15 min for separation of the germinal membrane from the surrounding cyst. Currently, three solutions are most commonly used: 70–95% ethanol, 15–20% hypertonic saline or cetrimide solution.

3. Treatment with albendazole or mebendazole 4 hrs prior to the procedure should be continued for 1 month postoperatively for albendazole, and for 3 months with mebendazole. This pre- and post-treatment reduces the risk for recurrence and secondary intraperitoneal seeding.

4. Post PAIR, good response is defined by the presence of one or more of the following factors: decrease in the size of the cavity, increased wall calcification, increased areas of solidification in the cyst and increased echo-genicity of the cyst (consistent with a pseudomass appearance)

***Surgical Treatment***

Surgical treatment leads to complete cure of hydatid cyst. Removal of the cyst and obliteration of cyst cavity are two main goals of the surgical treatment. Standard of care even for a surgical approach includes pre- and post-procedure adjunctive albendazole to prevent secondary seeding of the peritoneal cavity in case of a rupture. According to WHO guidelines, treatment with albendazole or mebendazole should be started 4 days prior to surgery, and continued after for at least 1 month with albendazole and for 3 months with mebendazole. In case of intra-operative spillage, immediate washout of the peritoneum should be performed with hypertonic saline and a scoliocidal agent, followed by a longer duration of postprocedure mebendazole therapy, up to 6 months. Lack of cysto-biliary communications should be confirmed before using hypertonic saline to avoid secondary sclerosing cholangitis.

***Indications***

1. Superficial/pedunculated

2. Multiple daughter cysts

3. Infected cyst

4. Biliary communication

***Results***

1. Operative mortality 0.5%

***Type of Surgery***

Two types of surgical approaches: conservative methods (partial cystectomy, cystectomy with external drainage, omentoplasy or capitonnage) and radical methods (total pericystectomy or hepatectomy). It can be performed either open surgical or laparoscopic approach. Although conservative surgical procedures are considered simpler and safer to perform, the rate of postoperative complications such as biliary fistula, residual cavity and recurrence and cavity suppuration has been reported to be about 35%. On the other hand, radical surgery can be performed with low risk of

recurrence. Combination treatment with albendazole plus surgery leads to a lower surgical recurrence.

**Wait and Watch Policy**

The hypothesis is that cyst types CE4 and CE5 should be left untreated but monitored closely. The fact that some cysts are heavily calcified and remain as fairly inactive. Follow-up with ultrasound in these cyst types is suggested.

**Management According to WHO Classification**

1. *CE1 and CE3a*: Cyst size less than 5 cm and inoperable with multiple cysts needs medical therapy. Cyst more than 5 cm, cyst likely to ruptured, pregnancy, bone marrow suppression and failure to medical therapy are indications for PAIR or surgical removal.

2. *CE2 and CE3b*: Surgical treatment

3. *CE4 and CE5*: Wait and watch with close follow-up

**Hydatid Cyst Ruptured into Biliary System**

1. Ruptured of hydatid cyst into the biliary system is seen in 3–17% of patients. More than 50% of patients with cyst diameter more than 8.8 cm have biliary communication.

2. Endoscopic retrograde cholangiopancreatography (ERCP) defines the cystobiliary relationship to guide management decisions during the pre- and postoperative periods. Preoperative endoscopic sphincterotomy may decrease the incidence of postoperative external fistula from 11.1% to 7.6%.

3. During the postoperative period, ERCP may provide an opportunity to manage postoperative external biliary fistulae.

**Species Causing Hydatid Cyst**

1. *E. granulosis*

2. *E. alveolaris*

3. *E. vogeli*

4. *E. oligarthrus*

**Site of Involvement**

1. Liver - 65%

2. Single organ - 87%

3. Lung - 25%

4. Solitary - 72%

**Life Cycle**

n Definitive host: Carnivores (dog) harbouring mature tapeworms in the intestine

n Intermediate host: Man

n Small tapeworms: 2–11 mm

n Adult worm has cephalic end called the scolex and 2–5 segments called proglottids.

n Terminal end of proglottid contains several hundred fertilized eggs.

n Surrounding the cyst is pericyst.

n Daughter cyst may develop from mother cyst, which gives rise to multivesicular cyst.

n Younger cysts contain clear fluid, whereas older cysts contain gelatinous fluid called matrix.

n Calcification can occur in pericyst, mother or daughter cysts.

**Further Reading**

1. Ammann RW, Eckert J. Cestodes: Echinococcosis. *Gastro-enterol Clin North Am* 1996;25:655–89.

2. WHO informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996;74:231–42.

3. Khuroo MS, Zargar SA, Mahajan R. Echinococcus granulosus cysts in the liver: management with percutaneous drainage. *Radiology* 1991;180:141–5.

4. Khuroo MS, Wani NA, Javid G, et al. Percutaneous drainage compared with surgery for hepatic hydatid cysts. *N Engl J Med* 1997;337:881–7.

5. Concepción Gomez i Gavara, Rafael López-Andújar, et al. Review of the treatment of liver hydatid cysts. *World J Gastroenterol* 2015 7;21:124–31.

6. Tina Pakala, Marco Molina, George Y Wu, et al. Hepatic echinococcal cysts: a review. *J Clin Transl Hepatol* 2016;4: 39–46.

7. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. WHO Informal Working Group*. Acta Trop* 2003;85:253–61.

Chapter 30.

**Malabsorption Syndrome**

**Introduction**

Gastrointestinal tract absorbs nutrients with remarkable efficiency. Less than 5% of ingested carbohydrate, fat and protein are excreted in the stool of adults on normal diet. Maldigestion is defined as defective digestion of complex nutrients to smaller molecules. Malabsorption is defined as a defective mucosal absorption. The digestion or absorption of a single nutrient component may be impaired (e.g., lactose intolerance due to lactase deficiency). When a diffuse disorder, such as celiac disease or Crohn’s disease, affects the intestine, the absorption of almost all nutrients is impaired. Clinically, sometimes it may be difficult to differentiate maldigestion from malabsorption. The prototype of maldigestion is chronic pancreatitis and that of malabsorption are celiac disease, tropical sprue and other causes of mucosal malabsorption.

**Clinical History**

1. **Diarrhoea**

Diarrhoea is defined as more than 3 stools per day, which are unusually liquid. In West, passage of more than 200 g stools per day is also considered as diarrhoea. However, this definition does not hold true in India as normal stool weight in healthy Indian adults is 311 g/day due to high fibre diets.

It is important to try to decide whether the patient is suffering from diarrhoea due to small bowel disease (malabsorption) or that due to large bowel disease (prototype being ulcerative colitis). This is important so as to avoid unnecessary investigations. Stools of patients with small bowel diarrhoea are bulky, greasy, frothy, pale, offensive and are large in volume; these patients do not have rectal symptoms, mucus or blood in stool. Pain of small bowel origin is usually periumbilical in contrast to that of large bowel origin, which is located in hypogastrium.

2. **Explanation of various symptoms**

n Stools are bulky mainly due to malabsorbed carbohydrate and water.

n Floating of stool in the toilet water can be due to either high fat content or high gas content.

n Explosive diarrhea (passage of stool with excess gas) is classical of carbohydrate malabsorption.

n Pathophysiologic basis of diarrhoea in malabsorption syndrome is due to decreased absorptive surface, secretory activity of bile acids and osmotic activity of short chain fatty acid.

n Stools may be greasy due to excess of fat. However, this is more marked in maldigestion (chronic pancreatitis) than malabsorption.

n Stools are pale as a fixed amount of stercobilin is dissolved in an excess amount of water in the stools.

3. **Flatulence**: Excess non-foul smelling flatulence is secondary to carbohydrate malabsorption, whereas foul-smelling flatulence is due to protein malabsorption.

4. **Abdominal pain**

n Dull, vague, poorly localized pain is due to excess flatulence.

n Severe, colicky pain with abdominal distension suggests conditions causing transmural involvement or intestinal stricture as in Crohn’s disease, lymphoma, tuberculosis and eosinophilic gastroenteritis.

Vitamin A Night blindness

Xerophthalmia

Vitamin D Tetany, muscle weakness,

paresthesia, bone pain

Vitamin E Paresthesia, muscle cramps

Vitamin K Easy bruisability,

ecchymoses, petechiae

Vitamin B Peripheral neuropathy,

complex glossitis, anaemia

Folic acid Glossitis, stomatitis, anaemia

1. Ascites – secondary to hypoalbuminemia

2. Pedal oedema – secondary to hypoalbuminemia

3. Stunted growth/failure to thrive; weight loss

4. Tiredness, fatigue, weakness

5. History suggestive of vitamin deficiency

**General Examination**

1. Low body mass index (BMI)

2. Signs of dehydration secondary to volume depletion

3. Clinical signs of nutrient deficiency **(Tables 30.1 and 30.2)**

**Abdominal Examination**

1. Abdominal examination may be normal.

2. Abdominal distension secondary to either excess gas or ascites.

3. Soft or firm, mild-to-moderate hepatomegaly either due to fatty liver or other hepatic complications associated with specific causes of malabsorption.

4. Exaggerated bowel sounds secondary to undigested materials.

**Neurological Examination**

1. Posterior column involvement (subacute combined degeneration) indicates vitamin B12 deficiency

2. Cerebellar signs

3. Peripheral neuropathy

**Investigations**

Evaluation of malabsorption includes:

1. Suspecting malabsorption

n History and clinical examination

2. Confirm malabsorption

n Laboratory parameters (D-xylose test, 72-hr fecal fat estimation using Van de Kamer’s technique)

n Laboratory tests to confirm malabsorption of specific nutrients **(Table 30.3)**

3. Aetiology of malabsorption

n By radiological, endoscopic, microbiological, serological, histological and immunological investigations

**AEtiology of Malabsorption**

**Endoscopic Examination and Mucosal Biopsy**

Endoscopic examination **(Figs 30.1–30.3)** and small intestinal mucosal biopsy is an important investigation modality in patients with malabsorption **(Table 30.4)**.

1. Endoscopic biopsy obtained at second part of duodenum may be diagnostic or highly suggestive of a variety of small bowel disorders resulting into malabsorption.

2. Wireless capsule endoscopy allows for visualization of the entire small bowel and evaluation of small bowel mucosal disease.

3. Causes of total villous atrophy:

n Celiac sprue

n Tropical sprue

n Giardiasis

n Crohn’s disease

n Small intestinal bacterial overgrowth

n Eosinophilic enteritis

n Small intestinal lymphoma

n Severe malnutrition

4. Following diagnosis can be established by small bowel biopsy - **Table 30.5**

**Imaging of abdomen**

1. Plain X-ray abdomen

n Dilated bowel loop and stasis

n Pancreatic calcification

n Kidney stone (oxalate stone)

2. USG abdomen

n Dilated bowel loop

n Generalized intestinal wall thickness secondary to hypoalbuminemia

n Evidence of parenchymal liver disease, obstructive biliary disease, pancreatic tumours

n Presence of ascites

3. Small bowel series

n Dilated loops of intestine, flocculation, dilution of barium

n Specific radiological features to identify the etiology of malabsorption is given in **(Table 30.6)**

4. Abdominal CT scan

n CT enterography and magnetic resonance (MR) enterography are used to detect small bowel mucosal disease and neoplasms.

n Enlarged abdominal lymph nodes in lymphoma or Crohn’s.

n Evidence of chronic pancreatitis.

n Identification of pancreatic tumour.

5. Serological tests:

n Serological tests are very useful in diagnosis of aetiology of malabsoption syndrome **(Table 30.7)**.

**Specific Diagnostic Tests for Specific Nutrient Malabsorption**

1. Carbohydrate malabsorption

n D-xylose test

n Hydrogen breath test

n Stool pH <5.5

2. Fat malabsorption

n Stool fecal fat analysis (Ch. 5)

n Serum concentration of â carotene

n 14C-triolein breath test

3. Protein malabsorption

n Measurement of fecal nitrogen content

n 14C octanoic acid or 13C egg white breath test

4. Vitamin B12 malabsorption

n Schilling test

n Serum vitamin B12 concentration

5. Bile salts malabsorption

n Fecal bile acid output

n 14C-taurocholate bile acid absorption test

n Selenium-75 labeled homotaurocholic acid test

6. Bacterial overgrowth

n Qualitative culture of small intestinal aspirate

n 14C-D-Xylose breath test

n Glucose hydrogen breath test

n Lactulose H2-breath test

7. Exocrine pancreatic function tests (Ch. 34)

**D-xylose Test**

1. It is a pentose sugar, incompletely absorbed from intestine.

2. It is not metabolized, therefore, its excretion into urine or its concentration into blood after standard oral dose are considered as tests for small intestinal absorption.

3. Around 25% of oral dose is excreted in the urine.

4. After overnight fasting, either 5 or 25 g is given orally, and the patient is encouraged to take water to maintain urine output.

5. Increased dose of xylose causes nausea/vomiting, thus 5 mg dose of D-xylose test is very well accepted. However, sensitivity and specificity of 25-g D-xylose are somewhat better than that of 5-g D-xylose.

6. Normally >5 g and >1 g D-xylose is excreted, respectively in urine after 25 g and 5 g D-xylose ingestion over 5 hrs.

7. Blood level – 25 mg/dL after 1 hr after 25 g.

***False Positivity***

1. Renal failure

2. Ascites

3. Portal hypertension

4. Concomitant NSAID

5. Laxative use

6. Dehydration

7. Delayed gastric emptying

***False Negative***

1. Mild disease

2. More distal disease

**Pathophysiology of malabsoption**

Physiological process of digestion and absorption is divided into three major phases: luminal, mucosal and post-absorptive phase.  The luminal phase is the stage in which dietary carbohydrates, fats and proteins are hydrolyzed and solubilized by secreted digestive enzymes and bile in to easily digestible substances like peptides and mono-saccharides. The mucosal phase relies on the integrity of the brush-border membrane of intestinal epithelial cells to transport digested products from the lumen into the cells. In the postabsorptive phase, key nutrients are transported via the lymphatics and portal circulation from epithelial cells to liver by splanchanic circulation.

**Management of malabsoption syndrome**

Two main principles of treatment: (a) correction of nutrition deficiency and (b) treatment of aetiology of malabsoption syndrome.

Caloric and protein replacement is most important. Supplement the patient with various minerals, such as calcium, magnesium, iron and vitamins, which may be deficient in malabsorption. Medium-chain triglycerides can be used as fat substitutes, because they do not require micelle formation for absorption and their route of transport is portal rather than lymphatic. Parenteral nutrition may become necessary in severe intestinal disease such as extensive regional enteritis and following a massive resection.

A gluten-free diet is useful to treat celiac disease. Lactose-free diet helps correct lactose intolerance. Pancreatic enzyme supplementation helps to improve pancreatic insufficiency. Antibiotics are used to treat small intestinal bacterial overgrowth and tropical sprue. Cortico-steroids, anti-inflammatory agents, such as mesalamine, and other therapies are used for inflammatory bowel disease.

**Further Reading**

1. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464–86.

2. Owens SR, Greenson JK. The pathology of malabsorption: current concepts. *Histopathology* 2007;50:64–82.

3. Holt PR. Diarrhea and malabsorption in the elderly. *Gastroenterol Clin North Am* 2001 Jun; 30:427–44.

4. Ranjan P, Ghoshal UC, Aggarwal R, et al. Etiological spectrum of sporadic malabsorption syndrome in northern Indian adults at a tertiary hospital. *Indian J Gastroenterol* 2004;23:94–8.

5. Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician* 2011;15:1119–26.

6. Anunayi J, Neelima G, Amanulla Khan Mohd, et al. An overview and diagnosis of malabsorbtion syndromes-review of literature. *Indian Journal of Mednodent and Allied Sciences* 2015;3:108–14.

**Chapter 31.**

**Gastrointestinal Tuberculosis**

**Introduction**

Gastrointestinal tuberculosis (TB) is defined as tuberculous infection of intestines, peritoneum and abdominal lymph nodes and intraabdominal solid organ. It consists of 5% of total cases of tuberculosis worldwide and 11% of extra pulmonary tuberculosis. Ileocecal region is the most common site of involvement. It is prevalent in developing countries as a complication of pulmonary TB, as a part of disseminated infection and often as an isolated presentation. The incidences are increasing due to HIV co-infection.

**Clinical History**

1. ***Abdominal pain***

n Abdominal pain is the most commonsymptom, present in around 80% of patients.

n Diffuse/dull pain when peritoneum and mesentery are involved.

n Colicky severe abdominal pain associated with subacute intestinal obstruction due to stricture.

n Often located in right iliac fossa with a lump.

2. ***Diarrhoea***

n Diarrhoea is present in around 10–20% of patients.

n Blood in stools is uncommon and may be due to intestinal ulcerations and rarely massive.

n Diarrhoea in intestinal tuberculosis is multifactorial. Apart from malabsorption, contributing factors are inflammatory response in the intestine and subsequent effect of cytokines, leukotrienes and prostaglandins on fluid and electrolyte transport and due to increase in intestinal motility.

3. ***Malabsorption***

n Seen in 15–20% of cases

n Due to:

- Decreased total absorptive area due to extensive ulceration

- Lymphatic obstruction

- Small intestinal bacterial overgrowth

4. ***Fever***

n Usually low grade in 40–70% of patients

5. ***Weight loss***

**Past History/Family History**

Past history or family history of pulmonary tuberculosis (20%).

**General Examination**

n Lymphadenopathy – usually present in disseminated disease

n Cutaneous markers of TB or HIV

n Signs of malnutrition

**Abdominal Examination**

“Doughy abdomen” in 6–10% (extensive intra-abdominal fibrous adhesion and inflammation). Ascites presents in peritoneal tuberculosis while organomegaly seen in solid organ tuberculosis.

**Respiratory System Examination**

n Evidence of parenchymal involvement

n Pleural effusion in disseminated tuberculosis

**Investigations**

1. ***Routine***

n Anaemia and hypoproteinemia is secondary to malabsorption

n Lymphocytic leucocytosis

n Elevated ESR

2. ***Mantoux test***

n The use of tuberculin skin testing (TST) as a diagnostic tool in patients with ileo-colonic inflammation has limitations.

n Cross reactivity with BCG, a high prevalence of environmental mycobacteria and widespread latent M. tuberculosis infection makes interpretation of a positive TST difficult.

n In a Cape Town study, 66% of HIV negative healthy volunteers were found to be TST positive. Anergy in HIV, primary TB and disseminated TB further limits the diagnostic utility of this test.

3. ***Chest radiograph***

n Pulmonary lesion is seen in 24–28%.

n Active pulmonary tuberculosis in 10–15%.

4. ***Plain X-ray abdomen***

n Calcified lymph node/granuloma may be seen.

n Dilatation of terminal ileum

n Dilated loops with air-fluid levels in case of obstruction

5. ***Barium study***

n Early sign – Hypersegmentation and flocculation.

n Irregularly thickened folds, mucosal ulceration, which may be linear and situated along the circumference of the wall **(Fig. 31.1)**.

n Inverted umbrella/Fleischner’s sign – Thickened ileocecal valve gives triangular appearance, base of which lies near caecum.

n Sterling sign – Rapid transit and lack of barium retention in terminal ileum.

n String sign – Narrow segment before ileocecal valve.

6. ***USG abdomen***

n Bowel mass is made up of bowel loops, omentum.

n Ascites, free or multiloculated.

n Club sandwich appearance – due to interloop ascites.

n Uniform concentric bowel wall thickening (Crohn’s disease – eccentric thickening).

n Discrete or conglomerated (matted) lymph nodes, echotexture is usually heterogeneous in tuberculosis and homogenous in lymphoma.

n Pseudo kidney signs – pulled up ileocaecal region to a subhepatic position.

7. ***Spiral-CT abdomen/MRE***

n To assess intraluminal and extraluminal pathology, and disease extent.

n Thickening and narrowing of intestinal lumen with or without proximal dilatation.

n Enlarged lymph nodes with central necrosis/calcification.

n CT or MRI without bowel distension by neutral oral contrast should be avoided as the small intestine cannot be reliably assessed in a collapsed state.

8. ***Colonoscopy***

n Tuberculous ulcers tend to be circumferential and are usually surrounded by inflamed mucosa. A patulous ileocecal valve with surrounding heaped up folds or a destroyed valve with a fish mouth opening is more likely to be caused by TB than CD.

n Nodule/superficial ulcers/polyp in the terminal ileum and cecum **(Fig. 31.2)**.

n Stricture at ileocecal junction/incompetence.

n Yield of biopsy is 30–80%.

9. ***FNA from mass***

n Fine needle aspiration by either EUS or transabdominal US guided have diagnostic utility in case of large abdominal lymph nodal mass.

10. ***Serology and molecular tests***

n QuantiferonTB TB gold (QFT-G) is a blood test that uses an interferon gamma release assay (IGRA) that measures the release of interferon gamma after stimulation *in vitro* by *M. tuberculosis* antigens. Most of the studies on this test have been performed on pulmonary TB. Latest guideline does not support the use of this test as routine practice.

n Measurement of gamma producing T-cell responses to early secreted antigenic targets of mycobacterium tuberculosis (ELISPOT) has shown some promising results.

n The GeneXpert MTB assay is an automated nucleic acid amplification test that can simultaneously identify *M.*

*tuberculosis* and rifampicin resistance. Among 547 patients with suspected extra pulmonary TB in India and 1068 patients in Europe, the sensitivity and specificity of the GeneXpert assay were 81 and 99 percent, respectively.

n PCR assay showed high specificity (95%) for the diagnosis of intestinal tuberculosis. Thus PCR assay is useful for rapid and accurate diagnosis of intestinal TB, and helps to differentiate from CD.

n Line probe assays: These are drug susceptibility tests, which use PCR and reverse hybridization methods for identification of *M. tuberculosis* complex as well as rapid detection of mutations in the mycobacterial genome associated with drug resistance (MTBDR plus is capable of detecting rifampin and isoniazid resistance mutations, whereas MTBDRsl for resistance to fluoroquinolones and injectable agents). However, there are certain disadvantages with these assays, such as increased susceptibility to cross contamination and an increased risk of false-positive results. Further, line probe assays are not approved by FDA yet.

11.***Ascitic fluid***

n Exudate fluid (SAAG < 1.1, Ch. 23)

n Variable ADA levels have been published in the literature; level above 39 units/L is favouring tuberculous ascites.

n Ascitic fluid Ziehl-Neelson stain has a reported sensitivity of 0–6% and culture has yield of less than 20%.

n Diagnostic yield of GeneXpert assay on ascitic fluid samples is lower than culture.

12.***Laparoscopy***

n Typical peritoneal tubercles can be seen and biopsied.

13. ***Histology***

n Tuberculous granuloma characteristically contains epithelioid macrophages, Langhans giant cells and lymphocytes. The centres of tuberculous granuloma often have characteristic caseation (cheese-like) necrosis; organisms may or may not be seen with acid-fast staining.

n One of the limitations of mucosal biopsies is that granuloma, the primary differentiating feature of TB from CD, are found in only 50–80% of intestinal mucosal biopsies from patients with clinically confirmed intestinal tuberculosis, whereas 15–60% of clinically confirmed Crohn’s disease.

**Organisms Causing Abdominal Tuberculosis**

1. *M. tuberculosis*

2. *M. bovis* – Rare

3. Atypical mycobacterium – in HIV

**Pathogenesis**

Gastrointestinal TB can be primary or secondary:

1. From swallowing of infected sputum in active pulmonary TB/laryngeal TB.

2. Ingestion of milk/food, contaminated by *M. bovis.*

3. Hematogenous spread from active pulmonary tuberculosis; miliary tuberculosis.

4. Direct extension from adjacent organ (organism may be disseminated in the bile from hepatic granulose).

**Classification of Abdominal Tuberculosis**

1. **Gastrointestinal tuberculosis**

n Ulcerative

n Hypertrophic

n Ulcerohypertrophic

n Sclerotic

n Diffuse colitis

2. **Peritoneal tuberculosis**

n Acute tuberculous peritonitis

n Chronic tuberculous peritonitis

n Ascitic form

n Encysted form

n Fibrous form (either adhesive or plastic form)

3. **Tuberculosis of mesentery**

4. **Tuberculosis of solid organ viscera**

5. **Others – retroperitoneal lymph node**

**Morphological types of Gastrointestinal Tuberculosis**

1. **Ulcerative form (20%)**

n Adult malnourished patients

n Diarrhoea is the most predominant feature.

n Multiple/solitary ulcers

n Transverse to long axis of the gut – “girdle ulcer”

n Healing and fibrosis result in stricture formation –napkin ring stricture

n Adhesion between bowel loops prevents free perforation

n Ulcer margins are everted and indented

n Rarely penetrate beyond muscularis propria

2. **Hypertrophic (10%)**

n Young and well-nourished patient.

n Mass and dull abdominal pain are the predominant features.

n Cecum is the most common site.

n Due to low volume of infection, low virulent organism and high host immunity.

n Mass containing adherent bowel, mesentery and lymph node.

n Lymphoid follicular hyperplasia with hyperplastic germinal centre.

n Granuloma usually absent, even though AFB culture can be positive.

n May present as exophytic mass from mucosa, indistinguishable from carcinoma.

3. **Ulcerohypertrophic (70%)**

n Low-density, low-virulence bacteria/good host immunity.

n Most common type

These morphological types can coexist. Small intestinal lesions are usually ulcerative or stricturous whereas large intestinal lesions are ulcerohyper-trophic. Colonic lesions are usually associated with ileocecal involvement. Peritoneal involvement may be of either an ascitic or adhesive (plastic) type. The lymph nodes in the small bowel mesentery and the retroperitoneum are commonly involved. Caseation and calcification are prominent morphological features of tuberculous abdominal nodes.

**Why ileocecal area is most commonly affected?**

1. Presence of lymphoid tissue

2. Physiological stasis

3. Fluid and electrolyte absorption

4. Minimum digestive activity permitting greater contact time between the organism and mucosa. It has been shown that the M cells associated with Peyer’s patches can phagocytise BCG bacilli.

**Complications**

1. Obstruction

2. Intestinal haemorrhage

3. Perforation

4. Fistulae

5. Malabsorption

**Why obstruction is the most common complication?**

1. Inflammatory thickening of the bowel wall with luminal narrowing.

2. Luminal contraction from fibrosis following healing of ulcer.

3. Kinking/constriction of the intestine by intraperitoneal adhesion.

4. Lymphadenopathy leads to narrowing of lumen by extrinsic compression.

**Differential Diagnosis**

1. Crohn’s disease

2. Yersinial infections

3. Carcinoma

4. Amebiasis

**Medical Management**

1. Traditionally the 9-month AKT was given to the patients with abdominal Koch’s; however, it is now proven that the 6-month therapy is as effective as 9-month therapy (with cure rate of >91%) in patients with intestinal/peritoneal TB and may have the additional benefits of reduced treatment cost and increased compliance. Statistics regarding prevalence of MDR and XDR strains in intestinal TB are very limited in the present literature. Drug-induced liver injury (DILI) is the most common reason to discontinue or altered anti-tuberculous treatment.

2. Role of steroid is limited, but theoretically it reduces the fibrosis.

3. Surgery (stricturoplasty or resection) should be reserved for complications.

**Indication for Surgical Management**

1. Obstruction (20%)

2. Free perforation (5%)

3. Abscess

4. Fistula (5%)

5. Haemorrhage

**Diagnostic Criteria of Intestinal Tuberculosis (*Am J Gastroenterol* 1993)**

1. Histopathological evidence of caseating granulomas/acid-fast bacilli.

2. Presence of *Mycobacterium tuberculosis* in sputum/tissue/ascitic fluid.

3. Clinical/radiological/operative evidence of proven tuberculosis elsewhere with good therapeutic response.

4. Good therapeutic response to anti-tuberculosis chemotherapy.

**Tuberculosis versus Crohn’s Disease**

Crohn’s disease and TB are both chronic granulomatous conditions that affect the gastrointestinal tract in a similar manner. *Mycobacterium tuberculosis* is the causative organism in intestinal TB whereas the aetiology of CD is multi-factorial and includes genetic, immunological, environmental and microbial factors. It is not surprising given striking morphological similarities that they share many common immune pathways of pathogenesis. Both trigger potent adaptive Th1 cytokine responses, which result in granuloma formation and are characterized by robust production of interferon-gamma (IFN-), IL-12 and IL-23. This is necessary to contain *M. tuberculosis* and prevent dissemination. The protective effect of these cytokines is best demonstrated by the predisposition to disseminate

in individuals with deleterious mutations in the IL-12 D, IL-23 D IFN-.

Despite their morphological and immunopathogenic similarities, the natural history of these two conditions is divergent. Intestinal TB is associated with significant morbidity and mortality but can be cured with a 6-month course of anti-tuberculous chemotherapy. By contrast, CD is a chronic condition that tends to progress with time and may require lifelong therapy to maintain disease remission in the majority of patients. Differentiating CD from TB is notoriously difficult and although diagnostic criteria for both diseases exist they are not mutually exclusive. Both diseases have similar clinical, radiological and endoscopic features and current methods of confirming a diagnosis have limitations.

In practice, sometimes it is difficult to differentiate intestinal tuberculosis from Crohn’s disease. There are few differentiating points stated below on the basis of location, colonoscopic appearance **(Tables 31.1–31.4)** and histologic features.

**Tuberculosis prophylaxis in patient required biological therapy in inflammatory bowel disease**.

About one-third of the world population is infected with *Mycobacterium tuberculosis* of which the highest burden is carried by the developing world.

**Site TB Crohn’s**

Mouth – 8–9%

Oesophagus <1% <1%

Stomach/duodenum 2–3% 1–5%

Small bowel 30% 30%

Small + Large bowel 40–50% 40–50%

Large bowel 10% 10–15%

Perianal Rare 3–36%

Ninety percent of this tubercular burden is shared by latent tuberculosis (LTB), which is defined as immune response against *M. tuberculosis* in the absence of clinical manifestations. Most of the individuals with LTB remain silent in their entire life; however, LTB can progress to active tuberculosis (tubercular reactivation) in case of immune deficiency such as HIV infection and treatment with anti-TNF agents. TNF- is one of key mediators in granuloma formation and maintenance, and thus control of tubercular infection. Thus, active pulmonary or extra-pulmonary TB is an absolute contraindication to the use of biologic therapy (anti-TNF-  therapy) in patients with inflammatory bowel disease. These patients should ideally receive full anti-tuberculosis therapy before initiation of anti-TNF- treatment. According to WHO, latent tuberculosis (LTB) is diagnosed based on the positive Mantoux (>10 mm) or IGRA (interferon gamma release assays). Evidence of healed tuberculosis on chest X-ray or CT (pleural thickening, fibrotic scarring, calcified nodules and calcified hilar or mediastinal lymphadenopathy). Reactivation was demonstrated in 8–11% of cases in various parts of the world.

The choice of drug regimen and duration of therapy currently remains unclear and recommendations vary. The most abundant practice is starting biological agent after 1–2 months of initiation of ATT. There are several possibilities: isoniazid 9 months, rifampicin for 4 months or rifampicin plus isoniazid for 3 months. Short course therapy with rifampicin and pyrazinamide should be avoided due to unacceptable risk of hepatotoxicity. In high-burden TB areas with increasing emergence of multi-drug resistant TB, rifampicin monotherapy would not be considered appropriate. Isoniazid monotherapy is effective and widely used. Prophylaxis should be continuing until 2 months of completion of anti-TNF therapy.

**Further Reading**

1. Bhansali SK. Abdominal tuberculosis: experiences with 300 cases. *Am J Gastroenterol* 1977;67:324–37.

2. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res* 2004;120:316.

3. Kapoor VK. Abdominal tuberculosis: the Indian contribution. *Indian J Gastroenterol* 1998;17:141–6.

4. Lingenfelser T, Zak J, Marks In, et al. Abdominal tuberculosis: still a potentially lethal disease. *Am J Gastroenterol* 1993;88:744–9.

5. Anand BS, Nanda R, Sachdev GK. Response of tuberculous stricture to anti-tuberculous treatment. *Gut* 1988; 29:62–9.

6. John B Marshall. Tuberculosis of the gastrointestinal tract and peritoneum. *Am J Gastroenterol* 1993;88:989–1000.

7. Pravin Rathi, Pravir Gambhire. Abdominal tuberculosis. *JAPI* 2016;64:37–47.

8. Debi U, Ravisankar V, Prasad KK, et al. Abdominal tuberculosis of the gastrointestinal tract: revisited. *World J Gastroenterol* 2014;20:14831–40.

9. Riquelme A, Calvo M, Salech F, et al. Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis. *J Clin Gastro-enterol* 2006;40:705–10.

10. Rufai SB, Singh S, Singh A, et al. Performance of Xpert MTB/RIF on ascitic fluid samples for detection of abdominal tuberculosis. *J Lab Physicians* 2017;9:47–52.

**Chapter 32.**

**Lymphoma of the Gastrointestinal Tract**

**Introduction**

The gastrointestinal (GI) tract is the predominant site of extranodal non-Hodgkin lymphomas (NHLs). Primary NHLs of the GI tract are rare, accounting for only 1–4% of malignancies arising in the stomach, small intestine or colon. In contrast, secondary GI involvement is relatively common, occurring in approximately 10% of patients with limited stage NHL at the time of diagnosis, and up to 60% of those dying from advanced NHL. Tumour should be limited to GI tract and its contiguous lymph nodes to be labeled as a primary gastrointestinal lymphoma. Gastric lymphoma is the most common extranodal site of lymphoma in North America. The vast majority of these lesions are either extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) type or diffuse large B cell lymphoma. Primary small intestinal lymphoma is common in Middle-East and Mediterranean countries. The incidence of Burkitt lymphoma (BL, an obstructing lesion in the terminal ileum) is common in Africa.

**Dawson’s criteria for Primary GI Lymphoma**

1. Absence of palpable peripheral lymphadenopathy

2. No mediastinal adenopathy on chest imaging

3. Normal peripheral blood smear

4. At laparotomy, only involvement of GI tract or only the regional lymph nodes (excluding retroperitoneal lymph node).

5. No involvement of liver or spleen except by direct spread of the disease from a contiguous focus.

**MALT Lymphoma**

**Introduction**

1. Extranodal marginal zone lymphoma (EMZL) account for 5–10% of non-Hodgkin lymphomas overall, but make up approximately half of lymphomas in particular sites, such as the stomach, ocular adnexa and lung.

2. *H. pylori* is present in around 90% patients with gastric MALT lymphoma.

**Clinical History**

1. Nonspecific epigastric discomfort

2. Symptoms of gastroesophageal reflux disease

3. Gastric outlet obstruction in case of large tumour or tumour situated near the pylorus

4. Abdominal mass (35%)

5. Symptoms B like anorexia, weight loss, low-grade fever presents in 12% of cases.

6. Occult GI bleeding.

**Investigations**

1. ***Upper Endoscopy***

n Exophytic mass with or without ulceration in the stomach.

n One of the most frequent and typical feature is the presence of gastric nodularity or enlarged folds located at the antrum or body of the stomach.

n Endoscopically it can be ulcer with elevated margins or protrusion (47%), erosions (23%) or erythema (30%).

n Cobblestone appearance of mucosa is sometimes seen.

n Lesions may be multifocal (33%).

n Duodenal involvement.

n Endoscopic biopsy for histological confirmation.

2. ***Histology*** *(upper endoscopy biopsy)*

n Histology is more than 90% sensitive to diagnose MALT lymphoma.

n Histology can differentiate low-grade vs high-grade via immunohistochemistry.

3. ***EUS***

n Most accurate method of staging localized MALT.

n Accurately predict the response to antibiotic therapy in stage I disease.

4. ***CT abdomen/PET scan***

n Used for staging of lymphoma.

n 2/3rd of MALT lymphoma has positive node involvement.

n PET/CT scan is useful only for DLBCL, independent of the affected anatomic site; but a role of PET/CT is controversial in MALT lymphomas, because of its indolent nature.

**Staging of MALT Lymphoma**

***Lugano Staging System***

I: The tumour is confined to the gastrointestinal tract. It can be a single primary lesion or multiple, non-contiguous lesions.

II: The tumour extends into the abdomen. This is further subdivided based on the location of nodal involvement.

II1: Involvement of local nodes (paragastric nodes for gastric lymphoma or para-intestinal nodes for intestinal lymphoma).

II2: Involvement of distant nodes (paraaortic, paracaval, pelvic or inguinal nodes for most tumours; mesenteric nodes in the case of intestinal lymphoma).

IIE: The tumour penetrates the serosa to involve adjacent

organs or tissues.

III: There is no stage III disease in this system.

IV: There is disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement.

***Musshoff Staging***

IE Tumour confined to GI tract

I1 Mucosa, submucosa

I2 Beyond submucosa

IIE1 Tumour with regional lymph node

IIE2 Tumour with extra regional but below diaphragm

(distant LL)

III Penetration to serosa to involve adjacent organs

IV Diffuse, disseminated extranodal involvement

***Blackledge (Modified) System***

I Tumour confined to GI tract

II Regional nodes

IIii Extraregional nodes

IIIe Serosal invasion & involvement of adjacent

structure

IV Disseminated (No. Stage III)

***Paris Staging System for Primary Gastrointestinal Lymphomas***

TX Lymphoma extent not specified

TO No evidence of lymphoma

T1 Lymphoma confined to the mucosa/submucosa

T1m Lymphoma confined to mucosa

T1sm Lymphoma confined to submucosa

T2 Lymphoma infiltrates muscularis propria or

subserosa

T3 Lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures

T4 Lymphoma invades adjacent structures or organs

NX Involvement of lymph nodes not assessed

NO No evidence of lymph node involvement

N1 Involvement of regional lymph nodes

N2 Involvement of intra-abdominal lymph nodes beyond the regional area

N3 Spread to extra-abdominal lymph nodes

MX Dissemination of lymphoma not assessed

MO No evidence of extranodal dissemination

M1 Non-continuous involvement of separate site in

gastrointestinal tract (e.g., stomach and rectum)

M2 Non-continuous involvement of other tissues (e.g., peri- toneum, pleura) or organs (e.g., tonsils, parotid gland, ocular adnexa, lung, liver, spleen, kidney, breast, etc)

BX Involvement of bone marrow not assessed

B0 No evidence of bone marrow involvement

B1 Lymphomatous infiltration of bone marrow

**Management of MALT Lymphoma**

Careful staging, including endoscopic ultrasound, is needed before treatment. To some extent this can predict the chances of *H. pylori* treatment leading to lymphoma regression but eradication of *H. pylori* is indicated in all cases of MALT lymphoma in which it is found.

***Surgery***

1. Surgical treatment is not well defined.

2. The use of chemotherapy and immunotherapy has been reported in gastric MALT lymphoma of all stages; however, there is no evidence to indicate the most effective regimen.

3. Many reports say that stage I disease has excellent outcome following surgery.

4. Beyond stage II: Surgery plus adjuvant chemotherapy and/or radiotherapy.

5. Some reports says that chemotherapy +/- radiotherapy produce equal results as surgery.

***Radiotherapy and Chemotherapy***

1. Chemotherapy and radiotherapy are reserved for cases, which do not respond to *H. pylori* eradication in low-grade lymphoma.

2. MALT lymphomas respond well to both of these modalities.

3. Single-agent chemotherapy (with cyclophosphamide, chlorambucil or even rituximab) or low-dose radiotherapy gives a 5-year disease-free survival of 50–80%, varying in different reports. R-bendamustine is also highly effective and well tolerated.

***Anti H. pylori Therapy***

1. Approximately 70% of cases of low-grade gastric MALT lymphoma are successfully treated by *H. pylori* eradication.

2. Effective *H. pylori* treatment is important to achieve an early response and avoid emergence of antibiotic resistant strains, which can be hard to eradicate. The two main

causes of treatment failure are antibiotic resistance and lack of full compliance with treatment.

3. The best recognized regimens are triple therapy with full-dose proton pump inhibitor twice daily, clarithromycin 500 mg twice daily, and either amoxicillin 1 g twice daily or metronidazole 400 mg twice daily.

4. Although 1 week of treatment has been shown to be effective in Northen European trials, meta-analysis shows that 2 weeks gives better eradication rates worldwide.

5. One month after treatment of *H. pylori*, success can be checked by the non-invasive urea breath test. For this, patients must have been off proton pump inhibitors for at least 2 weeks.

6. Follow-up endoscopies needed later to assess the response of the tumour given the opportunity to double check on *H. pylori* treatment success.

7. EUS predicts the outcome before anti-*H. pylori* therapy.

8. Anti-*H. pylori* therapy should be given even in high-grade lymphoma before definitive therapy to prevent recurrence.

***Surveillance Following Treatment of MALT Lymphoma***

1. Surveillance is mainly required in who are treated with anti-*H. pylori* therapy.

2. Surveillance is not well defined.

3. Histological remission after antibiotics takes 2–15 months.

4. Biopsy every 6–12 months for 1–2 yrs is suggested following anti-*H. pylori* therapy.

5. Endoscopic ultrasound is increasingly being used for follow-up as an adjunct to endoscopy and biopsy.

**Prognostic Criteria**

1. Deep stomach wall infiltration

2. Lymph node involvement

3. High-grade lymphoma

**MALT Lymphoma and *H. pylori***

There is now compelling evidence that gastric MALT lymphoma is caused by infection with *H. pylori*. Appro-ximately, 5–10% of gastric MALT lymphomas appear not to be associated with *H. pylori*, and the aetiological factor in these cases remains unclear. Normal stomach is devoid of MALT, but it develops following antigenic stimulation by *H. pylori* infection. *H. pylori*-induced gastritis first leads to the accumulation of CD4+ lymphocytes and mature B cells in the gastric lamina propria. Antigens derived from *H. pylori* drive the activation of T cells, B cell proliferation and lymphoid follicle formation, which if persistent can evolve into a monoclonal lymphoma.

In a subset of patients, MALT tissue undergoes trans-formation to lymphoepithelial lesion (LEL). Transformation of LEL to lymphoma is not known. MALT lymphoma recapitulates structure of Payer's patches of distal ileum. MALT may undergo hyperplasia in response to chronic antigenic stimulation. Peristalsis is normal in the stomach because of sparing of the muscular layer till late stage of the disease.

There are two types of MALT lymphoma – low grade and high grade. Conversion to high-grade lymphoma from low-grade lymphoma is antigenic, independent and not responding to antibiotics. It may be associated with loss of bcl 1-2 gene, p53 mutation and p16 deletion.

**Summary of MALT Lymphoma**

1. Low-grade gastric MALT lymphoma is usually caused by *H. pylori* infection.

2. It is an indolent disease, but may become locally aggressive, spread or undergo high-grade transformation.

3. Treatment of the infection cures the disease in approximately 70% of cases.

4. Resistant or non-localized disease is treated with low-dose radiotherapy or single-agent chemotherapy; surgery is now used only for complications.

5. Accurate staging requires endoscopic ultrasound; most tumours of stage IIE or above do not respond to *H. pylori* treatment.

6. Molecular testing for chromosomal translocations is now simple and informative.

**High-grade Lymphoma**

1. Diffuse large B cell lymphoma (DLBCL) is most common type of high-grade gastric lymphoma. With improved various treatment modalities, outcome of DLBCL is equally good like MALT lymphoma.

2. Oncogene Bcl-6 is frequently present in the majority of extranodal high-grade lymphomas.

3. Chemotherapy is the cornerstone of the treatment; surgery is indicated only in the case of massive GI bleeding, perforation or obstruction.

4. The commonly used chemotherapeutic regimen for DLBCL of the stomach is a combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and R-CHOP (with Rituximab).

5. Chemoimmunotherapy with 3–4 cycles of standard R-CHOP followed by "involved-field" radiotherapy could be considered as a gold standard option for localized stages (stages I and II in the Lugano classification). Advanced stage patients (Ann Arbor stage III/IV) usually undergo 6–8 cycles of R-CHOP.

**IPSID (IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE)**

**Introduction**

There are mainly two types of small bowel lymphoma, B-cell and T-cell. IPSID (Mediterranean lymphoma, Seligmann

disease) is a form of extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT), with the same histologic features of gastric EMZL with marked plasma cell differentiation. It is the most common form of heavy chain disease (HCD) and occurs in patients from the Mediterranean region or Middle East, usually young males, and is often associated with relatively poor sanitation.

**Clinical History**

1. Diarrhoea

n Large volume, bulky, foul smelling diarrhoea

2. Abdominal pain

n As IPISD is a mucosal disease, abdominal pain is remarkable, unlike non-IPISD, which involves entire intestinal wall.

3. Features of malabsorption (Ch. 30)

4. Anorexia

5. Significant weight loss

6. Growth retardation (in children)

**Physical Examination**

1. Evidence of malabsorption

2. Finger clubbing

3. Pedal oedema secondary to hypoalbuminemia

4. Hepatosplenomegaly

5. Peripheral lymphadenopathy (in late stage)

**Investigations**

1. Upper endoscopy

n Thickened indistensible mucosal folds

n It may reveal nodules or ulceration on the mucosa

2. Small intestinal series

n Diffuse dilatation of proximal small intestine

n Serology

**Diagnosis**

1. Infiltration of the jejunal mucosa with plasmacytoid cells is the most frequent pathologic feature. The duodenum and ileum are less often affected.

2. The diagnosis depends on the recognition of a monoclonal alpha heavy chain without an associated light chain in the serum, urine, intestinal secretions or cells infiltrating the intestinal mucosa.

3. The serum protein electrophoretic pattern is normal in one-half of cases, and in the remainder an unimpressive

broad band may appear in the alpha-2 or beta mobility regions. The amount of alpha heavy chain in the urine is small.

**Staging**

***WHO Staging System***

1. Diffuse, dense, compact and apparently benign lympho-proliferative mucosal infiltration.

2. As in the above plus circumscribed "immunoblastic'' lymphoma, in either the intestine and/or mesenteric lymph nodes.

3. "Diffuse immunoblastic'' lymphoma.

***Salem Staging System***

0 Benign-appearing lymphoplasma cytic mucosal infiltrates (LPI), no evidence of malignancy

I LPI plus malignant lymphoma in either intestine (Ii) or mesenteric lymph nodes (In), but not both

II LPI plus malignant lymphoma in both intestine and mesenteric lymph node

III Involvement of retroperitoneum and/or extra-abdominal lymph nodes

IV Involvement of non-contiguous non-lymphatic tissues

**Management**

1. Stage 0 Antibiotics alone for 6 months (tetracycline with or without metronidazole)

2. Stage I-IV CHOP ± Tetracycline

**Pathogenesis of IPSID**

1. It is analogue to *H. pylori* associated gastric MALT. In gastric MALT, *H. pylori* is stimulus. While in IPSID, intestinal MALT may be stimulated by infectious agents.

2. Prolonged antigenic stimulus to intestinal MALT leads to the production of an unusual IgA heavy chain protein, and malignant degeneration to immunoblastic lymphoma.

**Non-IPSID**

1. **Marginal cell B-cell lymphoma**

n Elderly patients presented with melena

n Indolent variety

n Single annular or exophytic tumour anywhere in the small intestine

n Treatment is surgery

2. **Diffuse large cell B-cell lymphoma**

n Indolent variety

n Patients presents with abdominal pain, gastrointestinal bleeding or intestinal obstruction.

n Treatment is surgery, with or without chemotherapy

3. **Mantel cell lymphoma**

n Presents with multiple lymphoid polyps.

n Ileocecal region is the most common site.

n Patients present with diarrhoea, abdominal pain or obstruction.

n Treatment is surgery with chemotherapy.

4. **Follicular lymphoma**

n Rare lymphoma

n Obstructing lesion in terminal ileum is the most common feature.

n Treatment is surgery plus chemotherapy.

**Enteropathy-Associated Intestinal T-cell Lymphoma**

1. It is a rare tumour that accounts for less than 5% of all gastrointestinal lymphomas and less than 1% of all non-Hodgkin lymphomas.

2. Patients with untreated celiac disease have a substantially increased risk of developing EATL, especially those diagnosed at an older age (i.e., age >33 yrs).

3. Monoclonal proliferation of intraepithelial T-cells leads to either refractory sprue, ulcerative jejunitis or lymphoma.

4. Jejunum is the most common site.

5. Unresponsive to gluten-free diet.

6. Abdominal pain, diarrhoea, weight loss are the presenting complaints.

7. Prognosis is very poor.

8. Treatment is not well defined but surgery plus chemotherapy is recommended.

**Colorectal and oesophageal lymphomas**

1. **Colorectal lymphoma** is an uncommon form of GI lymphoma and may present with abdominal pain, overt or occult bleeding, diarrhoea, intussusception or rarely, bowel obstruction. Colonoscopy with biopsy is the principal diagnostic modality for colorectal lymphomas. The most common histologies include diffuse large B cell lymphoma, mantle cell lymphoma and Burkitt lymphoma.

2. **Oesophageal lymphoma** is perhaps the most uncommon site for primary GI lymphoma and appears to more commonly involve the distal oesophagus. Most patients are asymptomatic or present with complaints of dysphagia or odynophagia. There is a diverse appearance on imaging and the diagnosis is made by endoscopic biopsy in most cases.

**Further Reading**

1. Loehr WJ, Mujahed Z, Zahn FD, et al. Primary lymphoma of gastrointestinal tract: a review of 100 cases. *Ann Surg* 1969;170:232.

2. Ehrlich AN, Stalder G, Geller W, Sherlock P. Gastro-intestinal manifestations of malignant lymphoma. *Gastroenterology* 1968;54:1115.

3. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classification of gastrointestinal tract lymphoma. *Ann Oncol* 1994;5:397.

4. Zettl A, deLeeuw R, Haralambieva E, Mueller-Hermelink HK. Enteropathy - type T - cell lymphoma. *Am J Clin Pathol* 2007;127:701.

5. Ming-Qi Du, Isaccson PG. Gastric MALT lymphoma: from etiology to treatment. *The Lancet Oncology* 2002;3:97–104.

6. Wotherspoon AC, Doglioni C, Isaacson PG. Low-grade gastric B cell lymphoma of mucosa-associated lymphoid tissue (MALT): a multifocal disease. *Histopathology* 1992; 20:29–34.

7. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994; 330:1267–71.

8. Thiede C, Wundisch T, Neubauer B, et al. Eradication of Helicobacter pylori and stability of remissions in low-grade gastric B cell lymphomas of the mucosa-associated lymphoid tissue: results of an ongoing multicenter trial. *Recent Results Cancer Res* 2000;156:125–33.

9. Papa A, Cammarota G, Tursi A, et al. *Helicobacter pylori* eradication and remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma: a long-term follow-up study. *J Clin Gastroenterol* 2000;31:169–71.

10. Al-Saleem T, Al-Mondhiry H. Immuniproliferative Small Intestinal Disease (IPSID): A model for mature B-cell neoplasm. *Blood* 2005;105:2274–80.

11. Wotherspoon AC, Ortiz Hidalgo C, Falzon MR, et al. *Helicobacter pylori*-associated gastritis and primary B-cell lymphoma. *Lancet* 1991;338:1175–6.

12. Nakamura S, Yao T, Aoyagi K, et al. *Helicobacter pylori* and primary gastric lymphoma. A histopathologic and immunohistochemical analysis of 237 patients. *Cancer* 1997; 79:3–11.

13. Luis Miguel Juárez-Salcedo, Lubomir Sokol, Julio C Chavez, et al. Primary gastric lymphoma, epidemiology, clinical diagnosis, and treatment. *Cancer Control* 2018;25:1–12.

14. Thieblemont C, Cascione L, Conconi A, et al. A MALT lymphoma prognostic index. *Blood* 2017;130:1409–17.

**Chapter 33.**

**Pseudocyst of Pancreas**

**Introduction**

Pancreatic pseudocyst is a non-epithelial lined cystic fluid collection that arises from disruption of a pancreatic duct following an episode of pancreatitis, with leakage of amylase-rich pancreatic juice into surrounding peripancreatic tissue. Pseudocyst differs from a true cyst is not having an epithelial lining, and develops in around 10% of cases of interstitial edematous pancreatitis. Pseudocysts account for around 75% of all cystic lesions of the pancreas. Despite being diagnosed easily, treatment exercise is still at crossroads whether in the form of internal or external drainage or endoscopic, laparoscopic, or open intervention with a good radiological guidance. Management of pseudocyst is only discussed in this chapters as management of wall-off necrosis (WON) and infected necrosis is discussed in chapter 42.

**Clinical History**

1. Abdominal pain – pressure effect of pseudocyst

2. Insidious onset upper abdominal pain in mid epigastrium, aggravated by eating food, with radiation to the back.

3. Exacerbation of a pre-existing pain or sudden onset of pain indicates haemorrhage into the cyst or rupture into the peritoneum.

4. Persistent vomiting – duodenal obstruction

5. Jaundice – biliary obstruction (<10%)

6. Fever – infected pseudocyst

7. Abdominal distension – ruptured pseudocyst leading to pancreatic ascites

**Past History**

1. Past history of acute pancreatitis

2. Past history of recurrent biliary colic indicates biliary pancreatitis

3. History of abdominal trauma

**Personal/Social History**

1. Alcohol – alcoholic pancreatitis

**General Examination**

1. High temperature indicates infected pseudocyst.

2. Icterus – biliary obstruction

3. Pallor – haemorrhage in the cyst due to ruptured pseudo-aneurysm

**Abdominal Examination**

1. Abdominal examination may be normal in case of small pseudocyst.

2. In case of large pseudocyst mass lesion – size, shape, location, movement with respiration, intrinsic mobility, tenderness, margin and arterial bruit.

3. Splenomegaly – associated splenic vein thrombosis

4. Ascites – pancreatic ascites

**Respiratory System Examination**

1. Pleural effusion, especially on the left side

**Investigations**

1. ***Biochemistry***

n Leucocytosis – infected pancreatic pseudocyst

n Direct hyperbilirubinemia and raised alkaline phosphatase – biliary obstruction due to pseudocyst

n Serum amylase and lipase – mainly in patients with abdominal pain to rule out ongoing pancreatitis

2. ***Plain X-ray abdomen***

n Displacement of gastric bubbles

n Cyst wall calcification indicates cystic neoplasm

3. ***USG abdomen***

n Initial investigation of choice, cheap, safe and can be performed at bedside

n Size, number, location of pseudocyst

n Wall thickness, presence of internal debris

n Internal septations, calcification or mural nodules indicate cystic neoplasm of pancreas

n Evidence of chronic pancreatitis

n Ascites

4. ***Spiral CT abdomen/MR abdomen***

n Contrast-enhanced CT is now the primary tool of investigation for initial diagnosis of pancreatic pseudocysts.

n Size, number, location, presence of internal debris, wall thickness.

n Impression of pseudocyst on stomach or duodenum.

n Evidence of chronic pancreatitis by duct dilatation, intraductal stones, parenchymal atrophy and parenchymal calcification.

n To identify vascular complications like pseudo-aneurysm or splenic vein thrombosis.

n Uncomplicated pseudocyst shows 0–20 Hounsfield unit (HU) in CT scan, whereas complicated pseudocyst in the form of infection or haemorrhage shows more than 40 HU.

n MRI outperforms CT in the assessment of the ratio of fluid to necrotic debris in collections older than 4 weeks. Therefore, MR imaging is a valuable alternative to contrast-enhanced CT for planning interventions.

5. ***Endoscopic ultrasound***

n Popular modality to evaluate cystic lesions of the pancreas.

n EUS is usually used as a secondary test to further evaluate pancreatic cyst detected by other imaging modality (US, CT or MRI).

n Can delineate complex wall structures and internal cyst contents.

n EUS-guided fine needle aspiration (FNA) can differentiate cystic neoplasm from a pseudocyst.

n EUS can also assist in localizing the site for pseudo-cyst drainage by excluding gastric varices, submucosal vessels and other vascular structures at the drainage site.

6. ***ERCP***

n Diagnosis as well as therapeutic purpose.

n ERCP is sometimes done before any drainage procedure to rule out proximal pancreatic duct stricture.

n Therapeutic ERCP can be used for transpapillary drainage of pseudocyst. Duodenoscope is used for transgastric drainage of the pseudocyst.

n It helps sometimes to diagnose chronic pancreatitis.

7. ***Image-guided fine needle aspiration***

n Imaging-guided fluid collection aspiration or necrotic tissue fine-needle aspiration to help diagnose infection prior to invasive procedures debatable.

n Fine-needle aspiration has fallen out of favour in recent years, due to a shift in preference toward early conservative management with percutaneous drainage, which may delay or even obviate surgical intervention.

**Management**

Spontaneous resolution of pseudocyst occurs 8–70%. There are several factors decreasing the possibility of spontaneous resolution, like the presence of multiple cysts, location in the tail of the pancreas, communication with the main pancreatic duct and co-existence of stricture and increasing in size during follow-up. On the other hand, pancreatic pseudocyst due to chronic pancreatitis is rarely resolving spontaneously, mainly due to abnormalities of the pancreatic duct and strictures produced by calcification and fibrosis. In the absence of life threatening events, timing of intervention should be delayed up to 6 weeks from the pancreatitis episode,

in order for the pseudocyst wall to mature and become

thicker, aiding in the success of any type of drainage. There is no unanimous agreement on how to treat them, and various methods are proposed.

There are three management approaches to treat pancreatic pseudocyst that can be used depending on their size, number, location and whether they are infected, as also whether surgery is otherwise indicated say for gallbladder stones:

1. Percutaneous drainage

2. Endoscopic drainage

3. Surgical drainage

**Percutaneous Drainage**

It can be either needle aspiration or continuous catheter drainage **(Table 33.1)**. Percutaneous drainage (PD) is extremely helpful in cases of fragile patients, with severe comor-bidities, that cannot tolerate any other surgical or endoscopic procedure. On the other hand, PD has severe limitations such as the scarcity of a safe access route, presence of active haemorrhage into the pseudocyst and demonstration of pancreatic duct obstruction or disruption, which will probably lead to the formation of pancreatic fistula.

**Needle Continuous drainagec aspiration catheter**

Success 50–60% 80%

Recurrence 63% 7–10%

Failure 54% 16–20%

Complications 20% 18%

***Contraindications for Percutaneous Drainage***

1. Suspicious of malignancy

2. Intracystic haemorrhage

3. Pancreatic ascites

4. Proximal pancreatic duct stricture

**Endoscopic Drainage**

1. It can be either transmural (transgastric or trans-duodenal) or transpapillary drainage **(Table 33.2)**.

2. Pseudocyst drainage by transpapillary approach is possible when there is a communication between the pancreatic duct and the pseudocyst. At ERCP, a guide wire is advanced into the main pancreatic duct into the pseudocyst cavity.

Over the guide wire 5 or 7 Fr stent is placed. This will lead to drainage of pseudocyst by transpapillary route.

**Transpapillary Transenteric**

**drainage drainage**

Success rate 84% 82%

Recurrence 9–10% 15–18%

Complications 10–12% 8%

- Lack of resolution

- Bleeding

Mortality 0% 0%

1. Transenteric (endoscopic cystogastrostomy or cysto-duodenostomy) drainage of pseudocyst should be undertaken upon a clear impression of the pseudocyst into the wall of the stomach or duodenum. Arterial pseudo-aneurysm should be excluded by either contrast CT scan or linear endoscopic ultrasonography (EUS). A diathermy incision is made at the area of maximum bulge with a needle-knife papillotome followed by cystotome to enter the pseudocyst. After introducing guide wire into the pseudocyst, transmural tract is dilated using CRE balloon, and multiple 7 or 10 Fr stent are placed into the cyst cavity to maintain patency. The stent is left in place until ultrasonography confirms pseudocyst resolution. EUS-guided drainage, allows the drainage of non-bulging pseudocysts, with a cyst-lumen distance of 1–1.5 cm, under direct visualization. Recent evidence shows EUS-guided pseudocyst drainage is consider as standard of care.

2. Complications of pseudocyst drainage by either approach include pancreatitis, bleeding, perforation and infection.

**Surgical Drainage**

Cystogastrostomy, cystoduodenostomy and cystojejuno-stomy are the usual types of operations, performed either open or laparoscopically, creating an anastomosis between the GI tract lumen and the cyst, using suturing or stapling devices. Laparoscopic drainage was associated with 98.3% achievement of drainage, 2.5% recurrence, 5.7 days mean hospital day and <2% of complications rate.Creation of a wider stoma for drainage and possible debridement in cases of underlying pancreatic or peripancreatic necrosis are the major advantage of surgical drainage. Role of surgical drainage is limited in view of advancement in endoscopic drainage.

***Indications for Surgical Drainage***

n Recurrent pseudocyst

n Pseudocyst in chronic pancreatitis where transpapillary drainage is technically difficult

n Suspicious of cystic neoplasm

n Suspecting infected pancreatic necrosis

n Severe duodenal obstruction

**Pathology**

In the early phase, pseudocysts always communicate with the pancreatic ducts, but this connection tends to disappear as the cyst “matures.” Non-communication is essential if the cyst is to resolve spontaneously. Pseudocysts may be single or multiple and are found in all segments of the pancreas, but usually the head or tail. However, it is not uncommon to find them outside the pancreas, such as in the abdominal cavity or pelvis, due to intraperitoneal spread of the pancreatic juices and necrotic/haemorrhagic debris during the acute phase.

**Complications**

Pancreatic pseudocyst needs close follow-up to early detect the most dreadful complications.

A. *Infection*: Infection occurs either spontaneously or after therapeutic or diagnostic manipulations. Although infected pseudocyst can initially be treated with conservative means, a majority of patients will require intervention. Traditionally, surgery has been the preferred modality but endoscopic treatment is gaining acceptance.

B. *Haemorrhage*: Haemorrhage can greatly complicate the course of a pseudocyst and can be devastating, and is usually due to erosion of a major vessel in the vicinity of the pseudocyst. Interventional radiology can play an invaluable role both in locating the source of bleeding and in embolization of the bleeding vessel. Without prior information of the bleeding point, surgical exploration can be hazardous and challenging.

C. *Splenic infarction and thrombosis*: Complications of pseudocyst include massive haemorrhage into the pseudocyst, sepsis with splenic infarction and splenic vein thrombosis.

D. *Rupture*: Rupture of a pseudocyst can have either a favourable or an unfavourable outcome, and this depends on whether it ruptures into the gastrointestinal tract, into the general peritoneal cavity or into the vascular system. Rupture into the gastrointestinal tract either results in no symptoms or leads to melena or haematemesis that usually requires urgent measures.

Rupture into the general peritoneal cavity results in features of peritonitis and occasionally haemorrhagic shock. Emergent surgical exploration is usually required. While an internal drainage should always be aimed for, usually a thorough abdominal lavage and external drainage are all that can be achieved safely.

E. *Biliary complications*: Biliary complications occur due to a large cyst in the pancreatic head region obstructing the common bile duct and resulting in obstructive jaundice. Therapeutic endoscopy with short-term biliary stenting is valuable in this situation. It can be retained until either the pseudocyst resolves or is treated by intervention.

F. *Portal hypertension*: Portal hypertension can result from compression or obstruction of the splenic vein/portal vein either by the cyst alone or by the cyst in conjunction with underlying chronic pancreatitis.

G. *Gastric outlet obstruction*: Pseudocysts around the head of the pancreas are likely to cause gastric outlet obstruction. Once the features of gastric outlet obstruction develop, it needs certainly intervention and decompression or drainage of the cyst.

**D’Egidio and Schein Classification of Pseudocyst**

1. **Type I or acute post necrotic pseudocyst**

n Following attack of acute pancreatitis

n Normal duct anatomy

n No duct-cyst communication

2. **Type II or post necrotic pseudocyst**

n After acute-on-chronic pancreatitis

n Abnormal duct anatomy

n Duct-cyst communication

3. **Type III or retention cyst**

n Seen in chronic pancreatitis

n Associated with pancreatic duct stricture

n Duct-cyst communication

**Nealon and Walser Classification**

(Based on Pancreatic Duct Anatomy)

1. Type I: Normal duct/no communication with the cyst.

2. Type II: Normal duct with duct-cyst communication.

3. Type III: Otherwise normal duct with stricture and no duct-cyst communication.

4. Type IV: Otherwise normal duct with stricture and duct-cyst communication.

5. Type V: Otherwise normal duct with complete cutoff.

6. Type VI: Chronic pancreatitis and no duct-cyst communication.

7. Type VII: Chronic pancreatitis with duct-cyst communication.

**Common Causes of Acute Pancreatitis**

Alcohol Hereditary pancreatitis

Gallstones Trauma

Hypercalcaemia Infection

Hypertriglyceridemia Pancreas divisum

Chronic pancreatitis

Drugs:

- Sodium valproate

- Azathioprine

- Pentamidine

Sphincter of Oddi dysfunction

**Causes of Cystic Lesions of Pancreas**

1. Pseudocyst (70–90%)

2. Cystic neoplasm (10–15%)

n Serous cystadenoma

n Mucinous cystadenoma

n Intraductal papillary mucinous tumour

3. Retention cyst (10%)

4. Congenital cyst (5%)

n Polycystic disease of pancreas

n Dermoid cyst

**The Revised Atlanta Classification for pancreatic fluid collections**

The revised Atlanta classification makes an important distinction between collections that contain purely fluid and collections that contain necrotic debris in addition to fluid (those encountered in necrotizing pancreatitis). The terms acute pseudocyst and pancreatic abscess have been aban-doned. Similarly, the use of the term pseudocyst in radio-logy reporting to describe any pancreatitis-related collection is misleading to treating physicians, as the term implies that these collections always contain purely fluid, which is not the case in necrotic collections. Instead, the revised classification includes new definitions that more accurately describe the various types of collections encountered: APFC, pseudocyst, ANC and WON. The important distinctions for classifying collections correctly are the time course (4 weeks or >4 weeks from onset of pain) and the presence or absence of necrosis at imaging **(Table 33.3)**.

APFCs are always peripancreatic in location. If a similar-appearing collection is seen within the pancreatic parenchyma, it is by definition an ANC, and the diagnosis is no longer IEP but necrotizing pancreatitis.

Once acute fluid collection has not resolved within 4 weeks, it becomes more organized, with the development of a capsule that manifests as an enhancing wall at contrast CT.

Clear fluid without any necrosis or solid component, it is referred as pseudocyst. If there is even a small area of fat or soft-tissue attenuation in an otherwise fluid-attenuation collection, the diagnosis is not pseudocyst but WON.

Pancreatic fluid collection can be sterile or infected although infection occurs far more frequently in necrotic collections. Clinically, infection is suspected in a previously

stable patient who experiences decompensation with signs of infection. The only imaging finding of an infected collection is the presence of gas within the collection.

**Further Reading**

1. Pitchumoni CS, Agarwal N. Pancreatic pseudocysts. When and how should drainage be performed? *Gastroenterol Clin North Am* 1999;28:615–39.

2. D’Egidio A, Schein M. Pancreatic pseudocysts: a proposed classification and its management implications. *Br J Surg* 1991;78:981–4.

3. Nabi Z, Basha J, Reddy DN. Endoscopic management of pancreatic fluid collections-revisited. *World J Gastroenterol* 2017;23:2660–72.

4. Yang D, Amin S, Gonzalez S, et al. Transpapillary drainage has no added benefit on treatment outcomes in patients undergoing EUS-guided transmural drainage of pancreatic pseudocysts: a large multicenter study. *Gastrointest Endosc* 2016;83:720–9.

5. Beckingham IJ, Krige JE, Bomman PC, et al. Endoscopic management of pancreatic pseudocysts. *Br J Surg* 1997;84:1638–45.

6. BR Foster. The Revised Atlanta Classification of Acute Pancreatitis. *RadioGraphics*2016;36:675–87.

7. Habashi S, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol* 2009;15:38–47.

8. Andalib I, Dawod E, Kahaleh M. Modern management of pancreatic fluid collections. *J Clin Gastroenterol* 2018; 52:97–104.

9. Christos Agalianos, Ioannis Passas, Ioannis Sideris, et al. Review of management options for pancreatic pseudocysts. *Transl Gastroenterol Hepatol* 2018;3:18–25.

**Chapter 34.**

**Chronic Pancreatitis**

**Introduction**

Chronic pancreatitis (CP) is a syndrome involving inflam-mation, fibrosis and loss of acinar (exocrine) and islet (endocrine) cells, which manifests as unrelenting abdominal pain, malnutrition and exocrine and endocrine insufficiency.

Diagnosis of CP is straightforward in patients with advanced disease with overt steatorrhoea, pancreatic calcification or a dilated main pancreatic duct. Accurate diagnosis of the condition is challenging in patients with less advanced disease or minimal changes in pancreas. Treatment of CP remains challenging because of the often refractory and centrally mediated pain and a lack of consensus about the indication of endoscopic therapy and surgery. Recent studies indicate that acute pancreatitis (AP), recurrent AP (RAP) and CP represent a disease continuum.

**Clinical History**

1. Abdominal pain

n Pain is the predominant presenting complaint in the majority of patients with CP.

n Severe, persistent epigastric pain with radiation to the back, relieved by stooping forward position is typical pancreatic pain. However, this typical pattern is not seen in all patients.

n Natural history of pain is variable.

n Two types of pain have been described. Type A pain refers to recurrent bouts of short-term relapsing pain episodes, whereas type B pain refers to characterized as prolonged and persistent. Type B pain is thought to be associated with large duct CP, presumably associated with increase intraductal pressure or secondary complications of CP (e.g., pseudocyts or biliary obstruction).

n Pain is more frequent and severe in early onset of CP, while, around 50% late onset of CP have no abdominal pain (this mainly applies to the idiopathic pancreatitis).

*Abdominal pain in patients with CP is multifactorial*:

n Pancreatic inflammation

n Pancreatic duct obstruction

n High pancreatic tissue pressure (compartment syndrome)

n Encasement of sensory nerves

n Neuropathy

n Complications like biliary stricture and pseudocyst

n Development of malignancy

2. Steatorrhea

n Steatorrhea indicates far more advanced acinar cell destruction. It does not occur until pancreatic lipase secretion is reduced to less than 10% of normal.

n As maldigestion of fat is predominant in chronic pancreatitis, watery diarrhoea, excess gas and abdominal cramps are uncommon.

n Fat digestion is dependent on pancreatic lipase and, in patients with CP, pancreatic lipase output decreases earlier compared to other pancreatic enzymes.

3. Weight loss

n Weight loss may be minimal since the patient increases calorie intake.

n Profound weight loss suggests development of malignancy.

4. Diabetes mellitus

n Development of diabetes also indicates advanced disease with considerable damage to the pancreatic endocrine component.

n Around 60–70% of patients with CP develop diabetes (type 3c DM).

n Ketosis is uncommon as -cell function is partially preserved.

n Pancreatic diabetes is brittle type of diabetes because of deficiency of both insulin and glucagon.

**Past History**

Past history of recurrent abdominal pain indicates recurrent acute attacks of pancreatitis.

**Family History**

Hereditary pancreatitis refers to otherwise unexplained pancreatitis in an individual from a family in which the phenotype for pancreatitis appears to be inherited through a disease-causing genetic mutation expressed in an autosomal dominant pattern with high disease penetration (80%). Hereditary pancreatitis usually presents in childhood with recurrent episodes of AP.

About half of the patients progress to CP. Estimated risk of developing pancreatic cancer is 40%. Pancreatic cancer

can occur in patients in their 40s. Hereditary pancreatitis is due to gain-of-functions, single-point mutation in the cationic trypsinogen gene (PRSS1).

**Personal/Social History**

1. **Alcohol intake**

n The pathogenesis of alcoholic pancreatitis is poorly understood, but it is thought that chronic alcohol consumption sensitizes the acinar cell to injury by interfering with mechanisms that protect against endoplasmic reticulum stress. The M-AHHEIM classification system of CP has grouped alcohol consumption into patterns of moderate (<20 g ethanol/day), increased (20–80 g ethanol/day) or excessive (>80 g ethanol/day). It is interesting that while alcohol is the most commonly recognized factor in the development of CP, only about 10% of patients with chronic alcoholism develop CP. CP is not merely the alcohol injury but a complex chronic inflammatory disorder that is linked to genetic, metabolic and environmental factors. Genetic variants in the *CLDN2* gene loci have been shown to influence the risk for alcohol-related pancreatitis.

n Results from a recent multicentre study from North America (NAPS2) showed a significant association between alcohol and CP only with the consumption of five or more alcoholic drinks per day, which suggests a threshold level of drinking.

2. **Smoking**

n Several epidemiological studies indicate that smoking has independent effects on the development of CP.

n The risk of CP in smokers is linear. The risk increases with the amount of smoking.

n Smoking reduces pancreatic bicarbonate secretion, serum trypsin inhibitory capacity and 1-antitrypsin level.

n Smoking leads to disease progression in alcoholic pancreatitis and it accelerates calcification in alcoholic pancreatitis.

3. **Cassava intake**

n Cassava, a tuber, contains almost pure starch with only small quantity of protein and devoid of essential amino acids. The high carbohydrate and low protein

content of cassava is thought to be responsible for tropical pancreatitis. However, this is not yet proven.

n Cassava also contains cyanogenic glycosides like linamarin and lotavastralin, which is converted into thiocyanates in the stomach. During this process methionine is used up.

n Pancreas, being the organ with highest protein turnover, is affected most by methionine deficiency.

**Physical Examination**

1. Physical examination is not very helpful in diagnosing CP.

2. Mild-to-moderate upper abdominal tenderness may present during acute exacerbation.

3. Signs of malnutrition may be evident in advanced disease.

4. Presence of icterus indicates biliary obstruction either secondary to fibrotic process in the head or due to pancreatic head malignancy.

5. Palpable mass may indicate pseudocyst or pancreatic malignancy.

6. Splenomegaly indicates thrombosis of splenic vein as a consequence of CP.

7. Hepatomegaly suggests co-existent alcoholic liver disease.

**Investigations**

1. ***Biochemistry***

n Routine biochemistry may be normal except hyperglycemia.

n Hypercalcaemia indicates hyperparathyroidism.

n Hypertriglyceridemia can cause CP.

n Altered liver function test, particularly direct hyperbilirubinemia and elevated serum alkaline phosphatase suggest biliary obstruction secondary to either benign or malignant process.

2. ***Plain radiograph of abdomen***

n Plain radiograph of abdomen has limited sensitivity, but it is the most inexpensive screening test.

n Plain radiograph may show pancreatic calcifications.

n There is poor correlation between presence of pancreatic calculi and pancreatic functional reserve.

3. ***Ultrasonography***

n Ultrasonography is inexpensive, non-invasive and extremely useful in the diagnosis.

n Pancreatic duct (PD) dilatation, presence of parenchymal and intraductal calculi, and pancreatic gland atrophy are the major sonographic features of CP.

n Ultrasonography may be normal with early or mild disease with sensitivity of 60–70%.

4. ***Computed tomography***

n Spiral CT scan abdomen has good sensitivity in moderate-to-severe CP. It is non-invasive and widely available imaging modality.

n It is also useful to identify complications like biliary stricture, pseudocyst and malignancy.

n CT scan has 75–90% sensitivity for demonstration of pancreatic calcification.

n Ultrasound (USG) or Computed tomography (CT) grading of CP according to Cambridge Classification:

- **Normal**: Normal entire gland without abnormal findings

- **Equivocal**: One of the following:

- Mild dilatation of pancreatic duct (2–4 mm) in the body of the gland

- Gland enlargement < two-fold normal

**Mild-to-moderate**: Equivocal + at least one of the following:

n Pancreatic duct (PD) dilatation

n PD irregularities

n Cavities < 10 mm

n Parenchymal heterogeneity

n Duct wall echogenicity

n Focal necrosis of parenchyma

**Severe Mild/moderate** + one or more of the following

n Cavity >10 mm

n Intraductal filling defects

n Calculi/pancreatic calcification

n Ductal stricture

n Severe PD dilatation

5. ***Magnetic resonance imaging***

n MRCP has emerged as an accurate non-invasive method for evaluating pancreatic duct.

n The normal pancreatic duct measures 2–3 mm in diameter, increasing from the tail to the head, as shows smooth margins in MRCP.

n Complete visualization of pancreatic duct is possible by MRCP in 100% of cases. When the pancreatic duct is not dilated, it can be visualized by MRCP in the head and body in 97% of cases and in the tail in 83% of cases. Secretin stimulation of pancreatic secretion significantly increases these figures. Pancreatic side branches are not seen on MRCP unless dilated. Secretin-enhanced MRCP (S-MRCP) helps to evaluate side branch ectasia, mild duct dilatation and ductal irregularities.

6. ***ERCP***

n In the absence of tissue diagnosis, which is the gold standard, ERCP should be considered as the most sensitive (90%) and specific (100%) test for the diagnosis of CP.

n Ductal changes are best visualized by ERCP. Side-branch ectasia is the earliest features. Other findings are multifocal dilatations, strictures and irregular side branches; intraductal calculi and pseudocyts.

n Although ERCP has been considered as the most sensitive imaging method for detecting the early changes of CP; it is operator depended, expensive and invasive.

Cambridge grading of CP by ERCP is given below **(Table 34.1)**.

**Grade Main Side pancreatic duct branches**

Normal Normal Normal

Equivocal Normal <3 abnormal

Mild Normal >3 abnormal

Moderate Abnormal >3 abnormal

Severe Abnormal with at

least one of the

following:

Large cavity

(>10 mm)

Duct obstruction,

intraductal filling

defects, severe duct

dilatation

7. ***Endoscopic ultrasonography***

n EUS allows the detailed examination of pancreatic parenchyma and pancreatic duct.

n EUS is highly sensitive and specific for detecting CP. In the early stages of CP, the ductal system remains normal but the parenchymal changes can be detected by EUS. Lobular pattern of the pancreas; hypoechoic areas surrounded by hyperechoic septae are the earliest features appear on EUS.

n Criteria for diagnosis of CP by EUS are given below **(Table 34.2)**.

8. ***Pancreatic function tests***

n Fecal chymotrypsin or elastase

- Low fecal chymotrypsin/elastase level is seen in majority of CP with steatorrhea. But it may be normal in mild-to-moderate chronic pancreatitis.

- Fecal elastase is very stable and very easy to estimate.

- These are the screening tests for steatorrhea.

n Serum trypsinogen

- Low levels of serum trypsinogen are seen in advanced CP. However, in patients with less advanced disease, it may be normal.

n Direct test:

- Gold standard for the measurement of pancreatic exocrine function.

- Combination of CCK and secretin provides information about both acinar and ductal secretion.

- Direct test measures volume, bicarbonate and enzyme output following intravenous secretin and CCK.

- It requires duodenal intubation.

n Other tests:

- Lundh test meal – this test is more physiological but requires gastric and duodenal intubations.

- N-benzoyl-L-tyrosyl-para-amino benzoic acid (NBT–PABA) test.

- Pancreolauryl (fluorescein dilaurate) test (gastric and duodenal intubation is not required).

- S-MRCP - Assessment of pancreatic secretory function by secreting-MRCP is based on the volume of fluid output in the duodenum following intravenous administration of secretin. The duodenal filling volume has been graded as: grade 0, no fluid observed; grade I, filling of duodenal bulb; grade II, fluid filled up to second part; grade III, the duodenum largely filled beyond second part. Duodenal filling grade less than 3 is defined as exocrine dysfunction.

**Parenchymal Ductal**

**abnormalities abnormalities**

n Hyperechoic foci n Main duct dilatation

n Hyperechoic strands n Duct irregularity

n Lobularity of contour n Hyperechoic

of glands ductal margins

n Cysts n Dilated side branches

n Stones

*Function tests have lost their importance with the advent of sensitive imaging modalities.*

**Diagnostic Criteria for CP**

Usual or calcifying CP can be diagnosed in patients with recurrent pancreatitis who have at least one of the following features:

1. Histology shows typical features of usual CP.

2. Pancreatogram shows marked abnormalities (Cambridge II or III).

3. Calculi in the pancreatic duct are seen on plain X-ray of the abdomen, computed tomography (CT), magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS).

4. EUS shows >5 criteria.

5. Pancreatic function is markedly depressed (pancreatic steatorrhoea).

**Two difficult diagnostic issues in cP**

1. How can one distinguish between an inflammatory mass of CP, pancreatic adenocarcinoma and focal autoimmune pancreatitis? Elevated IgG can occur in all three settings, tumour marker has no value. EUS or CT-guided core biopsy can be used to confirm autoimmune pancreatitis or a simple needle biopsy might identify tumour cells. 18F-Fluorodeoxyglucose PET with CT can be useful for neoplasm but increased uptake is also a feature of autoimmune pancreatitis. Pancreatectomy specimen is the only ultimate diagnostic tool.

2. Is genetic testing necessary in clinical practice? PRSS1 mutation testing for diagnostic purposes is acceptable in symptomatic young individuals or in those with a family history of pancreatitis, but counseling and clinical follow-up are needed if the results is positive. SPINK1 mutation testing is not indicated. At present, there is no rationale for CFTR mutation testing in the setting of pancreatitis alone.

**Management**

1. The treatment of patients with CP is aimed at managing pain, diabetes and steatorrhea.

2. Abdominal pain is the most common indication for medical management. Pain in CP is variable, natural history of abdominal pain is not well understood and mechanism of pain is multifactorial.

3. Because of all these reasons no consensus has emerged to manage pain in CP.

**Medical Therapy for Pain in CP**

1. **Acid suppressive agents**: Inhibition of gastric acid secretion by proton pump inhibitors leads to a higher duodenal pH and might therefore lesson stimulus driven pancreatic secretion.

2. **Analgesic and pain modulators**: The treatment of pain in CP is performed according to the three-step ladder of the World Health Organization for the relief of cancer pain. The first step is for mild-to-moderate pain and consists of non-opiod analgesics. The second step is for moderate-to-severe pain and consists of mild opioids like dextromethorphan and tramadol. The third step is for severe pain and requires morphine.

Adjunctive pain medication such as tricyclic antidepressants, gabapentin, pregabalin and selective serotonin-reuptake inhibitors have been used either alone or in combination with opioids with variable results.

3. **Octreotide**

n A somatostatin analogue, octreotide, reduces pancreatic secretion and reduces plasma CCK levels.

n Role of octreotide is not established.

4. **Pancreatic enzyme supplements**

n PERT has been widely utilized in treating pain in CP patients. Pathophysiologically, PERT is used for pain relief because it can degrade CCK-releasing factor in the duodenum and, by doing so, lowers CCK levels; additionally, through this mechanism, it reduces pain. The data supporting enzymes in this setting are limited.

5. **Antioxidants**

n It is hypothesized that reduction in oxidative stress improves pain in CP.

n There is increasing evidence to support that a daily micronutrient supplement improves the quality of life in patient with CP.

n Long-term micronutrient treatment might halt the progress in patient with CP, irrespective of cause, duration of the disease or ductal anatomy.

6. **Nerve plexus blockage**

n Visceral afferents traverse the celiac ganglia, which lie adjacent to the aorta below the diaphragm at the level of the celiac trunk. Then, they follow the same course of sympathetic nerves, which relay motor signals to the gland. These afferents often cross the midline and travel along the splanchnic nerves adjacent to the spinal column before synapsing in the dorsal root ganglia and sending axons to the dorsal horn of the spinal cord.

n One of the methods to relieve the pain is to interrupt the neural transmission.

n Interruption of neural transmission can be achieved either by a celiac plexus block or a splanchnic nerves block. Injection of anaesthetics and/or corticosteroids for achieving a temporary block is called celiac plexus block, whereas injection of absolute alcohol that permanently destroys the plexus is called celiac plexus neurolysis. The effect of celiac plexus block is variable and transient and lasts around 2–4 months.

n To date, few studies have reported about thoracoscopic splanchnectomy.

n The role of transcutaenous electrical nerve stimulation has not been proven thus far in patients with CP.

**Endoscopic management**

1. The goal of endotherapy is to relieve obstruction and improve pancreatic drainage.

2. The best candidates for the successful treatment of pain associated with CP with first-line endoscopic treatment are those with obstruction of the main pancreatic duct with an obstructing stone or stricture in the head of the pancreas. The current approaches for endotherapy for CP are directed at: (a) relieving the obstructing pancreatic duct stones, (b) relieving the pancreatic duct strictures,

(c) draining the pancreatic pseudocysts, (d) administering celiac plexus nerve blocks and (e) relieving benign biliary strictures. Endotherapy comprises pancreatic and biliary sphincterotomy, stricture dilation and stenting, stone extraction and lithotripsy. Endoscopic removal of stones is difficult, particularly when the stones are in the body and tail of the pancreatic duct.

3. Extracorporeal shock wave lithotripsy (ESWL) helps to fragment the stones. ESWL for pancreatic stones is a difficult procedure even for experienced professionals; it is associated with significant risks, and patients may require protracted therapy (>10 sessions) for successful clearance of the duct. Various studies have reported that despite successful ESWL, most patients experience no improvement in pain.

4. Pain improvement occurs in two-third of patients following pancreatic stenting. But, around half of the patients have recurrence of symptoms after 6 months. Long-term stent placement is associated with complications such as stent blockage, stent migration and development of a new stricture. According to European Society of Gastrointestinal Endoscopy (ESGE) guidelines, endotherapy is not useful in patients with asymptomatic and uncomplicated CP. To date, no study has reported any benefit of endotherapy in these patients, including in the preservation of exocrine or endocrine pancreatic insufficiency.

5. Endoscopic ultrasound (EUS)-guided celiac plexus nerve block relieves pain in about 50% of patients, and the effect lasts for a maximum of a few weeks with risk of side effects such as postural hypotension and diarrhoea. Hence, a celiac plexus block is rarely applied in CP and is not recommended unless there is concomitant pancreatic malignancy.

**Surgical Management**

1. As many as 50% of all the patients with CP ultimately require surgical treatment, because of the intractable pain refractory to medical management or pancreatitis-associated complications.

The main aim of surgery in CP is to ameliorate pain, to treat local complications, and to preserve or improve endocrine or exocrine function. In patients with an obstructed dilated pancreatic duct (pancreatic duct >7 mm), drainage and decompression of the duct may be effective, whereas in patients with a dominant inflammatory mass, resection of the mass may be beneficial. If neither of these features is present, surgical treatment options are limited.

2. Drainage procedures: This surgical approach improves pain by decreasing the intrapancreatic ductal and parenchymal

pressure. Lateral pancreatico-jejunostomy (**modified the Puestow–Gillesby procedure**) drains the pancreatic duct even in the presence of multiple strictures or stones without distal pancreatectomy and splenectomy. Lateral pancreatico-jejunostomy is associated with low rates of morbidity and mortality, and pain relief has been reported by approximately 60–70% of patients. Best results of drainage procedure are achieved in patients with a pancreatic duct diameter for at least 7 mm and an absence of an inflammatory mass.

3. Resection procedures: The head of the pancreas is most frequently affected and has been characterized as the pacemaker of the disease process. Thus, resection of the pancreatic head is an option for surgical management in patients with non-dilated pancreatic duct. The rationale for duodenum-preserving pancreatic head resection (DPPHR, **Beger Procedure**), includes removal of the main inflammatory process, whereas preserving the upper gastrointestinal tract. Preservation of the duodenum has been shown to be very important because the duodenum is essential for the regulation of glucose metabolism and gastric emptying. **Classic Whipple resection** and **pylorus-preserving Whipple resection** became historical in the management of inflammatory pancreatic head mass. Total pancreatectomy with islet auto transplantations may be used as one of the therapies in future in patients with small duct diffuse inflammatory diseases.

4. Resection and drainage procedures: **Frey procedure** is a modification of the DPPHR: longitudinal pancreatico-jejunostomy with a local pancreatic head resection. The efficacy of both DPPHR and the Frey procedure is similar in terms of controlling pain in around 90% of patients in the late follow-up. **Izbicki procedure** is a V-shaped excision of the ventral pancreas with secondary and tertiary ducts draining into Roux loop of the jejunum.

5. Modified procedures: Berne modification of Beger procedure and Hamburg’s modification of Frey procedure.

6. Beger procedure can potentially resolve common bile duct obstructions, pancreatic duct stenosis and obstruction of the retropancreatic vessels by removing the inflammatory mass in the head of the pancreas. Procedure-related mortality varies from 0 to 2% and the morbidity varies from 15 to 54%. At 5 years of follow-up, approximately 80% of patients show pain relief and endocrine as well exocrine functions are well preserved. Moreover, the overall morbidity associated with Frey procedure is lower than that associated with Beger procedure (Frey: 9–22% vs Beger: 20–32%).

7. **Total pancreatectomy with islet autologous transplantation (TP–IAT)**: Subgroups of patients with CP have recalcitrant pain resistant to medical and surgical treatments. To date, the selection criteria for patients with TP–IAT remain to be established. A consensus for TP-IAT was established recently at a conference in 2014; it indicated that TP–IAT should be primarily indicated in patients with intractable pain and impaired quality of life because of CP or recurrent AP in whom medical, endoscopic and previous surgical therapy has been unsuccessful.

**Management of Pancreatic Exocrine Insufficiency**

1. Pancreatic exocrine insufficiency (PEI), characterized by inadequate pancreatic secretion of digestive enzymes and bicarbonate. PEI is one of the most significant complications of CP, which affects >50% of patients with CP and results in compromised digestion, absorption and metabolism of nutrients. Symptomatic PEI does not occur until approximately 90% of pancreatic exocrine function is lost. Exocrine insufficiency manifests as steatorrhoea (often without diarrhoea), weight loss, malnutrition, metabolic bone disease and vitamin and mineral deficiency. Severe PEI tends to develop between 5 and 10 yrs after an initial diagnosis of CP. Low levels of fecal elastase (<200 µg/g stool although even lower levels are more specific) or serum trypsin (<20 ng/mL) are usually observed in patients with PEI.

2. Cornerstones in the treatment of PEI are pancreatic enzyme replacement therapy (PERT), support to cease smoking and alcohol consumption, consultation with a dietitian and a systematic follow-up to assure optimal treatment effect. Treatment is aimed at the normalization of digestion, alleviation of PEI-linked symptoms and prevention of morbidity and mortality associated with malnutrition as well as disease progression. To guarantee optimal efficacy of oral PERT, it is necessary to ensure proper administration, dose and adjuvant therapy.

Currently available enzyme products are mainly enteric-coated capsules and are identified by the amount of lipase (USP units) they contain.

3. Capsules should be administered with meals (as opposed to before or after) for optimal effect. The normal pancreas produces at least 90,000 USP units of lipase with each meal. The starting dose for PERT should be at least 40,000–50,000 USP units of lipase with each meal and half that amount with snacks. If signs or symptoms of maldigestion persist, the dose of PERT can be increased

up to 90,000 USP units of lipase with each meal, and proton pump inhibitors can be added, as bicarbonate secretion is impaired in CP. The addition of proton pump inhibitors ensures that the lipase is protected from denaturation by gastric acid, as pancreatic lipase has been shown to be irreversibly inactivated at a pH below 4. Acid suppression is required if a non-enteric-coated preparation is used. A low-fat diet is no longer recommended to reduce steatorrhea because of the risk of exacerbating PEI-related weight loss and deficiencies of lipid-soluble vitamins.

**Management of Diabetes Mellitus**

1. Diabetes secondary to CP is commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus (DM). More than half of all patients with CP develop DM because of the loss of complete islet cell mass. Diabetes in CP is resistant to ketosis.

2. A unique characteristic of patients with type 3c diabetes is that they lose counter-regulatory hormones such as glucagon and pancreatic polypeptide and are more susceptible to hypoglycaemia. In addition, type 3c diabetes also puts patients at a particularly high risk of developing secondary pancreatic carcinoma.

The use of an insulin-sensitizing agent such as metformin may reduce the risk of cancer in these patients. Mal-digestion associated with PEI often releases higher levels of gut hormones, including GLP-1; therefore, the effectiveness of insulin secretagogues and incretin drugs is very low. PERT requires that incretin secretion and nutritional status be improved in addition to administration of diabetic medications.

**Recurrent Ap and Cp**

Over the past 20 yrs, clinical data accumulated from human studies confirms that AP, RAP and CP represent a disease

continuum. The SAPE (Sentinel Acute Pancreatitis Event)

hypothesis built upon the necrosis-fibrosis theory suggests that AP is a sentinel event in the pathogenesis of CP, which, in the presence of continuing exposure to risk factors and aberrations in the repair process, leads to CP. The definition of RAP refers to the presence of at least two separate documented episodes of pancreatitis with a period of resolution in between, and the absence of definitive changes of CP. The differentiation between RAP and CP is based on the morphological and/or histological examination of the pancreas. To date, no consensus has been established about the definition of CP. Recently, CP has been defined as *a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.* “Minimal change CP” (MCCP) specifically refers to minimal morphologic changes in the presence of inflammation-associated pancreatic disease. A conceptual model used for defining CP has been shown in a diagram below **(Fig. 34.1)**.

**Autoimmune CP**

Autoimmune pancreatitis (AIP, 2–4% of patients) can be a part of a multisystem disease (type I) or can affect the pancreas alone (type 2). AIP type 1 is most commonly seen in middle-aged men. Patients with AIP type 1 present with painless obstructive jaundice, which is similar to that observed in patients with pancreatic cancer. AIP type 1 is a systemic fibroinflammatory disorder, which affects the pancreas. On the basis of its histological features, AIP type 1 is also called lymphoplasmacytic sclerosing pancreatitis. The inflammatory component consists of a lympho-plasmacytic infiltrate rich in IgG4-positive cells, which responds to steroid therapy. AIP type 2 affects only the pancreas and is called idiopathic duct-centric pancreatitis; moreover, it is

not associated with IgG4. AIP type 2 is commonly observed in younger patients presenting with AP. No biomarker is available for detecting AIP type 2, and it is strongly associated with IBD. Intense fibrosis may lead to permanent structural damage and functional insufficiency. It is a relatively painless disorder. Auto-immune CP may be diagnosed by using either the Japan Pancreas Society criteria or the recently described Mayo Clinic HISORt criteria. Treatment with steroids is associated with a rapid relief of symptoms in patients with AIP. The treatment includes an initial of dose 30–40 mg/day of prednisolone, which is tapered over 3 months; further, serum IgG concentrations are monitored and findings obtained on imaging are recorded. Long-term maintenance with 5.0–7.5 mg/day of prednisolone is recommended to prevent relapses. Recurrences, which typically occur in type 1 disease, induce the development of pancreatic calculi. Before initiating a therapeutic trial, pancreatic malignancy must be ruled out in patients with AIP.

**Japanese Pancreas Society (JPS) diagnostic criteria for aIP**

Mandatory diagnostic imaging criteria detected by ultrasound, CT and/or magnetic resonance imaging:

1. Narrowing of main pancreatic duct with irregular wall

2. Diffuse or localized enlargement of the pancreas

***Plus 1 of the following***

1. Antibodies: High serum gamma-globulin, IgG, or IgG4, OR positive autoantibodies (e.g., antinuclear antibody and rheumatoid factor).

3. Histology: Marked interlobular fibrosis with lymphocyte and plasma cell infiltration of periductal areas and occasionally lymphoid follicles in the pancreas.

Exclude pancreatic or biliary malignancy.

**Mayo Clinic Criteria for AIP**

The Mayo Clinic proposed diagnostic criteria for AIP based on the acronym HISORt (Histology, Imaging, Serology, Other organ involvement, Response to therapy). Diagnosis requires at least 1 of the following sets of findings:

n Diagnostic histology

n Characteristic imaging on computed tomography and pancreatography (see JPS criteria) with elevated serum IgG4 level.

n Response to corticosteroid therapy of pancreatic/extra-pancreatic manifestations of AIP.

**TIGAR-O Classification System for Cp**

1. Toxic metabolic

a) Alcohol

b) Tobacco smoking

c) Hypercalcaemia

d) Chronic renal failure

2. Idiopathic

n Early onset – Mean age of the onset around 20 yrs. Pain is the predominant features, whereas pancreatic calcification; exocrine insufficiency and/or endocrine insufficiency are extremely rare at presentation (<10%).

n Late onset – Mean age of onset around 50 yrs. Painless pancreatic calcifications with endocrine and exocrine insufficiency are the characteristic features.

n Tropical

- ***Tropical calcific pancreatitis***: Characterized by multiple episodes of severe abdominal pain in childhood, extensive pancreatic calcifications and signs of pancreatic dysfunction, but no diabetes mellitus at the time of the diagnosis.

- ***Fibrocalculous pancreatic diabetes***: Diabetes in patients with tropical pancreatitis is called fibro-calculous pancreatic diabetes by some authors.

3. Genetic

n Autosomal dominant cationic trypsinogen mutation

n Autosomal recessive

- CFTR mutation

- SPINK1 mutation

4. Autoimmune

5. Recurrent pancreatitis

6. Obstructive pancreatitis

n Pancreas divisum

n Ductal obstruction by tumour

n Sphincter of Oddi disorders

**The M-ANNHEIM multiple risk factor classification of cp**

**M** – Pancreatitis with multiple risk factors

**A** – Alcohol

**N** – Nicotine

**N** – Nutrition

**H** – Hereditary

**E** – Efferent duct syndrome like pancreas divisum,

sphincter of Oddi dysfunction

**I** – Immunological like autoimmune

**M** – Miscellaneous like hypercalcaemia and

hypertriglyceridemia

**Genetic Implications on Pancreatitis**

**Trypsinogen (PRSS1) Mutations**

n The cationic trypsinogen gene, also called protease-serine 1 (PRSS1), has a central role in hereditary pancreatitis.

n Two mutations, R122H and N21I, are found in two-third of patients with hereditarily pancreatitis. They are not commonly observed in other types of CP.

**Pancreatic Secretory Trypsin Inhibitor (SPINK 1) Mutations**

n SPINK 1, also called pancreatic secretory trypsin inhibitor (PSTI), appears to play a key role in protecting the pancreas from prematurely activated trypsin (first-line defense).

n SPINK 1 mutations are present in about 1–2% of the general population.

n The incidence of SPINK 1 mutations is 15–25% in children with idiopathic pancreatitis, but it is 5–10% in adults with idiopathic or alcoholic CP.

n SPINK 1 mutations alone are not sufficient to cause CP.

**CFTR Mutations**

n Around one-third of all patients with idiopathic CP have CFTR mutations.

n CFTR-associated chronic pancreatitis appears to be a complex disease that is caused by various genetic or environmental factors.

**Further Reading**

1. Babak Etemad, David Whitcomb. Chronic pancreatitis: Diagnosis, classification, and new genetic development. *Gastroenterology* 2001;120:682–707.

2. Whitcomb DC. Genetic risk factors for pancreatic disorders. *Gastroenterology* 2013;44:1292–302.

3. Gupte AR, Forsmark CE. Chronic pancreatitis. *Curr Opin Gastroenterol* 2014;30:500–5.

4. Talamini G, Bassi C. The “natural” history of pain in chronic pancreatitis. *Gastroenterology* 2000;118:235–7.

5. Tandon RK, Sato N, Garg PK; Consensus Study Group. Chronic pancreatitis: Asia-Pacific consensus report. *J Gastroenterol Hepatol* 2002;17:508–18.

6. Reddy DN, Prasad SS. Genetic basis of chronic pancreatitis in Asia Pacific region. *J Gastroenterol Hepatol* 2011;26:2–5.

7. Balakrishnan V. Chronic pancreatitis. A prospective nationwide study of 1086 subjects from India. *JOP* 2008 2; 9:593–600.

8. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016;16:218–24.

9. Azhar Perwaiz, Amanjeet Singh, Adarsh Chaudhary. Surgery for chronic pancreatitis. *Indian J Surg* 2012;74:47–54.

10. Issa Y, van Santvoort HC, van Goor H, et al. Surgical and endoscopic treatment of pain in chronic pancreatitis: a multidisciplinary update. *Dig Surg* 2013;30:35–50.

11. Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology* 2011;141:1690–5.

12. Nakeeb A. Laparoscopic pancreatic resections. *Adv Surg* 2009;43:91–102.

13. Hart PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. *Gastroenterology* 2015;149:39–51.

14. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144:1252–61.

15. Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database Syst Rev* 2015;3:CD007884.

16. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med* 2007;356:676–84.

17. Alexander Schneider J, Matthias Lohr, Manfred V Singer. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007;42:101–19.

**Chapter 35.**

**Ulcerative Colitis**

**Introduction**

Ulcerative colitis (UC) and Crohn’s disease (CD) are the results of an inflammatory injury to the gastrointestinal tract and may involve certain extraintestinal manifestations. Both the diseases differ in the degree of bowel involvement, disease progression and response to medical therapy. UC is a chronic inflammatory disorder that affects the rectum and extends proximally to affect a variable extent of the colon. UC although prevalent worldwide, the areas with the highest incidence and prevalence of UC include North America, Northern Europe, England and Australia. Among children, the incidence of CD (but not UC) has greatly increased. Long standing UC is associated with higher risk of development of colonic cancer.

**Clinical Features**

1. Age

n Peak age distribution in between 15 and 30 yrs of age

2. Diarrhoea

n Most patients with active disease have diarrhoea. Mechanism of diarrhoea in UC are increased mucosal permeability, reduced Na+/K+ ATPase pump activity and altered membrane phospholipids.

n Rectal symptoms like urgency and tenesmus are present in a majority of the patients with active disease. It is due to poor compliance and loss of reservoir capacity of rectum.

n Around 20–30% of patients with proctitis or procto-sigmoiditis may complain of constipation.

3. Rectal bleeding

n Rectal bleeding is often associated with active colitis.

n In patients with only proctitis, blood streak on the surface of hard stool and can have mucus too. In proctosigmoiditis, blood usually admixed with the stool. With more proximal involvement, liquid stool containing blood, pus and fecal matter.

n Passage of blood clots is unusual in UC and suggests other diagnosis like infectious colitis, haemorrhoids, diverticular disease and colorectal cancer.

4. Abdominal pain

n Abdominal pain is not a predominant symptom in all patients. Many patients do get severe cramping pain with defecation.

n Vague, mild lower abdominal pain is more common.

n Severe attack of the disease is associated with more severe abdominal pain.

n The cause of the pain is unknown but may be due to increased tension within the inflamed colonic wall during muscular contractions.

5. Systemic symptoms

n Fever, anorexia and nausea are usually associated with severe attack.

n Hypercatabolism, protein loss through the mucosa and downregulation of albumin synthesis led to weight loss and hypoalbuminemia.

6. Back pain and joint pain

n Extraintestinal manifestation of UC.

**Physical Examination**

1. Patients with mild disease often exhibit no physical signs.

2. Pallor is secondary to blood loss, whereas primary sclerosing cholangitis (PSC) needs to keep in mind in patient with icterus.

3. Pedal oedema due to hypoproteinemia indicates involvement of entire colon as well as severe left-sided colitis.

4. Aphthous ulcer/stomatitis is around 10% of cases, whereas episcleritis is in around 5–8% of patients.

5. Erythema nodosum (2–4%): Multiple tender and inflamed nodule on extensor surface of the limbs and seen on other areas of the body.

6. Pyoderma gangrenosum (1%): Multiple pustules on the legs and trunk, which break down, ulcerate and coalesce with considerable necrosis.

7. Tenderness on sacroiliac joint is observed in 12–15% of patients.

8. Abdominal examination is frequently normal. Sometimes mild tenderness on the affected part of the colon.

9. Digital rectal examination is frequently normal, but mucosa may feel “velvety” and oedematous and there may be blood on finger.

**Investigations**

1. ***Biochemistry***

n Low haemoglobin due to blood loss.

n Leucocytosis and elevated platelet count in case of active disease.

n Low serum albumin suggests extensive colonic involvement as well as severe left-sided colitis.

n C-reactive protein (CRP) can be normal in one-fourth of the patients with active UC, thus is not useful to assess the severity of the disease.

2. ***Stool examination***

n Stool examination to rule out *Cl. difficile* infection.

n Other enteric infections that could mimic UC include infection with *Escherichia coli* (*E. coli* O157:H7), *Salmonella*, *Shigella*, *Yersinia* and *Campylobacter* and parasitic infections such as amebiasis.

n Diagnosis of fecal leucocytes are neither helpful to diagnose nor to assess the severity of the disease.

3. ***Colonoscopy***

n Sigmoidoscopy is enough to diagnose UC, whereas colonoscopy is useful to determine the extent of disease. Colonoscopy enhances the risk of perforation in severe cases, thus sigmoidoscopy is enough to initiate therapy in severe cases. Deep ulcerations or suspected toxic megacolon are contraindications to colonoscopy.

n In UC, the inflammation begins in the rectum and extends proximally to the point where the visible disease ends without skipping any areas. The ileum is normal in most UC patients; involvement of ileum (Backwash ileitis) is seen in 10–20% of the cases. Involvement of ileum should raise the possibility of CD.

n Earliest sign of UC is superficial erosions, hyperemia and loss of vascularity **(Fig. 35.1)**.

n Granular, friable and ulcerated mucosa is seen in more severe disease **(Fig. 35.2)**.

n Granularity means small rough grain size mass of tissue containing blood vessels and fibroblast, whereas nodule means raised area or small mass of cells bigger than granules.

n Biopsies also should be obtained from the endoscopically normal-appearing colon proximal to the inflammation.

n Routine upper endoscopic evaluation is not required in newly diagnosis of UC.

n Endoscopic assessment of disease activity is described below, mainly two score are used, UCESI (UC Endoscopic Index of Severity) score and partial Mayo score **(Fig. 35.3)**.

Endoscopic mucosal healing is the target of the treatment and has great prognostic implications, thus endoscopy is not only important in the diagnosis but also in the management of the UC.

4. ***Plain X-ray abdomen***

Plain radiograph abdomen supine and upright films should be obtained in all patients with severe attack of UC. Plain abdominal radiographs may be normal or show oedematous, irregular margin of colon, thickening of colonic wall or dilated colonic segments in toxic megacolon.

5. ***Barium enema***

n In modern colonoscopy era, barium enema is rarely used to diagnose IBD.

n Double contrast enema is safe in mild-to-moderately active disease.

n It is helpful to evaluate possible strictures of the bowel.

n Patients with severe attack with dilated colonic segments, barium examination is contraindicated.

n Following are the characteristic features of barium enema in UC:

- Fine granular mucosa

- Irregularly thickened mucosa

- Superficial and deep ulceration

- Oedematous and thickened haustral folds

- Shortening of colon

- Presence of pseudopolyps

- Widening of pre-sacral space (>1 cm)

6. ***Other imaging modalities***

n Sensitivity of CT colonography (virtual colonoscopy) for colonic IBD changes has been reported to be 69–84%. For ulcerated lesions, colonoscopy is superior to virtual colonoscopy, whereas for elevated lesions virtual colonoscopy has good correlations with colonoscopy. As biopsies are often required to exclude dysplasia and neoplasm, as well as infection, there is little indication for CT colonography in patients with UC.

n MR colonography is also one of the imaging modalities, which show increased wall thickness and increased enhancement. Reported MRI criteria for UC include wall thickening from the rectum to the proximal colon and enhancement of the mucosa with no or less enhancement of the submucosa.

7. ***Histopathology***

n The principle components are disruption of glandular architecture and an inflammatory infiltrate. Primary distinction between chronic inflammatory bowel disease such as UC and acute self-limited (infectious) colitis is architectural distortion. In UC, vertical (“test-tube”) alignment of glands is distorted and, often branched or irregularly shaped.

n UC is inflammation directed at the crypt epithelium lining the base of the mucosa. Acute cryptitis is the earliest histological finding, due to the migration of polymorphonuclear leukocytes from the basal capillary of the lamina propria into the crypt epithelium.

Acute cryptitis progresses to form a crypt abscess.

n Thus, acute cryptitis, crypt abscess, mucin loss and diffuse mucosal inflammation are the pathological features of UC; however, none of these are pathognomonic and may occur in other diseases that cause colitis. Histological assessment of disease activity is described in **Table 35.1**.

**Grade Criteria**

**0** Normal

**1** No significant inflammation

**2** Oedema, vascularity, increase acute

and chronic inflammatory cells but

intact epithelium

**3** Heavy inflammatory cells, crypt

abscess and surface epithelial

ulcerations

8. ***Serologic markers***

n The role of serologic markers in the diagnosis of IBD and in the differentiation of UC from CD has not been determined yet.

n The prevalence of perinuclear anti-neutrophil cytoplasmic antibody (pANCA) in UC has been reported to be 50–60%, whereas 10–15% in patients with CD.

9. ***Fecal calprotectin***

n Fecal calprotectin (FC) is a neutrophilic marker of inflammation and is elevated in infectious and inflammatory colitis but not in non-inflammatory causes of diarrhea such as irritable bowel syndrome.

n FC is a non-invasive marker of UC disease activity and to assess response to therapy and relapse.

n Higher levels of FC correlate with more endoscopically severe disease.

**Mild** Stool frequency less than 4 times per day

with or without blood, with no systemic

disturbances and a normal ESR

**Moderate** More than 4 times per day stool frequency

with minimal systemic disturbance

**Severe** Stool frequency of more than 6 times per

day with evidence of systemic disturb-

ances and elevated ESR > 30

**Classification of UC**

Various classifications are proposed in patients with UC. They are either based on symptoms, extent and severity of the disease and colonoscopy findings. In 1955, Truelove had proposed the disease severity and use of corticosteroid in patients with UC **(Table 35.2)**. Mayo score is used more often than other criteria in clinical practice **(Table 35.3)**. American College of Gastroenterology (ACG) has proposed UC index **(Table 35.4)**. The PRO2 (patients-reported outcome, derived from components of the Mayo score) is one of the disease severity index used in clinical trials.

**Site of Involvement in UC**

The extent colonic involvement defining the classification of UC: proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction, E1 according to Montreal classification), left-sided colitis (extending from the sigmoid to the splenic flexure, E2) or pancolitis/extensive colitis (extension of disease beyond splenic flexure, E3). The extent of involvement does not necessarily imply severity but does impact both prognosis (e.g., the risk of can­cer) and treatment selection.

n Proctosigmoiditis: 40–50%

n Left-sided colitis: 30–40%

n Pancolitis: 20%

**Extraintestinal Manifestation of Uc**

Extraintestinal manifestation is reported in around 6–47% of patients with IBD. Exact pathogenesis is not known, but inflamed gastrointestinal mucosa trigger immune responses at the extraintestinal site due to shared epitopes. Peripheral arthritis, oral aphthous ulcers, episcleritis or erythema nodosum, are associated with disease activity of IBD and usually improve with the treatment. While uveitis or ankylosing spondylitis are not associated with disease activity, in pyoderma gangrenosum and primary sclerosing cholangitis cases, the association with disease activity is unclear.

1. Skin

n Erythema nodosum (15% CD, 10% UC) – Raised, tender, red or violet inflammatory subcutaneous nodules of 1–5 cm in diameter, typically on the anterior extensor surface of the lower extremities.

n Pyoderma gangrenosum (0.4–2%) – Erythematous pustule or nodule that spreads rapidly to the adjacent skin and develops into a burrowing ulcer with irregular violaceous edges.

n Sweet’s syndrome, or acute febrile neutrophilic dermatitis (tender or papulosquamous exanthema or nodules involving the arm, legs, trunk, hands or face), is a rare dermatologic manifestation of IBD.

2. Mouth

n Aphthous ulcer

n Sore tongue

n Stomatitis

3. Eye (2–5%)

n Episcleritis – Painless hyperemia of the conjunctiva and sclera

n Anterior uveitis

4. Joint (5–10%)

n Acute arthropathy – Type 1 (pauciarticular, < 5 large joints, asymmetrical, migratory, knee most common) is self-limiting associated with disease activity. Type 2 (polyarticular, >5 small joints, symmetrical, non-migratory, metacarpophalngeal joint most common) is not related to disease activity and can persist more even more than 3 yrs.

n Sacroiliitis

n Ankylosing spondylitis (1%) – Most are HLA B27 negative.

5. Liver

n Primary sclerosing cholangitis

6. Thromboembolism

**Complications of UC**

1. Haemorrhage

2. Perforation

3. Toxic megacolon

4. Stricture with or without cancer

5. Colorectal cancer

Development of colon cancer and/or the requirement of colectomy and/or the presence of extra-intestinal manifes-tations define complicated UC. Young age at presentation, male gender, extensive colitis, severe disease activity at presentation, high histological inflammation score, the presence of primary sclerosing cholangitis, steroid use and steroid resistance are clinical predictors for complicated UC.

**Management**

**Aim**

Primary aim of therapy is induction and maintenance of remission in patient with active ulcerative colitis. Secondary aim is to maintain adequate nutrition and to improve quality of life.

Various definition of remission is proposed: Symptomatic remission is improvement in PROs; endoscopic remission is restoration of intact mucosa without friability. Corticosteroid-free remission is based on symptoms, endoscopic findings, or disease impact without ongoing corticosteroid use. Deep remission is a combination of

symptomatic remission and endoscopic remission. Optimize PRO is resolution of rectal bleeding and urgency, normalization of bowel habits, and improvement in general well-being.  The Selecting Therapeutic Targets in Inflammatory Bowel Diseases (STRIDE) consensus statement suggests endoscopic healing is the primary target of the therapy.

**Medical Management**

Various drugs are available that induce as well as maintain the remission. They are:

1. Aminosalicylates

2. Glucocorticoids – not used to maintain remission.

3. Immunomodulators

4. Biological treatment

5. Other therapies like antibiotics, probiotics and nicotine – No placebo controlled trials show convincing evidence of inducing or maintaining remission.

***Aminosalicylates (5-ASA)***

*Introduction*

1. Sulfasalazine is parent compound of all aminosalicylates used in ulcerative colitis and Crohn’s disease.

2. Sulfasalazine consists of 5-aminosalicylates linked to sulfapyridine by an azo bond, which is poorly absorbed in the upper gastrointestinal tract. Mesalamine (5–ASA) is the principal therapeutic moiety of sulfasalazine in IBD and the sulfapyridine acts as an inactive carrier largely preventing 5–ASA absorption in the small intestine.

3. Colonic azo-reductase enzyme split the azo bond to release the two compounds (sulfapyridine + 5–ASA).

4. Beneficial effects of 5-ASA is topical delivery to the affected mucosa.

5. Mesalamine (5–ASA) is absorbed completely from the upper gastrointestinal tract once given orally. Thus, various preparations are available to overcome rapid absorption of 5-ASA in upper gastrointestinal tract.

*Proposed Mechanism of Action of 5-ASA*

1. Decreases T-cell proliferation

2. Decreases presentation of antigen to T-cells

3. Decreases neutrophils and macrophages adhesion

4. Decreases IL-1 and TNF

5. Downregulation of NF-kB activity

6. Free radical scavengers

*Aminosalicylates Preparation*

There are various aminosalicylates preparations available, which lack the sulfapyridine moiety. They are classified as agents that contain an azo bond or are delayed pH-dependent

release or sustained release. The topical 5-ASA preparations are delivered rectally as an enema or suppository.

Balsalazide and Olsalazine are azobond 5-ASA preparations that lack the sulfa moiety of sulfasalazine. Mesalamine contains 5-ASA that has pH dependent release (Asacol dissolves at pH e” 6, Salofalk dissolves at pHe”7) or sustained-release (Pentasa) fashion **(Table 35.5)**. To improve pill burden and encourage adherence, 5-ASA is available in granules forms (1.0 g and 2.0 g) or in the multi-matrix system (MMX, mesalamine 1.2 g).

*Adverse Effects of Aminosalicylates*

1. Majority of side effects of sulfasalazine are dose dependent and are due to sulfa moiety.

Newer aminosalicylates are very safe with fewer side effects.

2. Common side effects of sulfasalazine ( not 5-ASA) are:

n Gastrointestinal upset like nausea, vomiting and anorexia

n Folate malabsorption (requires folic acid 1 mg/d supplementation)

n Headache and alopecia

n Hypersensitivity skin rashes

n Haemolytic anaemia

n Agranulocytosis

n Transient male infertility

*Topical Aminosalicylates*

Topical 5-ASA is highly effective for the treatment of mild-to moderate left-sided UC and proctitis. The suppository preparations reach the upper rectum, where the enema formulations reach the splenic flexure. Rectal formulations are superior to oral medications for the treatment of distal colitis and proctitis with remission rate of 76% vs 46% for oral mesalamine. The dose of mesalamine enema varies from 1 to 4 g/day. Topical mesalamine is effective for the maintenance of remission of distal colitis.

***Glucocorticoids***

Oral corticosteroids are indicated for the treatment of outpatients with moderately-severe UC. Oral corticosteroids have neither been effective nor indicated for maintaining remissions of UC. The optimal tapering regimen for systemic steroid has not been determined; the dose is usually reduced

over 8–12 weeks. Budesonide is a locally acting corticosteroid with high first pass metabolism and minimal systemic side effects. In patients with UC who fail to respond to 5-ASA, budesonide MMX (mix matrix preparation) 9 mg for 8 weeks was found to be superior in achieving remission in mild-to-moderate UC.

*Proposed Mechanism of Action*

1. Numerous anti-inflammatory and immunosuppressive effects.

2. Inhibition of the expression of proinflammatory cyto-kines, adhesion molecules and leukotrienes.

3. It inhibits elastase, collagenase and nitric oxide synthase.

4. Downregulation of NFkB and induction of inhibitory kB.

5. It reduces neutrophilic phagocytic activity.

*Dose*

1. For severe disease, intravenous hydrocortisone 100 mg every 6 hrs.

2. For moderately active disease, oral prednisone 40 or 60 mg daily.

3. For mildly active disease not responding to 5-ASA, oral prednisone 20 mg daily.

4. Many clinicians treat it an initial of 40 mg/day, in either single or divided doses once remission is attained, doses are tapered although no discrete tapering regiments have been established. In one study, 6-month outcomes were similar with a 4 weeks vs 12 weeks taper of methylprednisolone from an initial dose of 40 mg daily.

*Adverse Effects*

1. Neuropsychiatric symptoms like mood disturbance and insomnia

2. Cosmetic effects like acne, hair loss, hirsutism, cushing-oid appearance

3. Bone loss and myopathy

4. Glucose intolerance

5. Adrenocortical suppression

6. Posterior subcupsular cataracts

**Bone Loss Management on Corticosteroid**

Osteoporosis is a common and potentially devastating side effect of corticosteroid therapy when fractures occur. To minimize the bone loss, the management of patients on corticosteroid should include the following:

1. Use of the lowest possible dose of corticosteroids.

2. Smoking cessation, limitation of alcohol consumption, and 30–60 min of weight-bearing exercise per day.

3. History, physical examination and laboratory evaluation, including bone mineral densitometry.

n Dietary or supplemental calcium (1500 mg/day).

n Vitamin D (50,000 IU 1–3 times/week) or calcitriol (0.5 µg/day).

n Consideration of hormone (estrogen) replacement therapy where appropriate.

n Consideration of a bisphosphonates - antiresorptive agent.

**Topical Corticosteroids**

Topical corticosteroids (i.e., formulations applied per rectum) have long been recognized as an important therapeutic approach in patients with UC, as either first-line therapy in patients with disease limited to the distal colon or rectum, or as combination therapy in patients with more extensive colitis.

Patients with proctosigmoiditis may find improvement with a foam or liquid enema preparation, whereas those with inflammation extending past the sigmoid colon are best treated with the liquid enema formulation. Corticosteroid enemas are also useful in as adjunctive therapy in patients with severe colitis. Long-term use of topical corticosteroids is discouraged; patients should preferentially be treated with mesalamine-based product when possible, which comparative analysis has shown to be more efficacious than the corticosteroid-containing agents.

***Immunosuppressive Agents***

Immunosuppressants (immunomodulator) include antimetabolites (azathioprine, 6-mercaptopurine and methotraxate) and the calcineurin inhibitor (CNI, cyclosporine, tacrolimus). The immunomodulator tradi-tionally have been used in patients who are corticosteroid dependent, or refractory, although there has been a recent emphasis on starting these therapies earlier in patients with IBD. **Oral and intravenous methotraxate is failed produce positive results in clinical trials in patients with UC**.

1. **Thiopurine agents**

n Azathioprine (AZA) and 6-mercaptopurine (6-MP) have been the most widely used immunosuppressive agents that are effective for the treatment of steroid-dependent UC.

n Azathioprine is a prodrug converted to 6-MP in the liver.

n They impair purine biosynthesis and thus inhibit cellular proliferation.

n AZA and 6-MP are useful agents for the maintenance of remission in UC.

n Dose:

6-MP : 1.0–1.5 mg/kg/day – These are suggested maximum doses; many patients need fewer doses to maintain remission in UC.

Azathioprine : 2.0–2.5 mg/kg/day

n Side effects: Nausea, anorexia, fever, hepatic dysfunction, pancreatitis and bone marrow suppression.

n Thiopurine methyl transferase (TPMT) phenotype should be checked in all patients before initiating therapy with AZA or 6-MP, to avoid profound bone marrow toxicity and to facilitate more complete dos-

ing earlier.

n Patients who are wild type for the TPMT enzyme or who have high levels of TPMT activity may be eventually dosed with azathioprine at 2.0–3.0 mg/kg/day or 6-mercaptopurine at 1.0–1.5 mg/kg/day. However, those who are heterozygous for the TPMT genotype or have only intermediate levels of enzyme activity are typically targeted at 50% of the full dose. Patients who are homozygous deficient for both alleles, or in whom enzyme activity is very low, should not be treated with either agent.

n It is important to realize that nearly two-third of leukopenic events on these medications is *independent* of the TPMT enzymes. As a result, it is prudent to start patients at low doses of these drugs (1.0 mg/kg of azathioprine; 0.5–0.75 mg/kg of 6-mercaptopurine) and monitor complete blood counts, platelet count and differential and liver function tests every 2–3 weeks before accelerating dose. Once the doses are stable, it is advisable to follow the haematological studies every 3–4 months and the liver function test at least twice yearly.

n Switching between azathioprine and 6-MP may improve the side-effect profile. Acute pancreatitis (3–5%) usually happens in the first month of initiation of thiopurines, where switching between thiopurines is contraindicated. Leucopenia is the most common haematological side effects mainly in patients with low TPMT enzyme activity. Hepatotoxicity is seen in 2% of the patients. Thiopurines use is associated with increased risk of lymphoproliferative disorder and non-melanoma skin cancers.

2. **Cyclosporine**

n Cyclosporine is a lipophilic peptide that inhibits the proliferation and activation of T-helper cells by interfering with IL-2 production. Unlike AZA and 6-MP, intravenous cyclosporine has an onset of action within days.

n Many unresolved questions about its use in UC; mainly its use is in acute severe colitis not responding to steroid.

n Dose 2–4 mg/kg intravenous.

n High rate of relapse following discontinuation of cyclosporine in fulminant UC.

n Potential toxicity limits the use of cyclosporine, and common side effects include paresthesias, hypertrichosis, tremor, gingival hyperplasia, vomiting, nephrotoxicity and seizures. Prophylaxis against *Pneumocystis carinii* pneumonia is recommended for patients treated with cyclosporine.

3. **Tacrolimus**

n Tacrolimus has similar action like cyclosporine, but

is 100-fold more potent and a more rapid onset of action compared to cyclosporine.

n There is no comparative study between tacrolimus and cyclosporine.

n Tacrolimus has similar adverse effect as cyclosporine like nausea, diarrhoea, nephrotoxicity, hirsutism and gingival hyperplasia.

n The use of tacrolimus is currently not incorporated into standard practice.

4. **Biological treatment**

n Infliximab (ACT-1 and ACT-2), adalimumab (ULTRA 1 and ULTRA 2) and golimumab (PURSUIT-SC and PURSUIT-M) are effective anti-TNF class agents to induce and maintain remission. Infliximab is a chimeric, monoclonal antibody against TNF-, which binds to both soluble and membrane-bound forms of TNF-. Adalimumab is a fully humanized monoclonal antibody against TNF-, which is administered subcutaneously. Golimumab is a fully humanized monoclonal antibody against TNF-, which is administered subcutaneously.

n Efficacy of Certolizumab pegol, the first pegylated, humanized monoclonal antibody against TNF- is not proven in patients with UC.

n Combination therapy with Infliximab 5 mg/kg (loading 0, 2 and 6 weeks followed by maintance dose once every 8 weeks) and azathioprine (2.5 mg/kg orally) was superior to monotherapy with either agent. The recommended dose of adalimumab is 160 mg at week 0, 80 mg at week 2 followed by 40 mg once in 2 weeks. Dose of golimumab is 200 mg at week 0 followed by 100 mg as maintance dose once in 2 weeks.

n Pruritus, flushing, nausea, chest discomfort, dyspnea, hypertension, headache, urticaria, rash, dizziness and myalgia are the most common side effects of infliximab infusion.

n Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction despite adequate drug levels) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class.

n The anti-integrin drug ((inhibition of alpha-4 beta-7 integrins, GEMENI 1) vedolizumab is an effective

therapy for induction of remission of moderately to severely active UC.

n Tofacitinib (nonselective inhibitor of the Janus kinase enzyme, pan-JAK inhibitor, 10 mg bid) is approved in the treatment of moderate-to-severe UC in June 2018 based on the two studies OCTAVE 1 and OCTAVE 2.

n Infectious complications (herpes zoster, 5%) are more in patients receiving Tofacitinib. It can be used in

patients with anti-TNF non-responsive patients. Filgotinib (selective JAK1 inhibitors, 200 mg orally daily) is under phase III clinical trial under the heading of SELECTION (for UC) and DIVERSITY (for CD).

n Around 20–25% of patients receiving anti-TNF agents may not respond initially (PNR, primary non-response) and an additional 10–15% may lose response (SLR, secondary loss of response) every year despite an initial benefit. Concurrent intestinal infection, overlapping IBS and inadequate therapeutic drug concentration are the main reasons. Increased inflammatory burden, protein loss from a permeable inflamed mucosa, the development of neutralizing antidrug antibodies are the reason for low drug level. Higher drug concentration is associated with favourable therapeutic outcomes, such as clinical response or remission, normalization of CRP and FC and/or mucosal healing. Drug concentration during maintenance therapy is 3–7 g/mL for infliximab and 5–10 g/mL for adalimumab. Data showed that patients with subtherapeutic drug levels, but no anti-drug antibody (ADA), will benefit more from dose escalation or shorter the interval compared with switching to another anti-TNF.

n Anti-TNF agent can cause immunogenicity and development of ADA leading to negative therapeutic outcome. Therapeutic drug monitoring (TDM) is required in patients with suboptimal response.

5. **Antibiotics, probiotics and curcumin**

n Antibiotics have a limited role in management of UC.

n 5-ASA with probiotic VSL#3® at a daily dose of 3.6 3× 1012 CFU/day has been studied to improve symptoms compared with no treatment. In a metaanalysis of 22 studies of probiotics in the treatment of IBD, there was no benefit of probiotics in general for induction of remission.

n Role of curcumin is not proven in patient with UC.

6. **Fecal microbiota transplant**

n Fecal microbiota transplant (FMT) has variable benefits but not significant steroid-sparing effects. The variability in fecal donors, delivery systems, duration

of treatment and end points makes interpretation of

FMT results difficult. FMT is not currently recommended in the treatment for UC.

Various treatment modalities according to disease activity are shown in **Table 35.6**.

**Acute Severe Ulcerative Colitis**

Acute severe ulcerative colitis (ASUC) is defined as the presence of 6 or more bowel movements daily accompanied

by at least 1 systemic sign of toxicity including tachycardia, fever, anaemia (haemoglobin,10.5 g/dL) or elevated inflammatory markers (ESR - 30 mm/hr). All patients of ASUC should be admitted in the hospital. *C. difficile* infection should be excluded in all patients. Endoscopic evaluation is required to confirm the diagnosis if doubtful, severity of inflammation and taking biopsy for CMV infection. Sigmoidoscopy with minimal inflation by experienced endoscopy is required to minimize the risk of colonic perforation. About one-third of patients with ASUC who is refractory of steroid therapy have CMV colitis. Biopsies from the base of the ulcer give greatest yield for the diagnosis. Immunohistochemistry staining, rapid viral culture methods and PCR-based assays are the preferred modalities to diagnose CMV disease.

Whether CMV colitis is true pathogenic problem or simply “bystander” is a debatable issue, but CMV colitis is associated with high colectomy rate in patients with ASUC. Ganciclovir administered initially intravenously and subsequently orally for a 14-day course, with a response rate around 70%. Oral therapy with Valganciclovir has equal efficacy. Inflammatory bowel disease is associated with an increased risk of venous thromboembolism (VTE). This risk is particularly apparent in hospitalized patients and is associated with severity of inflammation. Loss of anti-thrombotic proteins, use of corticosteroids, reduced

mobility and abdominal surgery are other predisposing

factors. Thromboprophylaxis with low-molecular-weight heparin should be given to all hospitalized patients with acute colitis.

Toxic megacolon is defined as a transverse colon diameter of greater than 6 cm with loss of haustrations, and signs of toxicity like severe pain, fever, tachycardia, hypotension, haemorrhage, etc, in a patient with a severe attack of UC. *Toxic megacolon is* the most severe mani-festation of UC.

Complete bowel rest and total parenteral nutrition has little role in the management of ASUC. Systemic intravenous steroid is the main stay of therapy. Mean response rate of intravenous corticosteroid is 67%, and about one-third require colectomy. Initial response will start within first 3–4 days, response unlikely to improve after 7 days of steroid treatment. Dose higher than 60 mg of methylprednisolone is not beneficial. Topical corticosteroid therapy may additionally help patients with symptoms of distal involvement. Cyclosporine acts as a rescue treatment in patients with ASUC who is not responding to 5–7 days of

intravenous corticosteroids. In the short term, 80% of patients will be discharged from the hospital on oral cyclosporine and prednisone. There are variable data on colectomy, however, on an average 40% of patients will

have avoided colectomy at the 5-year follow-up. There are less data on the use of infliximab in the setting of acute IV steroid failure. The data on infliximab seem to be very similar to the data on cyclosporine: 70–80% of patients will improve in the short term, and approximately 40% of patients will have avoided colectomy after 2 yrs. Patients with severe hypo-albuminemia who have failed IV steroids has poor outcome without colectomy. Patients with very deep colonic ulcera-tions or denudation of the mucosa are also far less likely to achieve remission, probably with either cyclosporine or infliximab.

**Indications for Surgery in UC**

About 20–25% of patients with extensive UC eventually undergo colectomy, usually because their disease has not responded adequately to medical therapy. In UC, colectomy is a curative procedure in contrast to CD, in which there is a significant likelihood of recurrence sometime after colectomy.

1. Failure to discontinue corticosteroids despite other medical interventions

2. Severe attack that fails to respond to medical therapy

3. Complications of severe attack

4. Dysplasia or carcinoma

5. Chronic continuous disease, which impairs the quality of life

**Surgery**

1. Subtotal colectomy with ileostomy

2. Proctocolectomy with Brooke ileostomy

3. Colectomy with ileorectal anastomosis

4. Proctocolectomy with ileal-pouch anal anastomosis

The definition of chronic refractory UC can include either: (i) individuals who are refractory to induction of remission with biologics, corticosteroids or small molecule therapies or (ii) individuals who are corticosteroid dependent. The

type of surgery performed for UC varies from patient to patient and should take into account the nutritional status and health of the patient, the presence of dysplasia and patient’s desire to maintain continence. A total proctocolectomy with ileal pouch-anal anastomosis (IPPA, multi-stage procedure) is the surgical procedure of choice for UC. Early complications of colectomy (<30 days postoperatively) occurred in 9–65% of patients with UC, whereas late complications (>30 days postoperatively) occurred in 17–55% of patients.

**Uc and Colorectal Cancer**

Chronic colitis predisposes to colorectal cancer and the risk increases with duration of the disease. Ten-folds increase in the risk of colorectal cancer in patients with long-standing UC. Cumulative risk of cancer is 7% at 20 yrs and 17% at 30 yrs after the onset of colitis. Proctitis is not a risk factor for colorectal cancer. Progression from inflammation to CRC is supposed to follow a sequence from colitis without dysplasia, low-grade dysplasia (LGD) high-grade dysplasia (HGD) and finally carcinoma. The classical description of dysplasia in UC includes flat, spreading lesions rather than sessile or pedunculated polyps. Narrow-band imaging with standard-definition and high-definition colonoscopies did not demonstrate superior detection of dysplasia compared with white light.

Inflammatory “pseudopolyp” (non-malignant potential) present in patients with long standing UC, sometimes difficult to distinguish from dysplastic polyp. Recent reports have suggested that LGD can progress to colo-rectal cancer

without the intermediate stage of high-grade dysplasia. The optimum management of LGD in patients with UC remains debatable. Some advocate intensive colonoscopic surveillance while others recommend early colectomy. Recent meta-analysis has shown that once LGD is diagnosed during surveillance there is a nine-fold increase in the risk of developing cancer.

1. Risk factors for colorectal cancer:

n Pancolitis

n Total colitis duration greater than 8–10 yrs and 15–20 yrs for left-sided colitis

n Associated with primary sclerosing cholangitis

2. Surveillance

n Patients with 8–10 years duration of colitis proximal to rectum should undergo cancer surveillance. It is unclear whether segmental random biopsies are still required during surveillance colonoscopy in UC.

n Patients with UC and primary sclerosing cholangitis (PSC) should undergo a screening colonoscopy at the

time of diagnosis of UC and surveillance thereafter annually.

n Most neoplasia in UC is visible with standard- or high-definition white-light examinations. Endoscopist should identify raised lesions and abnormal pit patterns and perform targeted biopsies.

n Patients with high-grade dysplasia should undergo colectomy.

n Fecal DNA testing and CT colonography are not recommended for screening or surveillance.

**Cigarette Smoking and UC**

Smoking is the best-described environmental factor implicated in determining susceptibility to, and phenotype

of IBD. The dichotomous effect of cigarette smoking on the course of CD and UC is well described. Active smoking has been associated with a more benign disease course of UC. Meta-analysis of a case-controlled study showed increased UC risk 2.9 times in non-smoker than smoker. Cigarette smoking is protective in UC. But the precise mechanism by which nicotine controls inflammation in UC is unclear. It may inhibit proinflammatory cytokines and increased production of the protective mucus layer of the colon.

Smoker suffers less pouchitis, and protects against development of PSC. Several trials have reported clinical and symptomatic improvement with transdermal nicotine patches combined with 5-ASA or corticosteroids. Nicotine is not effective as monotherapy and not effective for maintaining remission.

**Further Reading**

1. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19(suppl A):5–36.

2. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: A systematic review. *Clin Gastroenterol Hepatol* 2018;16:343–56.

3. David T Rubin, Ashwin N Ananthakrishnan, Corey A Siegel, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;114:384–413.

4. Niraj Jani, Miguel DR. Medical therapy for ulcerative colitis. *Gastroenterol Clin N Am* 2002;31:147–66.

5. Sutherland L, Roth D, Beck P. Alternative to sulfasalazine: A meta-analysis of 5-ASA in the treatment of ulcerative colitis. *Inflamm Bowel Dis* 1997;3:665–78.

6. Podolsky DK. Medical progress: inflammatory bowel disease. *N Engl J* *Med* 2002;347:417–29.

7. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhos-pitalized ulcerative colitis: The Toronto consensus. *Gastroenterology* 2015;148:1035–58.

8. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:590–9.

9. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–23.

10. Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol* 2017;112:241–58.

11. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and metaanalysis. *Am J Gastroenterol* 2011;106:630–42.

12. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med* 2014;160:704–11.

13. Marcus Harbord, Rami Eliakim B, Dominik Bettenworth, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *Journal of Crohn’s and Colitis* 2017; 11:769–84.

14. Bressler B, Law JK, Al Nahdi Sheraisher N, et al. The use of infliximab for treatment of hospitalized patients with acute severe ulcerative colitis. *Can J Gastroenterol* 2008; 22:937–40.

15. Laharie D, Bourreille A, Branche J, et al. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut* 2018;67:237–43.

16. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;138:738–45.

17. Fernando Magro, Paolo Gionchetti, Rami Eliakim, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *Journal of Crohn’s and Colitis* 2017,11: 649–670.

**Chapter 36.**

**Crohn’s Disease**

**Introduction**

Crohn’s disease (CD) is manifested by focal, asymmetric and transmural inflammation of the digestive tract that may, or may not, be accompanied by granuloma formation. In contrast to the diffuse, continuous, superficial (mucosal) inflammation limited to the colon in ulcerative colitis, the inflammation of CD is patchier (focal), may be transmural and can involve any segment of the gastrointestinal tract from mouth to anus. Around 25% of the patients have colitis only, 25% is ileitis only and 50% have ileocolitis. The transmural nature of CD can lead to intestinal complications of stenosis (strictures) and fistulae. The histological finding of noncaseating granulomas is a hallmark of CD but these lesions are identified in only about 30% of patients; and are not necessary to make the diagnosis. Relapsing and remitting illness is peculiarity of CD.

**Clinical Features**

1. Diarrhoea

n Most patients with active disease involving small intestine and colon have diarrhoea.

n Possible mechanisms of diarrhoea are increased mucosal permeability due to mucosal inflammation, an imbalance in the luminal concentration of bile acids and bacterial overgrowth behind stricture.

2. Abdominal pain

n Abdominal pain is more common in CD than in ulcerative colitis.

n Stretching of receptors in the bowel wall as the food bolus passes through narrow segment leads to abdominal pain.

n It may be visceral pain due to inflammation of serosa.

3. Weight loss and malnutrition

n Intestinal malabsorption secondary to diseased bowel or following surgical resection.

n The possible causes of malabsorption in CD are protein loss through exudation of inflamed bowel, folate malabsorption due to sulfasalazine, hypercatabolic state and poor intake due to fear of eating-induced pain or diarrhoea.

4. Anorexia

n Associated with TNF- and delayed gastric emptying

5. Fever

n Secondary to leukotrienes like IL-1, IL-6 and TNF-

6. Smoking

n Smoking is a modifiable risk factor for CD. Smoking is associated with early onset disease, more frequent use of immunosuppression and requirement of surgery. Alter smooth muscle tone, increase oxidative stress, endothelial dysfunction through nitric oxide production, alter gut mucosal integrity and influence gut microbiota are the possible effect of smoking.

7. Diet

n Low dietary fibre intake is associated with increased risk of CD. Possible beneficial effects of dietary fibres are increase production of short chain fatty acid (SCFA), which inhibits pro-inflammatory mediators, and maintain gut mucosal barrier.

n Diet high in omega-6 fatty acid is associated with increased risk of CD.

n Dietary pattern affects gut microbiota. Enterotypes were strongly associated with long-term dietary patterns. Enterotype 1 (Bacteroides) correlates with diet rich in animal protein and saturated fat, whereas Enterotype 2 (Prevotella) correlates with a diet rich in fibre and carbohydrate.

8. Lifestyle

n Stress, lack of sleep and lack of exercise is associated with the increased risk of CD.

9. Appendectomy

n Relationship between appendectomy and CD has been long debated. Appendectomy done for perforating appendix has high incidence of CD than others indications for appendectomy.

**Physical Examination**

1. Anaemia

n Vitamin B12 deficiency due to extensive distal ileal involvement.

n Folate deficiency due to sulfasalazine.

n INF-, TNF-, IL-1 inhibit erythropoietin production leading to iron deficiency

2. Signs of malabsorption syndrome (Ch. 30)

3. Aphthous ulcer in the mouth

4. Skin lesions (details of extraintestinal manifestation of IBD, Ch. 35)

n Pyoderma gangrenosum

n Erythema nodosum

n Cutaneous vasculitis

n Sweet syndrome

n Cutaneous polyarteritis nodosa

5. Eyes

n Episcleritis, scleritis or uveitis

6. Musculoskeletal

n Waxing and waning type of joint pain associated with bowel symptoms flare. Knee and ankle are the most common joints involved.

**Abdominal Examination**

1. Abdominal examination may be normal in patients with CD. Abdominal distension and signs of intestinal obstruction are seen in case of luminal stricture.

2. Hepatomegaly seen in around 10% of the patients.

**Digital Rectal Examination**

**Inspection**

Around 24% of patients with CD have perianal lesion. Look for anal fissure (25%), ulcer, stenosis, abscess and fistula (15–35%).

**Palpation**

Digital rectal examination is necessary to see fistulous tract, perianal tenderness, blood on the tip of the finger, palpation of pseudopolyps.

**Investigations**

1. ***Biochemistry***

n Low haemoglobin due to blood loss.

n Leucocytosis in case of active disease.

n Elevated C-reactive protein and ESR in active disease stage.

n Low serum albumin suggests malabsorption and extensive intestinal involvement.

2. ***Colonoscopy***

n Endoscopic appearance of CD is highly variable and changes with disease activity and duration.

n Typically, CD spares the rectum and is most severe in the cecum, distal ileum and right colon.

n Skip lesions (areas of disease separated by normal mucosa) are characteristic of CD. The inflammation does not extend circumferentially but rather has a predilection for the antimesenteric border of the colon.

n Aphthous ulcers (due to submucosal lymphoid follicle expansion) are the earliest signs of CD. As the disease progresses, the aphthous ulcers coalesce into larger

ulcers (stellate ulcers, **Fig. 36.1**); whereas as disease severity increases submucosal oedema leads to cobble-stoning appears. Patients with severe disease may have large linear and deep serpiginous ulcers.

n The two most commonly used tools in CD patients are Crohn’s Disease Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn’s Disease (SES-CD). Rutgeert’s score is for the disease recurrence in postoperative CD patients.

n The endoscopic appearance of IBD is not specific enough to differentiate UC from CD. Following are the differentiating features between UC and CD **(Table 36.1)**.

3. ***Plain radiograph and* *Barium series***

n Plain radiograph abdomen both supine and erect films identify bowel dilatation, obstruction, bowel perforation and bowel wall thickening.

n Barium series are the procedure of choice for determining the extent of the involvement of the bowel. Small bowel follow-through and/or small bowel enteroclysis are needed to define the extent of the disease. Role of barium enema is diminished in era of colonoscopy.

n Isolated small bowel disease is seen in 30–40%, whereas isolated colonic disease is seen in 20–27% of patients with CD.

n Earliest sign is the aphthous ulcer (punctuated, slit-like collection of barium surrounded by radiolucent halo).

n As disease advances, aphthous ulcerations coalesce together to form stellate, serpiginous or linear areas of ulceration.

n Deep transverse and longitudinal ulcer separated by oedematous mucosa gives cobble-stone appearance.

**Ulcerative colitis Crohn’s disease**

Rectum is involved Rectum is usually spared

No skip lesion Skip lesion is seen

Normal appearing Ulceration in

terminal ileum terminal ileum

Fistulas are not seen Fistulas are seen

Loss of vascular Aphthous ulcers

markings

Mucosal Linear or serpiginous

granularity ulcers

Cobblestone mucosa Cobblestone

is not common mucosa

n Polyps, stricture and fistula can be identified.

n String sign: Markedly narrowed terminal ileum secondary to oedema, inflammation and spasm.

4. ***CT scan abdomen and MRI***

n Thickening of bowel wall, skip lesion on CT, perienteric inflammation, fistula formation.

n Fibrofatty proliferation of mesentery and increased vascularity of mesentery.

n Accurate modality for fistula, sinus tract and abscess.

n If mesenteric node >1 cm, suspect malignancy.

n Comb sign – Hypervascular mesentery may be seen traversing the mesenteric fat to penetrate the muscularis propria of disease segment of bowel.

n The diagnostic accuracy of MR enterography/entero-clysis is similar to that of CT scans and prevents ionizing radiation exposure. MR pelvis is modality of choice for the evaluation of perianal lesions.

n MRE is a preferred imaging modality for differentiation between fibrotic and inflammatory stricture because of its superior contrast resolution and functional information.

5. ***Histology***

n Focal intestinal inflammation is the hallmark of CD.

n The inflammation is not defined by the directionality of the crypt epithelium and may involve any portion of intestinal mucosa.

n Unlike UC, there is retention of goblet cell mucin in patient with CD.

n Presence of sarcoid like non-caseating granulomas (often seen in smaller ulcerations, because the epithelioid cell elements from which the granulomas arise are generally completely obliterated in the larger

ulcers), transmural inflammation and involvement of terminal ileum differentiate it from UC.

n As a result of chronic inflammation, free perforation is less common than walled off abscess or fistulous tract.

6. ***Fecal and* *serology markers***

n Role of fecal calprotectin in IBD is described in Ch. 35.

n The role of serologic markers in the diagnosis of IBD and in the differentiation of UC from CD has not been determined yet. The prevalence of *anti-Saccharomyces cerevisiae* (ASCA) antibody in CD has been reported to be 50–60%.

7. ***Capsule endoscopy***

n Wireless capsule endoscopy is being used to diagnose CD allowing access to part of the small bowel that cannot be reached by standard endoscopy. Capsule endoscopy may be more sensitive than conventional imaging studies, including CT enterography or small bowel enteroclysis, for identifying subtle lesions. Capsule endoscopy has a significant risk of capsule “retention” in patients with known or asymptomatic strictures.

**Montreal Classification**

1. Age at diagnosis

n A1 <16 yrs

n A2 17–40 yrs

n A3 >40 yrs

2. Location

n L1 Ileum (30%)

n L2 Colon (20–25%)

n L3 Ileocolonic (40%)

n L4 Upper GI (5–10%)

3. Behaviour

n B1

Non-cicatrizing

Non-fistulizing

n B2 – Stricturing

n B3 – Penetrating

n P – Perianal disease modifier

**Classification According to Disease Behavior**

1. Indolent

2. Cicatrizing

3. Aggressive

4. Fistulizing

**CDAi**

The instrument most commonly used to quantify disease activity has been the CDAI; however, because of its complex

derivation and lack of discrimination between symptoms and inflammation, the CDAI is mostly used in clinical trials.

**Active Disease**

CDAI >220 is considered as active disease. Active disease is divided in to mild (CDAI 150–220, CRP just above upper limit of normal, weight loss <10%), moderate (CDAI 220–450, >10% weight loss) and severe (CDAI >450, BMI <18, complications of CD like abscess or perforation).

**Response**

Reduction in CDAI score <100 is considered as response.

**Remission**

Persistent CDAI <150 for at least 12 months.

**Relapse**

CDAI >150 with increase in at least 70 points is considered as relapse.

**Extent of the Disease**

CD affecting < 30 cm is considered localized disease while >100 cm is called extensive disease. In between is “grey area.”

**CD of the Oesophagus, Stomach and Duodenum**

CD involving the upper gastrointestinal tract is most com-monly accompanied by small or large bowel involvement. Infrequently, CD involving the oesophagus, stomach or duodenum resents with symptoms that mimic gastro-esophageal reflux or peptic ulcer disease.

**Jejunoileitis**

CD involving, primarily, the proximal small bowel most often presents with vomiting and diarrhoea, cramping abdominal pain and weight loss. Diarrhoea is multifactorial and can be secondary to malabsorption as a consequence of inflammation, protein-losing enteropathy or stasis and small bowel bacterial over­growth proximal to strictures.

**Ileitis and Ileocecal CD**

CD most commonly presents as right lower quadrant abdominal pain and tenderness (often accompanied by an inflammatory mass), diarrhoea with or without rectal bleeding, weight loss, fevers, chills and night sweats.

**Crohn’s Colitis**

Approximately 15% of CD cases are limited to the colon. However, CD of the colon is more likely than UC to become accompanied by perianal manifestations (skin tags, perirectal

abscess or fistulae) and the rectum is often spared, whereas UC always involves the rectum.

**Perianal CD**

Perianal involvement in CD develops at some point in the course of CD in approximately 25% of patients and most often accompanies colonic disease. Perianal inflammation arises from the anal crypts at the anorectal junction and progresses through or around the anal sphincter, presenting as perirectal abscesses or fistulae.

**Complications of CD**

**General**

Patients with small bowel CD with malabsorption often need correction of deficiencies of iron, folate, vitamin B12, zinc, the fat-soluble vitamins (A, D, E and K), as well as other trace minerals and vitamins. They may develop a hypercoagulable state, which may lead to venous thromboses.

**Abscesses and Fistulae**

CD that penetrates through the bowel lining can result in the formation of a sealed off cavity containing succus, stool or pus (an abscess) or extension of the inflammatory process to the surrounding viscera or through the skin’s surface (a fistula). Roughly one-third of patients with CD are estimated to suffer from these penetrative complications.

***Abscesses***

Abscesses have been reported in up to 20% of patients with CD. Intraabdominal abscesses are located adjacent to the inflamed bowel, most typically the terminal ileum.

***Fistulae***

Fistulae have been reported in 20–40% of patients with CD. Often associated with a strictured area of diseased bowel, fistulae can originate in any portion of the bowel affected by CD.

Diagnostic studies for internal fistulae are also specific for their location. Enteroenteric fistulae may be shown on small bowel series or CT enterography, colic fistulae with CT with rectal contrast, and vesicular fistulae by cystography. Fistula entrance or exit sites may be seen endoscopically or with cystoscopy. The course of cutaneous fistulae may be determined by cannulation of the fistula exit point at the skin and instillation of contrast material to locate the source in the bowel.

Asymptomatic enteroenteric fistulae do not necessarily require a change in medical management, entero­vesicular fistulae that lead to repeated infections or pyelonephritis should be managed surgically.

***Obstruction***

The nature of CD with stricture leads to obstruction of the bowel many cases of long-standing disease.

**Treatment of CD**

CD is heterogenous disease, poises challenges in the management. Therapy of CD is based primarily on the location of the disease and severity of the disease. Primary goal of therapy is induction and maintenance of remission in patient with active disease. Traditionally, “step-up” approach is used in which less aggressive medicines used first followed by more aggressive medicines. While, recently accepted “top-down” approach, more aggressive treatment in the initial period to prevent irreversible damage followed by less aggressive treatment to maintain remission.

**Nutritional Management**

Nutritional therapy in CD can be directed toward one of two goals: treating nutritional deficiencies or reducing inflammation. Deficiencies of specific nutrients usually can be managed by supplementation. Even in the absence of clinical or biochemical evidence of micronutrient deficiency, it is reasonable to give multivitamin supplementation to patients with small bowel CD. Caloric deficiencies are made up by increasing the intake of complex carbohydrates. The use of total enteral administration of an elemental diet as specific therapy in IBD is controversial. Elemental diets consist of amino acids, monosaccharide, vitamins, minerals and essential fatty acids. Malnutrition is less common in UC than in CD.

**Medical Treatment of CD**

1. Before initiating medical treatment in patient with CD, it is vital to know the age of the onset, the duration of disease, the anatomic location of disease, prior treatment, prior surgery for CD and nutritional status of the patient.

2. Patients are typically classified according to the anatomic location of the diseases. They are ileocolic, colon, small intestine, upper gastrointestinal and anorectal.

3. Anatomic location of CD is very important as different drug delivery system of 5-aminosalicylate (5–ASA) and oral corticosteroid (Budesonide).

**Aminosalicylates**

1. Details of aminosalicylates is described in Ch. 35. Prevention of relapse is a major issue in the management of patient with CD. Corticosteroid is the mainstay of treatment of acute exacerbations, but it is not effective in maintaining the remission.

2. The role of aminosalicylates in the setting of CD has become more controversial. Numerous factors contribute to the debate regarding the role of aminosalicylates in CD including: the heterogeneous presentation (disease location, severity and complications), transmural nature of CD (vs the mucosal activity of aminosalicylates), definition of disease activity *and* response, dose and delivery systems of varied formulations.

**Corticosteroid**

1. Placebo-controlled trials have demonstrated that prednisone is effective in inducing remission in patients with mild-to-severe active CD. Steroids act more rapidly than 5-ASA. The optimal dosage and optimal tapering regime for corticosteroid has not been determined. But it is usually around 1 mg/kg prednisone as a starting dose that has to continue for 4 weeks followed by 2 weeks tapering dose. It is recognized that many patients who initially respond to prednisone, but relapse of symptoms with tapering dose, can be maintained in an asymptomatic stage by low-dose long-term prednisone therapy. But, because of toxicity associated with long-term prednisone use, steroid as maintenance therapy is not acceptable.

2. Budesonide (two formulations, controlled ileal release and multimatrix system), which undergoes extensive first-pass hepatic metabolism, is used in patients with CD to avoid systemic side effects. Clinical trials have used two dosage – either 6 mg/day or 9 mg/day. Budesonide (9 mg/day for 8–10 weeks) is effective for the treatment of active CD in the terminal ileus and/or ascending colon. Budesonide is more effective than mesalamine (5-ASA) for the treatment of active CD.

Budesonide is less effective than systemic corticosteroid, but has fewer side effects. The Cochrane analysis suggests 6 mg/day Budesonide is not effective for maintaining remission.

**Immunomodulator**

Immunomodulators are the most important in the maint-enance of remission in patients with CD. Thiopurines (azathioprine, 6-mercaptopurine) and methotraxate are the most commonly use immunomodulators.

**Thiopurines**

Thiopurines are the most important drugs to maintain the remission. It can be used alone or in combination with anti-TNF agent. Details of thiopurines are described in Chap. 35.

**Methotrexate in CD**

Methotrexate, a folate antagonist, is routinely used as an alternative agent to thiopurines to maintain remission in CD. It is better tolerated than thiopurines. Stomatitis, nausea, diarrhea, hair loss, leucopenia, interstitial pneumonitis and hepatic fibrosis are the side effects of methotrexate. Metho-trexate has teratogenic effects.

**Biological Therapy in CD**

Biological therapy is one of the most important landmarks in the management of patients with CD. TNF inhibitors are very effective at inducing and maintaining remission in CD. Biological therapy used in CD is given below.

1. TNF- inhibitors

n Infliximab

n Adalimumab

n Certolizumab Pegol

n Golimumab

2. Inhibitors of lymphocyte trafficking

n 4 -7 integrins antagonizes – Natalizumab and Vedolizumab

n Anti-sense to ICAM-1

n Antibody to 47 antibody

3. Inhibitors of Th1 response

n Anti IL-12 antibody

n Anti INF- antibody

n IL-10

n Anti-IL-2 receptors antibody like daclizumab and basiliximab

4. Anti-CD4 antibody

5. JAK inhibitors – Tofacitinib, Filgotinib

**Infliximab**

***Introduction***

Tumour necrosis factor is an important proinflammatory cytokine with a key role in several inflammatory conditions including CD. Infliximab inhibits TNF-. It is genetically engineered IgG1 murine-human chimeric monoclonal antibody. It is 75% human protein and 25% murine protein. Details of infliximab is described in chap 35.

***Pharmacological Action***

1. It neutralizes both soluble and transmembrane TNF-.

2. It also causes lysis of TNF- producing cell via complement fixation.

3. It also leads to antibody-dependent cytotoxicity.

4. It enhances apoptosis of T-lymphocytes.

***Dose***

Infliximab is delivered intravenously; IBD patients typically receive an initial loading dose regimen of three infusions at

weeks 0, 2 and 6, and subsequently receive maintenance infusions every 8 weeks. The standard dose is 5 mg/kg; higher doses up to 10 mg/kg have proved effective in patients who have lost response to the 5 mg/kg dose. Lower doses have not been shown to be effective.

***Efficacy***

1. Infliximab infusion as single dose of 5 mg/kg resulted in a clinical response rate of 81% for patients with moderate-to-severe Crohn’s disease(*Targan SR, et al. N Engl J Med 1997*).

2. Approximately one-third of CD patients develop fistula; the efficacy of infliximab in closing these fistulas is nearly around 55% with dose of 5 mg/kg *(Present DH, et al. N Engl J Med 1999).*

3. There is evidence from clinical trials to support using infliximab as maintenance therapy. Retreatment with infliximab every 8 weeks in initial responders is more effective than placebo in maintaining remission *(Hanaeur SB et al. ACCENT I randomized trial. Lancet 2002).*

4. Infliximab is also used in the maintenance of fistula remission. Aroundhalf (48%) of the infliximab-treated patients maintained fistula remission at week 30 compared with 27% of the placebo group *(Sands B et al. ACCENT II trial. Gastroenterology 2002).*

5. Infliximab monotherapy and combination therapy using infliximab and thiopurines are more effective than thiopurine monotherapy alone in the treatment of moderate-to-severe CD who have failed to respond to the first-line therapy and naive to immunosuppressive and biologic agents.

***Side Effects***

Headache, nausea, vomiting, respiratory infection are the common side effects. Rarely, anaphylactic reactions occur.

Human anitchimeric antibodies “HACAs” develop in approximately 13% of patients. Around 3% of patients develop infusion reaction. True case of lupus erythematous is very rare despite the development of anti-DsDNA antibody.

**Adalimumab**

Adalimumab is a monoclonal human IgG1, antibody that targets TNF-. It binds both free and membrane-bound TNF, and causes apoptosis of TNF-producing cells. Adalimumab is delivered subcutaneously in either a prefilled syringe or a self-injectable pen. Either device contains 40 mg Adalimumab, which is delivered as single dose. The induction regimen of 160 mg at week 0 and than 80 mg at week 2 was established in two clinical trials. The maintenance regimen is 40 mg given every 1–2 weeks.

**Certolizumab**

Certolizumab pegol is a pegylated humanized Fab-fragment that binds TNF-. Early studies have been promising in CD.

**Management of fistulous CD**

Management of perianal disease (fistulae, abscesses, in­flammatory skin tags) often involves a combined medical and surgical approach. Suspicion of an abscess should lead to prompt initiation of antibiotics (typically ciprofloxacin 1gm and metronidazole 10–15 mg/kg, or equivalent), surgical evaluation, and in some cases, pelvic CT scan (for abscesses) or MRI (for fistulae). Soaking the area multiple times a day (sitz baths) in very warm water may promote drainage. If antibiotic therapies alone are not sufficient, then initiation of azathioprine, 6-mercaptopurine, or perhaps methotraxate should follow, although the literature supporting these therapies is sparse.

Infliximab has emerged as the highly effective therapy for fistulous CD. After the initial loading dose of 5 mg/kg at weeks 0, 2 and 6, maintenance therapy with infusions every 8 weeks is recommended. Failure to continue infliximab often leads to reopening of the fistulae. Continuing antibiotic therapy until the fistula is closed and not tender is advisable to potentially decrease the risk of abscess.

**Surgical Management**

1. The surgical management of patients with CD can be complex and associated with complications. Around one-third of patients with CD require surgery.

2. The principle of surgery is to preserve length and function of intestine.

3. Surgical intervention for CD is not curative and is reserved for patients whose disease is unresponsive to aggressive medical therapy or who develop complications of the disease like abscess, fistula and obstruction.

4. Indications of surgery:

n Medically intractable fistula

n Intra-abdominal abscess

n Intestinal obstruction

n Toxic megacolon

n Haemorrhage

n Cancer

5. Surgery

n Resection and anastomosis

n Resection with stoma

n Stricturoplasty (longitudinal incision of the strictured segment, followed by transverse closure, used for multiple strictures to preserve the length of the intestine).

n Even in selected patients, the recurrence rate after surgery procedure is high, about 75% at 10 yrs. For patients with extensive disease including the rectum, the procedure of choice is total proctocolectomy with a Brooke ileostomy. Total colectomy with ileoanal anastomosis is not appropriate in Crohn’s colitis because recurrence of CD in the ileal segment forming the new pouch would require a repeat operation and loss of long segment of ileum.

6. Around 80% of patients who underwent surgical resection have endoscopic evidence of recurrence within 1 year, usually proximal to the anastomosis. Second intestinal resection requires in 25% of the patients at the end of 5 yrs and 35% at the end of 10 yrs after first surgery. Penetrating disease type and smoking are the risk factors for postoperative recurrence. Immunomodulators or anti-TNF agents should be started for postoperative CD recurrence.

**Pregnancy and IBD**

Oral or rectal 5–ASA, thiopurines and anti-TNF are safe in pregnancy and should be continue throughout pregnancy. Methotraxate should be discontinue 6 months prior to conception. Antibiotics should be started in pregnant CD patients with active perianal disease. Cesarean mode of delivery is ideal in patients with active perianal disease as well as patients underwent IPAA. Administration of live vaccines should be avoided for first 6 months in newborn of women who were treated with anti-TNF treatment.

**Genetics in CD**

1. There is abundant evidence to suggest that an interplay of genetic and environmental factors leading to an over-

active mucosal immune response leading to inflammatory bowel disease.

2. Following are the evidences that suggest IBD is heritable:

n Around 15% of patients of CD have family history of CD.

n Incidence of IBD is greater in monozygotic twins (20-50%) than dizygotic twins (10%).

n Genomic locus on chromosome 16 identified.

n The NOD2/CARD15 gene (IBD1 locus on chromosome16) has role in CD. Heterogeneous NOD2/CARD15 genes have 2–4 times increased risk of developing CD, whereas homogeneous alleles have 20–40 fold increased risk of developing CD The NOD2 mutations have been linked to CD with the early age of onset, small bowel disease (ileal or ileocolonic), and an increase in firbostenotic, stricturing and penetrating

disease. NOD2 variants have been linked to faster progression to surgery, especially in smokers. However, there has not been a clear relationship between NOD2 and CD disease progression. Many investigators have also studied the relationship between the NOD2 mutations and therapeutic response to therapy. There was no such relationship found with infliximab.

3. The class II MHC gene association that have been identified have been specifically for colitis (Crohn’s or ulcerative), rather than small bowel CD.

4. Genome-wide association studies (GWAS) have resulted in the rapid identification of multiple previously unknown or unverified IBD-related alleles, with the promise of many future findings.

5. The *interleukin-23 receptor gene (IL-23R)* has been identified as an IBD susceptibility gene for Crohn’s colitis, and may be involved in signaling between luminal bacteria and fungi.

**Further Reading**

1. Hanauer SB, Sanborn W. The management of Crohn’s disease in adults. *Am J Gastroenterol* 2001;96:635–43.

2. CosnesJ, Gower–Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–94.

3. Spekhorst LM, Visschedijk MC, Alberts R, et al. Performance of the Montreal classification for inflammatory bowel diseases. *World J Gastroenterol* 2014;20:15374–81.

4. Panes J, Gomollon F, Taxonera C, et al. Crohn’s disease: a review of current treatment with a focus on biologics. *Drugs* 2007;67:2511–37.

5. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:590–9.

6. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn’s disease. *Cochrane Database Syst Rev* 2013(4):CD000545.

7. Prefontaine E, Sutherland LR, Macdonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn’s disease. *Cochrane Database Syst Rev* 2009(1): CD000067.

8. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. *Gastroenterology* Nov 2007;133:1670–89.

9. Tsianos EV, Katsanos KH, Tsianos VE. Role of genetics in the diagnosis and prognosis of Crohn’s disease. *World J Gastroenterol* 2012;18:105–18.

10. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn’s disease. *N Engl J Med* 2010;362:1383–95.

11. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; 106:644–59.

12. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn’s disease in adults. *Am J Gastroenterol* 2009;104: 465–83.

13. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol* 2015;12:205–17.

14. Hashash JG, Binion DG. Endoscopic evaluation and management of the postoperative Crohn’s disease patient. *Gastrointest Endosc Clin N Am* 2016;26:679–92.

15. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:630–42.

16. Lobaton T, Vermeire S, Van Assche G, et al. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;39:579–94.

17. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn’s disease: current management. *J Crohn’s Colitis* 2010;4:28–62.

18. Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;130:940–87.

19. Fernando Gomollón, Axel Dignass, Vito Annese, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn’s Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn’s and Colitis* 2017;11:3–25.

20. Paolo Gionchetti, Axel Dignass, Silvio Danese, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn’s Disease 2016: Part 2: Surgical Management and Special Situations. *Journal of Crohn’s and Colitis* 2017;11:135–49.

**Chapter 37.Colorectal Cancer**

**Introduction**

The incidence and mortality rate of colorectal cancer (CRC) are the highest of all malignancy worldwide. Patients with CRC, 90% are older than 50 yrs. Disease is more aggressive in patients that are diagnosed at younger ages. CRC results from a complex interplay between carcinogenic exposure and host susceptibility. Around half of people diagnosed with CRC survive for at least 5 yrs after diagnosis. Only 39% of patients present with localized disease. 5-year survival is 90% for localized disease, whereas 70% for regional and 12% for distant metastatic disease.

**Clinical History**

1. Adenomas, a precancerous lesion of the CRC, rarely presents with overt bleeding or stool changes. Most of the adenomas are asymptomatic and require endoscopy or other investigational modality for their detection.

2. Most of the patients with CRC present either with luminal narrowing or by blood vessel disruption from the primary tumour leading to chronic blood loss.

The common presenting symptoms in order of occurrence are:

1. Change in bowel habits seen in 74% of patients.

n More common in left-sided tumours as the caliber of the lumen is less and the contents are solid.

2. Rectal bleeding

n Seen in around 50% of patients.

n Most common in combination with change in bowel habits.

3. Rectal mass seen in 24.5%.

4. Abdominal mass seen in 12.5%.

5. Symptoms of anaemia secondary to chronic blood loss:

n Iron-deficiency anaemia is the sole presenting feature in around 10–20% of cases.

n Chronic blood loss is more common in grossly ulcerated advanced tumour, mostly on right side.

6. Abdominal pain

n Dull, cramping type of pain is more common with proximal colon cancer.

n Severe acute abdominal pain indicates either acute bowel obstruction or spontaneous perforation.

n Observed in 3.8%.

7. Weight loss

8 Uncommon symptoms

n Fever of unknown origin or intraabdominal, retroperitoneal, abdominal wall or intrahepatic abscesses due to localized perforation of colon cancer.

n Disseminated intravascular coagulation

n Malignant ascites

n Palpable adenopathy

n Nodular hepatomegaly due to metastases

n Spontaneous bowel perforation

n Malignant fistula formation into small bowel, bladder or stomach

9. Symptoms that suggest more advanced stage

n Obstruction

n Perforation

n Marked weight loss

**Past History**

1. Past history of adenoma removal

2. Past history of inflammatory bowel disease/treatment

3. Past history of colorectal malignancy (metachronous lesion)

**Family History**

1. Family history of CRC

2. Family history of adenomatous polyposis coli

3. Suspected history of hereditary non-polyposis colon cancer (HNPCC)

**Personal/Social History**

1. Incidence and mortality of CRC have been disproportionately high in affluent countries and people with high socioeconomic class. This may be related to high consumption of fatty foods, mainly animal protein and sedentary lifestyle.

2. Increased total calorie intake has been identified as an independent risk factor for CRC.

3. Increased risk of CRC with high red meat intake.

4. High fibre diet reduces the incidence of CRC by 30%. But, recent clinical trials failed to demonstrate association between fibre intake and CRC.

5. Fresh vegetables and fruits protect against CRC.

6. More sedentary lifestyle is a risk factor for rectal cancer.

7. Prolonged cigarette smoking and alcohol consumption increase chances of CRC.

**General Examination**

1. High body mass index (BMI) is an independent risk factor.

2. Pallor suggests chronic blood loss.

3. Icterus is very rare until significant hepatic infiltration by the tumour cells.

4. Cutaneous manifestations of colorectal neoplasm are given in **Table 37.1**.

**Cutaneous lesions Interpretation**

*Acanthosis nigricans* Skin tag Colorectal cancer

Pigmented lesions in the Peutz-Jeghers syndrome

mouth, hands and feet

Osteomas of the mandible, Gardner’s syndrome

fibroma, lipoma and

epidermoid cyst

Retinal pigment hypertrophy Turcot’s syndrome

Trichilemmomas and Cowden’s disease

papillomas

Penile pigmentation Bannayyan-

Ruvalcaba Riley

syndrome

Alopecia, onycholysis Cronkite-Canada

and hyperpigmentation syndrome

of palm

**Abdominal Examination**

1. Abdominal examination may be normal.

2. Palpable mass is sometimes observed.

3. Nodular hepatomegaly indicates liver metastasis.

4. Digital rectal examination is most important for palpation of lower rectal tumour. If lesion is palpable, look for size, consistency, mobility, friability and blood on the tip of the finger.

5. Bimanual gynaecological examination is often required, as ovaries are frequent site of metastasis in colon cancer.

**Investigations**

1. ***Biochemistry***

n Microcytic hypochromic anaemia secondary to chronic blood loss.

n Altered liver function suggests hepatics metastasis.

n Elevated serum alkaline phosphatase (SAP) indicates bone metastasis or liver metastasis.

2. ***Chest X-ray***

n To evaluate the lungs for evidence of metastatic disease.

n Although yield for lung metastasis is low, it is a part of overall preoperative workup.

3. ***Colonoscopy***

n Colonoscopy is very important investigations as it identifies the site of tumour, associated synchronous lesions and histopathologic confirmation by taking biopsy.

n Malignancy is seen as ulceroproliferative growth **(Fig. 37.1)** or large sessile polypoidal lesion **(Fig. 37.2)**.

n Colonoscopy inspects entire colon to identify polyp (20%) or any synchronous lesion (5%).

4. ***Spiral CT abdomen***

n CT scan can be used to evaluate local extension of the tumour (T-stage), regional lymph nodes (N-stage) and hepatic metastasis (M-stage).

n Preoperative CT scan alters the surgical management in 16% patients.

n Questionable liver lesion is an indication for either intraoperative sonography of the liver or PET (positron emission tomography).

5. ***Endoscopic ultrasound (EUS)***

n EUS is an important tool for local and regional lymph node staging of rectal cancer.

n Better than CT scan abdomen to identify sphincter involvement but inferior for mesorectal fat and facia involvement.

n Accuracy of EUS to distinguish between T1 and T2 lesions from T3-T4 lesions is 95%, whereas for lymph node involvement is 80%.

n This is very important for neoadjuvant chemoradiation.

6. ***Serum carcinoembryonic antigen (CEA)***

n Measurement of CEA level has been recommended preoperative as well as after resection of CRC.

n Elevated preoperative CEA levels have been found to be an independent poor prognosticator.

n Elevated preoperative CEA levels returning to normal following resection suggest complete tumour resection.

n Persistently elevated CEA levels suggest occult residual disease.

n The interval recommended for postoperative CEA level is every 3 months for first 2 yrs.

7. ***CT colonography or virtual colonoscopy***

n Technique involves scanning of colon by CT or MRI after a bowel preparation to give images similar to that seen in colonoscopy.

n Mainly useful in incomplete colonoscopy, which is seen in around 12% of patients due to inability to reach the tumour or inability to see proximally because of obstruction, tortuous colon, etc.

n Similarly sensitive as colonoscopy and less invasive but inferior to colonoscopy.

8. ***Positron emission tomography (PET)***

n PET is very important in diagnosing hepatic metastasis preoperatively in patients with CRC.

n Numerous studies have demonstrated a strong role for FDG-PET in identifying recurrences of colorectal carcinoma in those whom the CEA is raising and conventional imaging is not conclusive.

n For diagnosing recurrent colon carcinoma, FDG-PET has been found to be more sensitive than CT at all

anatomic sites except the lung, where both the CT and PET are equivalent.

n Whole-body PET is especially useful for detecting distant metastatic disease because one-third of PET-positive metastases in the extrahepatic abdomen and pelvis are CT-negative. This is especially important in candidates for resection of hepatic metastases.

9. ***Liquid biopsy***

n Blood-based RAS testing (liquid biopsy) in patients with metastatic colorectal carcinoma showed great promise. Studies have also shown that detecting KRAS mutation in liquid biopsy postoperatively in patients with colon cancer strongly predicts disease recurrence.

**TNM Staging of CRC**

TX - Primary tumour cannot be assessed

T0 - No evidence of primary tumour

Tis - Carcinoma in situ. Intraepithelial or invasion of

lamina propria.

T1 - Tumour invades submucosa

T2 - Invades muscularis propria

T3 - Invades through the muscularis propria

to the subserosa

T4a - Tumour perforates visceral peritoneum

T4b - Tumour adheres or invades adjacent organs

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastasis

N1a - Metastasis in one lymph node

N1b - Two to three lymph nodes are positive

N2a - Metastasis in 4–6 lymph nodes

N2b - Seven or more lymph nodes are positive

M0 - No distant metastasis by imaging

M1a - Distant metastasis to one site or organ without

peritoneal metastasis

M1b - Metastasis to two or more sites

M1c - Metastasis to peritoneal surface alone or in

combination with other site or organ

**Management**

1. Surgery is the only curative treatment for CRC. The principle of surgery in CRC is an *en bloc* resection of the primary tumour, with adequate margins.

2. Preoperative bowel preparation and prophylactic antibiotics reduce the incidence of wound infection, intra-abdominal abscesses and anastomotic leak.

3. Adequate bowel resection includes removal of the primary feeding arterial vessels and its corresponding lymphatics.

4. Length of the bowel resection depends on the blood supply to that segment. Ligation of the origin of the primary feeding vessel ensures the inclusion of the apical nodes in resection.

**Pathological Staging System**

**Stage TNM Stage Duke’s stage**

0 Tis N0 M0 0

I T1-2 N0 M0 A

II A T3 N0 M0 B

II B T4 N0 M0 B

III A T1-2 N1 M0 C

III B T3-4 N1 M0 C

III C Any T N2 M0 C

IV Any T Any N M1 -

**TNM stage Approximate Approximate**

**frequency at diagnosis 5-year survival**

I 11% 83%

II 35% 64%

III 26% 38%

IV 28% 3%

**Surgical Management of Rectal Cancer**

n In rectal cancer, adequate distal margin and restoration of intestinal continuity are the most important management issues. **(Table 37.2)**

n There are various surgical approaches depending on the tumour location in relation to the anal verge.

1. **APR (abdominoperianal resection)**

n Resection of the rectum, sigmoid colon and both anal sphincters, with creation of permanent colostomy.

2. **LAR (low anterior resection)**

n Anal sphincters are preserved and intestinal continuity is established by an end-to-end manner.

3. **Transanal resection**

n Transanal excision is one of the surgical modality for low rectal cancer with T1–2 stage without lympho-vascular or perineural invasion.

n Early stage like T1–2 should be based on assessment of EUS or MRI.

n Criteria for transanal excision.

n Tumour <3 cm and <30% circumference involvement of the bowel

n Mobile, non-fixed tumour

n T1–2 stage without lymphovascular or perineural invasion

n Location of tumour within 8 cm of anal verge

4. **Total mesorectal excision (TME)**

n Total mesorectal excision involves precise, sharp dissection and removal of the entire rectal mesentery, including that distal to the tumour.

n Conventional surgery leaves residual mesorectum in the pelvis, which leads to high rate of pelvic recurrence.

n TME requires long operating time and increases rate of anastomotic leak.

n Sexual and urinary dysfunction is less compared to conventional surgery.

n In patients with hepatic metastasis, it is still important to remove primary colorectal tumour as it may lead to large bowel obstruction or continued bleeding leading to anaemia.

n Patients with non-rectal cancer, a bowel margin of more than 5 cm is adequate to ensure long-term survival. A bowel margin for rectal cancer is controversial. Studies

showed that margin of 2 cm are adequate for long-term success.

***Key Points***

1. Tumours located in upper and middle third of the rectum are amenable to LAR.

2. Tumours located 5 cm or less from the anal verge or tumour palpated during digital examination is managed by APR.

3. Negative margin of 2 cm is enough for long-term survival particularly in well-differentiated carcinoma.

**Tumour Located in Right Colon**

1. Tumour in the cecum, ascending colon or hepatic flexure warrants a right hemicolectomy.

2. Right hemicolectomy includes the distal 5–8 cm of the terminal ileum along with the cecum, ascending colon, hepatic flexure and proximal transverse colon and ileo-transverse anastomosis.

**Tumour Located in Transverse Colon**

1. Tumour located in proximal transverse colon requires extended right hemicolectomy or extended left hemicolectomy.

2. Tumour situated in mid or distal transverse colon poses technical problems. It has been treated by true transverse colectomy or subtotal colectomy with anastomosis of the ileum to the proximal rectum.

***Tumour Located in Left Colon***

Tumour located in the left colon is treated by removal of descending and sigmoid colon followed by anastomosis of transverse colon to the proximal rectum.

**Management of Synchronous Colon Cancer**

1. Synchronous colon cancer occurs in around 4% of the patients.

2. There are two surgical options, either to resect the two lesions separately or to perform a subtotal colectomy.

3. Synchronous bowel resections can be performed with the same anastomotic leak rate and mortality as patients undergoing resection with single tumour.

**Management of Tumour with Contiguous Organ**

**Involvement**

Contiguous organ involvement is seen in around 15% of patients. It should be treated by *en-bloc* resection.

**Adjuvant Chemotherapy**

1. Treatment failure in colorectal cancer is due to its distant spread in the liver, peritoneum and other sites due to micrometastases.

2. Systemic chemotherapy is the mainstay as an adjuvant therapy following resection in stage III colorectal cancer.

3. There is a 30% reduction in risk of recurrence and a similar reduction in mortality.

4. The optimal duration of therapy has not been defined well. In T1-3, N1 3 months of therapy may be enough, whereas in T4 or N2 stage 6 months can be helpful.

5. Its role as an adjuvant therapy in stage II disease shows conflicting data.

6. Various chemotherapeutic agents are used singly as well as in combination in the management of colorectal cancer:

n 5-FU

n 5-FU + Leucovorin

n FOLFOX regime – 5-FU + Leucovorin + Oxaliplatin

n CAPOX regime – Oxaliplatin + Capecitabine

n FOLFIRI regime – 5-FU + Leucovorin + Irinotecan

n Bevacizumab

n Capecitabine

n Cetuximab

- Adjuvant treatment of patients with stage III (Dukes’ C) colon cancer following surgery is either capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid.

- The side effects of chemotherapy include hair loss, emesis, diarrhoea, mucositis, febril neutropenia, hand-foot syndrome and cardiotoxicity.

***Radiation Therapy***

1. Radiation therapy has unproved efficacy as an adjuvant therapy for colon cancer.

2. Preoperative chemoradiation using continuous infusion of 5-FU plus radiotherapy shows benefit in patients with T3 or T4 rectal lesion. Neoadjuvant therapy decreases

the volume of the primary tumour and enhances sphincter preservation.

3. NCCN guidelines suggest that RT may be considered for colon cancer in those with T4 disease with spread to contiguous structures.

**Colonic Stents in Acute Large Bowel Obstruction**

Left-sided colonic lesions are ideal for colonic stent. Do not place self-expanding metallic stents in low rectal lesions or to relieve right-sided colonic obstruction or if there is clinical or radiological evidence of colonic perforation or peritonitis. Do not dilate the tumour before inserting the self-expanding metallic stent.

***Prognostic Factors in CRC***

There are various factors that affect adversely on the outcome in patients with CRC **(Table 37.4)**.

**Clinical** **Pathological**

- Bowel obstruction - Poorly differentiated

- Bowel perforation - Mucinous or signet-

ring histology

**Biochemical** - Venous invasion

- Elevated - Perineural invasion

preoperative - Lymphatic invasion

CEA - Distant metastasis

- Increased bowel

penetration

***Emergency Management for Complications of CRC***

1. **Colonic obstruction**

n Right hemicolectomy and anastomosis is safe and effective for treating right-sided colon obstruction.

n There are three options available for patients with left-sided colonic obstruction.

- Resection with end colostomy and Hartmann’s pouch

- Segmental resection, intraoperative colonic irrigation

- Subtotal colectomy with ileorectal anastomosis

n Insertion of colonic wall stents can relieve the obstruction in debilitated patients.

2. **Colonic perforation**

n Right colonic perforation is managed by resection with end ileostomy.

n Left colon cancer perforation is managed by Hart-mann’s resection.

***Role of Laparoscopy in CRC***

1. Laparoscopic CRC management is as effective as conventional open surgery for malignant disease of the large bowel.

2. Overall morbidity and mortality is equivalent with conventional procedure.

3. Conversion rate to open procedure is 10–20% of patients.

4. In view of technical reasons, laparoscopic procedures are limited to resection of the upper rectum and of the right, left and sigmoid colon.

5. Incidence of port-site tumour implantation is 2–20%.

6. Advantages of laparoscopic resection are less pain, shorter hospital stay and faster return to work.

**Postoperative Surveillance**

1. The nature and extent of postoperative surveillance is not defined. A year following resection, colonoscopy and CT abdomen has been shown to improve detection of early recurrence. But thereafter, yearly colonoscopy and spiral CT abdomen are not cost-effective modalities.

2. In general, following guidelines are used:

n History and physical examination every 3 months for 2 yrs, then every 6 months for total of 5 yrs.

n If preoperative colonoscopy is not performed, it should be performed within 3–6 months following resection.

n Initial colonoscopy at 1 yr after surgery and if normal once every 2–3 yrs.

n Serum CEA level estimation every 3 months for 2 yrs, then every 6 months for 2–5 yrs.

**High Risk and Increased Risk Population for Crc**

**High-risk Group for CRC**

1. **Family history of familial adenomatous polyposis coli (FAP)**

n It is an autosomal dominant disease with 80–100% penetrance.

n Gene involved is APC gene.

n FAP is characterized by thousands of adenomatous polyp.

n Patients are usually asymptomatic till puberty.

n Cancer develops in 3rd decade.

n Patients with family history of FAP should undergo surveillance colonoscopy at puberty to assess for emergence of adenomas.

n Patients with FAP should be treated by total colectomy with ileostomy or subtotal colectomy with ileorectal anastomosis.

2. **Family history of hereditary non-polyposis colon cancer (HNPCC)**

n It is an autosomal dominant disease with 80–100% penetrance.

n It is the most common hereditary CRC also called as Lynch syndrome.

n Lifetime risk for colon cancer is 80%.

n Mean age of diagnosis is 4th decade.

n Majority of the tumours are proximal to splenic flexure.

n Patients with a family history of HNPCC must be examined by colonoscopy, beginning at 25 yrs and then once every 2 yrs.

3. Inflammatory bowel disease (Ch. 35, 36)

**Increased Risk Group for CRC**

1. Patients with curative resection for CRC in past.

2. CRC in first-degree relatives before 60 yrs.

3. Large adenoma (>1 cm), multiple adenoma (>3 in number), adenoma with villous history or high-grade dysplasia.

***Metastatic Colorectal Cancer (mCRC)***

It is estimated that 50–60% of patients diagnosed with CRC

will develop metastases during the course of their disease (metasynchronous lesions), whereas about 15–25% of patients present with metastasis (synchronous lesions). For patients who undergo “curative resection” of colon cancer, tumour may recur in the peritoneum, liver and distant organs, whereas in rectal cancer patients, tumour more likely develops locoregionally. Adjuvant chemotherapy with fluorouracil (5-FU)/leucovorin for patients with stage III colon cancer has reduced recurrence in the first 2 yrs following surgery, as after 2 yrs the likelihood of recurrence is similar to that observed in patients who have not received adjuvant therapy. Finally, liver metastases are common, and at autopsy more than 50% of patients with mCRC have liver-only metastases. Thus, liver resection in these patients, together with resection of the primary tumour, will offer the opportunity for improved long-term survival, as 35–58% of patients will survive 5 yrs.

The surgical procedure may be performed in one or two stages. If the patient has synchronous metastases, then the planned surgery depends on the patient’s individual factors, the extent of disease and the experience of the surgeon.

If three or fewer segments of liver are involved, resection is called minor, and it can be performed as a single procedure with resection of the colorectal primary tumour. If the liver has more than three segments involved, then a synchronous resection of the primary tumour and metastases carries a higher mortality rate, and in most cases a two-stage (sequential) procedure is recommended. This is also recommended if both sides of the liver are involved (bilobar metastasis).

The NCCN recommends that, following surgical resection of the primary and metastatic lesion(s), patients receive adjuvant chemotherapy, for a combined pre- and post-operative total treatment period of 6 months. Unfortunately, more than half of patients with resected liver metastases experience disease recurrence within 2 yrs. Some patients will be able to undergo repeat metastectomy.

The majority of patients with mCRC have unresectable disease. Approximately 15–20% of selected patients with unresectable liver metastases can be downsized or converted to the resectable-disease category with conversion therapy.

Several chemotherapeutic agents are used to treat mCRC: 5-FU, capecitabine (Xeloda, a 5-FU prodrug), irinotecan, oxaliplatin, therapies targeting angiogenesis (bevacizumab, aflibercept, ramucirumab and regorafenib) and therapies that target the epidermal growth factor receptor (cetuximab or panitumumab).

Treatment of mCRC is mainly palliative and usually lifelong or until tumour progress. Extended treatment with 5-FU, oxaliplatin or irinotecan can cause liver injury. Steatosis and steatohepatitis are associated with all three

agents and can increase the risk of postoperative infection and morbidity. Oxaliplatin is associated with sinusoidal injury and increased perioperative bleeding. Bevacizumab increa-ses tumour response but brings with it the risk of perfora-tion, fistula formation and bleeding.

**Genetics and CRC**

CRC results from interactions between genes and environ-ment. Sporadic CRC accounts for about 80% of all CRC, whereas the hereditary accounts for the rest. The most known causative genes for genetic CRC that have been cloned and characterized within the past decade are those with polyps like familial adenomatous polyposis FAP, AFAP, juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome and with no polyps (hereditary nonpolyposis CRC, HNPCC). Genetic testing is helpful in individuals who have one additional first- or two additional second-degree family members with CRC, regardless of age at diagnosis or when CRC diagnosed under the age of 45 yrs.

**Molecular subtypes of CRC**

Four molecular subtypes of CRC (CMS, consensus molecular subtype): CMS1 is microsatellite instable and characterized by multiple mutations, hypermethylation and BRAF mutations. The consensus molecular subtypes 2, 3 and 4 (CMS2, CMS3 and CMS4) are chromosomally instable and differ based on their gene expression signal. Most KRAS-mutated CRCs fall within the CMS3 category.

**Role of RAS protein in CRC**

1. RAS genes are the most commonly mutated genes in human malignancy, found in 25% of all cases. The four RAS isoproteins (KRASA4, KRASB4, NRAS and HRAS) share approximately 80% sequence identity. KRAS mutations have a role in both the development and progression of colon cancer.

2. RAS proteins act as a link in the signal transduction induced by growth factors to promote cell survival. KRAS and NRAS genes (mutations affecting exon 2) are mutated in 52% of patients with colon cancer.

3. According to the latest NCCN guidelines, testing for RAS mutations should be done for all patients with metastatic colon cancer disease.

4. Patients with wild type RAS genes should be considered for anti-EGFR treatment (panitumumab and cetuximab).

5. More than 2 decades of research have failed to produce an effective and safe RAS-targeted therapy.

**Microsatellite Instability and Colon Cancer**

Microsatellite instability (MSI) is the condition of genetic hypermutability (predisposition to mutation) that results

from impaired DNA mismatch repair (MMR). During DNA replication, MMR corrects error spontaneously. The cells (colonocytes) with abnormally functioning MMR are unable to correct the error. These errors accumulate and lead to formation of novel microsatellite fragments. MSI is detected in about 15% of all CRCs and stratified as MSI-high (MSI-H), MSI-low (MSI-L) or microsatellite stable (MSS) colon cancers. MSI tumours in sporadic CRC (15%) result from the hypermethylation of the MLH 1 gene promoter, whereas MSI tumours in Lynch syndrome are caused by germline mutations in MLH 1, MSH 2, MSH 6 and PMS2. Colorectal tumours with MSI have unique features, including a tendency to arise in the proximal colon, lymphocytic infiltrate and a poorly differentiated, mucinous or signet ring appearance. The principal use of MSI testing in the clinic is to identify patients with Lynch syndrome. It has been suggested that fluorouracil-based adjuvant chemotherapy is beneficial in patients with stage II or stage III colon cancer exhibiting MSS or MSI-L tumours, but not in those exhibiting MSI-H tumours. The US Food and Drug Administration (FDA) has granted approval to pembrolizumab (Keytruda) for patients with microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient solid tumours.

Another type of MSI has been recognized that does not fit into the definition of MSI-high. This signature has been called “**elevated microsatellite alterations at selected tetranucleotide repeats” (EMAST)**. EMAST is most frequently found in noncolonic tumours and is associated with *p53* mutations.

**Crc Screening**

Colon cancer screening is perhaps the most successful cancer screening in terms of both prevention and early detection. Luminal colon cancer screening is mostly polyp screening. There is considerable evidence that adenomatous polyp removal results in colon cancer prevention. The best tool for luminal colon cancer screening appears to be colonoscopy although sigmoidoscopy, virtual colonoscopy (computerized tomographic colography) and possibly barium enema are reasonable substitutes. Tests based on finding fecal occult blood have also been shown to be effective in early detection of colon cancer but are of minimal utility in detecting precancerous polyps. Detection of stool DNA that indicates the presence of cancer or adenomatous polyps is likely more effective than fecal blood testing approaches.

There are several methods existing for the screening of CRC:

1. Digital rectal examination (DRE)

2. Fecal occult blood testing (FOBT) and fecal DNA test

3. Flexible sigmoidoscopy

4. Colonoscopy

5. Double contrast barium enema (DCBE)

**Digital Rectal Examination**

As only small percent of tumours occur within the reach of DRE, DRE accurately diagnoses 10% of all colorectal tumours.

**Fecal Occult Blood Testing**

FOBT is done most commonly with a guaiac-based system that reacts to peroxidases, including haemoglobin. Screening with FOBT reduces mortality from CRC. Previous studies showed around 33% reduction in mortality if annual FOBT is performed. The specificity and sensitivity of FOBT for CRC detection vary considerably, depending on the technique that is used for testing. Rehydration of FOBT cards increased sensitivity but lowered the positive predictive value.

**Fecal DNA Test/Fecal immunohistochemical Test**

Fecal DNA testing is a relatively new development. It is based on finding several specific tumour-related DNA changes in cells shed from colonic neoplastic lesions into the bowel contents (Kras, ACP, p53 and high levels of PDX1). The test appears to be somewhat more sensitive than guaiac-based FOBT. It is also uncertain how frequently the test should be done to adequately screen for colon cancer.

Fecal immunohistochemical test is to identify mono-clonal antibody reaction or specific polyclonal antibodies against human haemoglobin, albumin or other components of the blood feces.

**Flexible Sigmoidoscopy**

Flexible sigmoidoscopy examination visualizes the lower half of the colon and cannot detect lesions beyond the reach of the scope. It is an efficient screening tool in average risk population for CRC. Combination of annual flexible sigmoidoscopy and FOBT increase effectiveness of screening.

**Double Contrast Barium Enema**

Double contrast enema has higher sensitivity than single contrast enema. DCBE has very low sensitivity for detecting polyp size less than 1 cm in diameter. It has now been replaced by CT colonography or virtual colonoscopy.

**Colonoscopy**

It is best screening modality as it provides complete visualization of the colon. It also allows for tissue biopsy and the removal of polyps. Studies showed that removal of adenomas decreases CRC incidence by as much as 76–90%

compared with no screening methodology. Despite its high sensitivity, colonoscopy is not the ideal screening test for CRC screening for average risk population.

Flat adenomas are a potential neoplastic lesions missed at colonoscopy. They are defined as an adenoma whose diameter is at least twice its height. They account for almost 10% of colonic neoplasms but are 10 times more likely to contain carcinoma than pedunculated adenomas.

It is likely that flat or sessile lesions are missed more frequently than pedunculated adenomas in view of their anatomy.

***Recent Advances in Screening of CRC***

1. Virtual colonoscopy (Ch. 65)

2. Capsule endoscopy (Ch. 65)

**Guidelines for Screening for Adenomas or Cancer as per US Preventive Task Force for Colon Cancer**

Task Force on Colorectal Cancer had given screening guidelines that categorize screening tests into three tiers, based on their effectiveness.

**Tier 1** tests consist of the following:

1. Colonoscopy every 10 yrs

2. Annual FIT (fecal immunochemical testing for occult blood)

**Tier 2** tests consist of the following:

1. CT colonography every 5 yrs

2. FIT–fecal DNA every 3 yrs

3. Flexible sigmoidoscopy every 5–10 yrs

**Tier 3** testing is capsule colonoscopy every 5 yrs

Suggested timing of initial screening and intervals for subsequent testing for different risk populations are as follows:

1. For patients at average risk, testing with a tier 1 test should begin at age 45 yrs for African Americans and at age 50 for patients of all other races.

2. For patients with a family history of CRC or advanced adenoma that was diagnosed before age 60 years in one first-degree relative or at any age in two first-degree relatives, testing should begin with colonoscopy at an age 10 years younger than the youngest age at diagnosis of a first-degree relative, or age 40, to be repeated every 5 yrs.

3. In patients with one first-degree relative with CRC, advanced adenoma, or an advanced serrated lesion diagnosed at age 60 or older, screening should begin with a tier 1

test at age 40 and continue at the same intervals as in average-risk patients.

4. Colonoscopy screening should be discontinued in patients aged 75 or older with prior negative screening tests or whose life expectancy is less than 10 yrs, or in those 85 yrs or older without prior screening.

**Risk Factors and Possible Chemoprevention for CRCs**

1. **Body mass index (BMI) and physical activity**

n Higher body mass is generally associated with an increased risk of colorectal adenomas and CRC, mainly in the male than in female.

n BMI of above 30 is associated with about a 2-fold-increased risk of large colorectal adenomas.

n Lifelong physical activity has been shown to be associated with decreased adenoma and CRC risk. Exact mechanism is poorly understood.

n Physical activities stimulate intestinal peristalsis, decreasing the contact time with environmental agents, bile acids and carcinogens residing in the colon.

2. **Carbohydrates**

n Resistant starch has been associated with a protective effect for CRC.

n Resistant starch is fermented in the colon producing short-chain fatty acid (butyrate), reducing fecal pH, increasing bile acid excretion and reducing plasma insulin and glucose. Thus, inhibit the growth of colon cancer cells by inducing apoptosis.

3. **Fat**

n High levels of dietary fat, especially animal fat, are generally associated with increased CRC risk.

4. **Fibre**

n There are four types of dietary fibre available: Cellulose, hemicelluloses, lignins and pectins.

n Dietary fibre (roughage) cannot be digested and absorbed to produce energy.

n Foods high in fibre include cereals and flour, roots, vegetables, nuts and fruits.

n Dietary fibre increases stool bulk and stool water, thus decreasing the concentration of luminal carcinogens and tumour promoters and reduces gut transit time, thereby decreasing the duration of contact between luminal carcinogens and tumour promoters with colonic epithelial cells. Some types of fibre bind bile acids, lower stool pH and can be fermented by colonic bacteria to short-chain fatty acids such as butyrate, which are thought to have anticarcinogenic properties.

n Majority of epidemiological studies showed high fibre diet reduces the incidence of colorectal adenomas and cancer.

5. **Other foods**

n Yogurt has been found to be protective against colon cancer in a study by Pala. High fructose corn syrup has been shown to produce polyps, which also rapidly acquired high-grade dysplasia in an experimental study on mice.

5. **Alcohol**

n Total amount of alcohol intake rather than type of alcohol significantly correlate with colorectal neoplasm.

6. **Smoking**

n Smoking is the risk factor for development of CRC.

7. **Calcium and vitamin D**

n Epidemiological evidences indicate that calcium and vitamin D have protective effect for colorectal neoplasm.

n Intraluminal calcium binds and precipitates bile and fatty acids. Thus, reduces the cytotoxic and pro-proliferative effect of bile salt on colonic epithelium.

8. **Selenium**

n Selenium protects from colorectal neoplasm secondary to its antioxidant and apoptotic effect.

9. **Vitamin E, carotenoids, folic acid and vitamin C**

n Vitamin E, carotenoids, folic acid and vitamin C have protective effect on colorectal neoplasm by their antioxidant and antineoplastic effect.

***Basis of Chemoprevention***

*Primary Prevention*

Primary prevention is applied to general population, or population who is disease free, to reverse or retard the development of adenomas, and cancer. It includes well-balanced diet, regular exercise, moderate alcohol use and tobacco avoidance.

*Secondary Prevention*

Secondary prevention is identification of subclinical disease through screening, such as fecal occult blood tests, flexible sigmoidoscopy, colonoscopy or genetic testing for high-risk genetic mutations, such as the adenomatous polyposis coli (APC) gene or microsatellite instability.

*Tertiary Prevention*

Tertiary prevention means to prevent development of second neoplastic lesion following the resection of CRC or polypectomy.

Interventional studies for chemoprevention for colo-rectal neoplasm

1. Fat, fibre and fruits and vegetables: Low fat, high fibre and high fruits diet failed to show any chemopreventive effect on the incidence of colorectal adenomas.

2. Antioxidant agents: Most of the trials using vitamin A, C and E show conflicting data regarding their role in chemoprevention. Role of selenium is yet to be proven as chemopreventive agent.

3. Calcium: High calcium intake reduces the incidence of colorectal neoplasm by 15% at the end of 1 yr.

4. Nonsteroidal anti-inflammatory drugs: Most epidemiological studies strongly support an association between regular long-term aspirin use and a decreased mortality from CRC.

Celecoxib, a COX-2 inhibitor, reduces the number and size of adenomas in patients with familial adenomatous polyposis coli (FAP).

The Nurses Health Study and the American Cancer Society Study suggested that 3–4 aspirin tablets per week were adequate to obtain the protective effects. The Nurses Health Study also found a strong relationship between the duration of aspirin use and CRC risk. No reduction in risk was apparent until more than 10 yrs of use, and the relationship was not statistically significant until after 20 yrs of use. Current evidence strongly indicates that the NSAID class of drugs can inhibit the process of colonic carcinogenesis.

**Further Reading**

1. Jack S. Screening for colorectal cancer. *Gastroenterol Clin North Am* 2008;37:97–115.

2. Viner JL, Umar A, Hawk ET. Chemo-prevention of colorectal cancer: problems, progress, and prospects. *Gastroenterol Clin North Am* 2002;31:971–99.

3. Kendal WS, Cripps C, Viertelhausen S, Stern H. Multi-modality management of locally recurrent colorectal cancer. *Surg Clin North Am* 2002;82:1059–73.

4. Hawk ET, Umar A, Viner JL. Colorectal cancer chemo-prevention—an overview of the science. *Gastroenterology* 2004;126:1423–47.

5. Tepper JE, O’Connell M, Hollis D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex and local control—final report of intergroup 0114. *J Clin Oncol* 2003;21: 3623–28.

6. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005;352:476–87.

7. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. *Oncology* 2010; 78:237–48.

8. National Comprehensive Cancer Network (NCCN): Practice Guidelines in Oncology: Colon Cancer, v3.2011. Fort Washington, PA.

9. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for respectability of colorectal liver metastases. *Oncologist* 2008;13:51–64.

10. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; 360:563–72.

11. Juan José Granados-Romero, Alan Isaac Valderrama-Trevino, Ericka Hazzel Contreras-Flores, et al. Colorectal cancer: a review. *Int J Res Med Sci* 2017;5:4667–76.

12. Saeed O, Antonio Lopez-Beltran, Kurt W Fisher, et al. *J Clin Pathol* 2019;72:135–9.

13. Dienstmann R, Vermeulen L, Guinney J, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. *Nat Rev Cancer* 2017;17:79–92.

14. National Comprehensive Cancer Network Guidelines (NCCN Guidelines). Colorectal Cancer Screening. Washington: NCCN Guidelines; 2014.

Chapter 38.

**Colostomy**

**Introduction**

The term “ostomy” comes from the Greek “stoma” and means “mouth.” In medicine, stoma/ostomy refers to a surgically created opening of a hollow organ on the surface of the body to enable excretion of waste products. Colostomy can be created using either the small or the large bowel. More than 75% of all stomata are placed as part of the treatment of colorectal cancer. The incidence of stoma-related complications is reported to be 10–70%. Skin irritation, erosion and ulceration are the most common early complications, with a combined incidence of 25–34%, whereas stoma prolapse is the most common late complication, with an incidence of 8–75%. Ileostomies are usually created in right mesogastrium, colostomies as per exteriorized segment like transverse colon in right hypochondria and sigmoid in left iliac region.

**Classification of Stoma**

1. ***Input stoma***: These are usually temporary and facilitate nutrients being put into the gut like gastrostomy and jejunostomy.

2. ***Diverting stoma***: The intestine is not transected; rather the anterior wall is opened to create the ostomy. These divert the contents of the gastrointestinal tract away from diseased or damaged gut or distal anastomosis, like loop ileostomy and loop colostomy.

3. ***Output stomas***: The bowel is divided and the proximal stump is brought out. These provide an outlet for the elimination of bowel contents like ileostomy and colostomy.

4. ***Kock continent ileostomy***: A reservoir (the Kock pouch) fitted with a stop valve is brought out as a shallow ostomy in the abdominal wall. The valve prevents continuous leakage of stool, thus rendering the patient continent. The pouch is emptied by self-catheterization, enabling the patient to live without an ostomy bag.

**Conditions Requiring Surgery Involving a Stoma**

There are varieties of conditions, which may predispose to surgery involving the creation of a stoma. Broadly indications can be looked in as elective or emergency setting. Patients with anastomotic leak or lately presenting with perforation with severe peritonitis or tertiary peritonitis needs a diverting/end stoma as damage control surgery. Certain procedures where anastomotic site is potentially compromised covered using proximal diversion stoma.

**Paediatric age group**

1. Anorectal anomalies

2. Bladder exstrophy

3. Spina bifida

4. Hirschsprung’s disease

5. Necrotizing enterocolitis

6. Meconium ileus

**Adults**

1. Ulcerative colitis

2. Crohn’s disease

3. Familial polyposis coli

4. Colorectal cancer

5. Bowel ischaemia

6. Colonic obstruction

7. Anorectal incontinence

**Physiological Aspect of Stoma**

Stoma leads to reduction of surface area of bowel, thus water and nutrient absorption are impaired. Immediately after creation of end ileostomy, the absence of the resorption surface of the large intestine leads to loss of high volumes of a thin bilious fluid. On the resumption of oral feeding, the ostomy output will change both in colour (becoming brownish) and in consistency (becoming mushy). The output is mainly odourless, but consumption of certain foods, e.g., eggs and fish, may be connected with an unpleasant odour. In colostomy, the extent of physiological change depends on the ostomy site. Distal the stoma location, the better formed is the excreted material and the lower the volume. The output of a colostomy is more malodorous than that of an ileostomy due to the bacterial colonization of the colon.

**Colostomy**

Colostomies may be permanent or temporary, and can be categorized into four types, *viz*, ‘terminal’ or ‘end’ colostomy, loop colostomy, double-barrel colostomy and divided colostomy.

**Terminal (end) colostomy**: A terminal colostomy is most commonly situated in the left iliac region of the abdomen. As water absorption is not compromised, the patient can expect to pass a formed stool. Terminal colostomy is associated with surgeries like abdominoperitoneal excision for rectal cancer and Hartmann’s operation. Distal end can be brought out as mucous fistula at different site.

**Loop colostomy**: A loop colostomy is most commonly done due to following reasons:

1.To divert the major part of the fecal stream in emergency situations like distal colonic perforation or trauma.

2.To protect an anastomosis following low anterior resection.

3.To decompress the colon in large bowel obstruction.

4.To facilitate healing of colonic disease.

The most common sites for a loop colostomy are the transverse colon to the right of the midline or the sigmoid colon in left iliac region. Loop colostomies in the sigmoid colon are easier to manage because they occupy a more desirable position and the effluent contains less fluid.

**Double-barreled colostomy (Bloch-Paul-Miculicz)**: This type of colostomy is performed in patients with diverticular disease or sigmoid volvulus. The procedure involves resecting the diseased colon and forming a double-barreled colostomy by suturing the posterior wall to form a spur. The continuity of the bowel can later be restored using a gastrointestinal anastomosis.

**Divided colostomy (Devine operation)**: It is a historical procedure. A divided colostomy may be created in cases of obstructing carcinoma or colonic perforation. The procedure involves the excision of the lesion with the proximal bowel being fashioned into a colostomy. The distal end of the colon is fixed to the skin forming a divided colostomy with a bridge of skin between. The two ends of bowel are reunited during colostomy closure.

**Ileostomy**

Ileostomy can be end ileostomy or loop ileostomy depending of the pathological situations.

1. **Terminal (end) ileostomy**: Terminal ileostomy is performed during total colectomy, most commonly due to inflammatory bowel disease or patients with familial adenomatosis polyposis coli (FAP) in emergency setting. A terminal ileostomy is most commonly situated in the right iliac region of the abdomen. The ileostomy acts frequently, discharging a fluid effluent as there is no

colonic fluid reabsorption. The effluent does not normally have an offensive odour.

2. **Loop ileostomy**: A loop ileostomy is usually temporary to divert the faecal stream away from fistulae, distal ileorectal or coloanal anastomosis or acute Crohn’s disease of the rectum or anus. A loop ileostomy is constructed in a similar way to a loop colostomy. It is essential that the afferent loop form a spout to facilitate the collection of effluent without leakage.

There are several advantages of loop ileostomy over loop colostomy:

n It is a smaller stoma, therefore, requires a small appliance.

n Loop ileostomy occupies a site, which facilitates easier management.

n Effluent has little odour.

n Complications like prolapse, skin excoriation, minor bleeding and appliance leakage occur less often with loop ileostomy.

**Selection and Use of Stoma Care Appliances**

Many stoma appliances are disposable and incorporate hypoallergenic skin protective batteries. Most are made from soft, odour-proof plastic. These appliances have significantly improved the quality of life for stoma patients.

**Types of stoma appliances**

1. **Closed bags**: Suitable only for ‘end,’ ‘iliac’ or ‘sigmoid colostomy’ when the motions are formed.

2. **Drainable bags**: Suitable for semi-formed and fluid faeces for transverse colostomy, ileostomy and fistulae. The bag can be emptied as often as necessary as the bottom of the appliance is secured with a clip or tag.

The appliances can be further divided into two groups: one piece and two-piece systems **(Table 38.1)**.

**One-piece system**: As the name suggests, the appliance incorporates a method of securing the bag to the abdomen. This is usually an area of skin protective, such as a Karaya, carboxymethylcellulose or gum ring, and an area of hypoallergenic adhesive tape.

One-piece appliances usually have precut opening to fit over the stoma, which is invariably round. It is important to select the correct gasket size. Careful measuring will indicate the correct size to fit snugly around the stoma, protecting all the surrounding skin.

One-piece appliances are usually the most simple to apply and, for this reason, may be particularly suitable for patients with reduced manual dexterity, the elderly, or new patients, as less learning stages are required.

**Two-piece system**: These appliances consist of some sort of skin protective base plate, which adheres to the skin. The bags are then clipped onto this base. Some base plates are wafers or carboxymethylcellulose while others have a central area of skin protective surrounded by a hypo-allergenic adhesive tape, which usually proves to be more flexible.

**One-piece system Two-piece system**

Very flexible Less flexible

Comfortable

Most discrete Less discrete

Most hygienic Easy changing

More stressing Less stressing of the

of skin skin

High cost Low cost

The bags can be changed regularly and the base plate remains in position for several days depending on the specific product. Two-piece appliances have the advantage that they can be cut to fit the stoma no matter what its shape. The bag can be changed without disturbing the surrounding skin; hence, there is a lower incidence of skin irritation associated with its use.

**Stoma Sites**

The **ileostomy**: The site for an ileostomy is usually on the right of the abdomen overlying the outer third of the rectus muscle. It is possible to raise an ileostomy on the left side of the abdomen in cases where a suitable site on the right cannot be found.

The ileostomy is usually positioned at a point one-third to halfway along a line from the umbilicus to the anterior superior iliac spine.

The **iliac or end colostomy**: The colostomy is usually positioned at a point about one-third to halfway along a line from the umbilicus to the anterior superior iliac spine.

The **ileal conduit (urostomy)**: The ileal conduit is positioned as for the ileostomy.

The **transverse colostomy**: This is most commonly a loop colostomy and is positioned in the right upper abdomen, midway between the costal margin and the umbilicus in the line of the rectus abdominis muscle. A rough guide would be approximately 5–8 cm below the lower rib cage and 5–8 cm to the right of the umbilicus.

**Complications of Stomas**

1. ***Prolapse***

n Occurs when large opening in rectus sheath commonly seen after chemoradiation.

n Large prolapse leads to difficulty in fitting an appliance.

n It may lead to intestinal obstruction if the proximal bowel has prolapse.

n Sometimes it is possible to reduce the prolapse.

n Large prolapse is treated by dividing the loop colostomy to a single opening proximal colostomy.

2. ***Ischemia***

n Prolonged ischaemia leads to necrosis of stoma.

n Stoma will appear a dusky purple initially and black when truly necrotic.

n Ischemia can occur secondary to constriction of the stoma by an appliance.

n In many cases, the area of necrosis is confined to the mucosa. The necrotic tissue will often slough off leaving a healthy stoma.

n Surgery is required in case of non-viable stoma.

3. ***Stenosis***

n The outlet of the stoma becomes narrowed.

n It may be due to scar tissue or inappropriate technique.

n It can lead to intestinal obstruction.

n Mild stenosis can be treated with regular digital dilation. Surgical intervention is necessary for severe stenosis.

4. ***Retraction***

n Retraction of the stoma is due to tension on the bowel particularly in obese patients.

n Retraction may be due to inadequate fixing of the appliance or postoperative weight gain.

5. ***Herniation***

n It is frequently seen in iliac “end” colostomies. It is less common in ileostomy.

n Herniation is more common in elder patient due to diminished muscle tone.

6. ***s***

n A fistula can occur at the base of the stoma spout in the case of ileostomy.

n Postoperative fistula is due to a stitch being passed through the full thickness of the bowel.

n Fistula leads to skin excoriation and majority require surgical revision.

7. ***Bleeding***

n Bleeding near the stoma is due to formation of granuloma or overenthusiastic cleansing of stoma.

n Bleeding from the lumen of the stoma is due to ulcer or varices secondary to portal hypertension or tumour.

8. ***Skin complications***

n Excoriation

n Irritation

n Allergy

n Infection

**Further Reading**

1. Salvadalena G. Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review*. J Wound* *Ostomy Continence Nurs* 2008;35:596–607.

2. Ratliff CR, Scarano KA, Donovan AM, Colwell JC. Descriptive study of peristomal complications. *J Wound Ostomy Continence Nurs* 2005;32:33–7.

3. Ratliff CR, Donovan AM. Frequency of peristomal complications. *Ostomy Wound* *Manage* 2001;47:26–9.

4. Pine J, Stevenson L. Ileostomy and colostomy. *Surgery (Oxford)* 2014;32:212–7.

5. Shabbir J, Britton DC. Stoma complications: a literature overview. *Colorectal Dis* 2010;12:958–64.

6. Shellito PC. Complications of abdominal stoma surgery. *Dis Colon Rectum* 1998;41:1562–72.

SECTION 5

SELECTED REVIEWS

**Chapter 39.**

**Gastroesophageal Reflux Disease**

**Introduction**

Gastroesophageal reflux disease (GERD) is one of the most commonly diagnosed disorders in the practice of medicine. Its importance is highlighted by its predisposition to complications such as reflux oesophagitis, strictures, Barrett’s oesophagus and last but not the least, adenocarcinoma. However, in majority of patients, the diagnosis of GERD is predominated by the presence of oesophageal symptoms such as heartburn and regurgitation or extra-oesophageal symptoms such as cough and hoarseness. The latter group may not develop GERD complications, but may suffer from severe alteration in quality of life similar to other chronic diseases like congestive heart failure and diabetes. The incidence of GERD may be increasing especially in the western populations. There are significant regional differences in the prevalence of GERD symptoms as well as its complications such as Barrett’s oesophagus. Barrett’s oesophagus, seen in 10% of western GERD patients, may be seen only in a minority of south Asian patients including India. These differences may reflect variations in dietary intake, environmental factors and genomic constitution of various populations. GERD is a symptom-driven disorder but symptoms alone are unreliable in the diagnosis. Additional use of ambulatory pH monitoring, endoscopy and histology may aid diagnosis but neither of these tests can be labeled as the gold standard. Response to proton pump inhibitors, so-called “PPI test,” may be clinically attractive due to widespread availability and potential for prompt relief. However, its accuracy in predicting GERD is questionable. A large number of GERD patients may benefit from PPI therapy but some may need fundoplication for symptomatic control. Lately, there has been lots of interest in newer endoscopic therapies to mimic “surgical fundoplication” but early excitement has given way to guarded anticipation due to technical difficulties, less than predicted symptomatic relief and reports of procedure-related mortality in trials. This chapter will briefly discuss the aforementioned aspects of GERD.

**Epidemiology**

Most data on epidemiologic aspects of GERD has surveyed western populations but there are early reports describing the prevalence of GERD from the eastern hemisphere. It affects around 20–50% of adults in Western countries and approximately 25 million adults experience heartburn on a daily basis in the United States. A recent systematic review reported an increase in the prevalence of reflux symptoms in the general population in North America over the past 2 decades. Based on this, it is not surprising that traditionally, GERD has been viewed as a disease of the Western world and thought to be uncommon in the developing countries; <5% in one study. A study that compared dyspeptic British and south-east Asian subjects found that British subjects were more likely to present with heartburn than their south-east Asian counterparts (72 vs 41%, *p*<0.0001). Further supporting the higher prevalence of GERD in the former group, both oesophagitis and BE were five times more likely in the British subjects. However, recently it has been suggested that there is an increasing trend in the prevalence of GERD in Asia over the last 2 decades and that reflux disease is more common in Asian countries than previously recognized. Ethnic and geographic differences in GERD and its complications highlight environmental or genetic influences on aetiology and disease pathogenesis.

**Pathogenesis of GERD**

The mechanisms leading to GERD are not completely understood but appear to be related to anatomic and physiologic disruptions of the esophagogastric junction (EGJ). The integrity of the EGJ is a combination of physiologic – intrinsic lower esophageal sphincter (LES) pressure – and anatomic factors – extrinsic compression of the LES by crural diaphragm, intact phrenoesophageal ligament and the intra-abdominal positioning of distal esophagus maintaining an acute angle of His. Isolated disturbances in the individual factors may not be sufficient to cause gastric contents to reflux. Instead, a mechanical disruption of the EGJ along with abnormal LES pressure profile may be responsible for reflux episodes. The three main phenomena that have been implicated in the causation of GERD are transient lower oesophageal relaxations, hypotensive LES pressures and the mechanical disruption of EGJ with significant contribution of hiatal hernia. Transient lower esophageal sphincter relaxation (TLESR) may be the primary mechanism behind upright reflux while hypotensive LES pressures may play a significant role in night time reflux. The presence of hiatal hernia may contribute to both the

upright and supine reflux. Post prandial gastric pocket located just below LES where the pH is extremely low is responsible of reflux symptoms during supine position after eating and patients with hiatus hernia.

Risk factors of development of GERD are listed below:

1. Hiatus hernia

2. Obesity

3. Diet – High fat diet, high consumption of coffee, chocolate and citrus food

4. Tobacco and smoking – Strong association

5. Pregnancy – Progesterone causes relaxation of LES

6. Drug induced – NSAIDs, statin, ACE inhibitors, iron, bisphosphonates

**Diagnosis of GERD**

**History and Proton Pump Inhibitor Trial**

The presence of heartburn (reflux) and regurgitation is cardinal symptoms of most cases of GERD. Extraesophageal symptoms are chronic cough, asthma, laryngitis and dental erosions. Symptomatic response to PPI therapy does not equate to a GERD diagnosis. On average, 69% of patients with oesophagitis, 49% of patients with non-erosive reflux disease (NERD) and 35% of patients with normal endoscopy and pH-metry gain symptom relief from a PPI trial. A major limitation of the ‘PPI test’ is the strong modulation of symptoms by oesophageal hypersensitivity.

**Upper Endoscopy**

When classic GERD symptoms do not respond to empiric PPI therapy, upper endoscopy (EGD) is advised both to evaluate for GERD complications and to detect potential alternative diagnoses. Endoscopic confirmation of GERD is: High-grade oesophagitis (LA grades C or D), Barrett’s oesophagus or peptic stricture. Erosive oesophagitis is found in only 30% of treatment-naive patients with heart-burn.

A number of different classification systems for grading erosive oesophagitis have been described including the Savary-Miller, Los Angeles (LA), Hetzel-Dent, etc. The LA classification is a well validated, widely used system **(Table 39.1, Fig. 39.1)**. In general, as the grade of erosive oesophagitis worsens the degree of oesophageal acid exposure increases.

**Histology**

Histologically, acute reflux damage consists of superficial epithelial swelling and/or necrosis accompanied by intraepithelial neutrophilic infiltrates. Chronic reflux induces

eosinophilic infiltrates, basal cell hyperplasia, epithelial thickening and elongation of the vascular papillae (Ismail-Beigi criteria). Basal hyperplasia in excess of 15% and

papillary elongation in excess of 2/3 of the epithelial thickness have been proposed as criterion to diagnose reflux oesophagitis.

**Grade Definition**

**A** One or more mucosal breaks no longer than

5 mm, none of which extends between the tops

of the mucosal folds

**B** One or more mucosal breaks more than 5 mm

long, none of which extends between the tops

of two mucosal folds

**C** Mucosal breaks that e xtend between the tops

of two or more mucosal folds, but which involve

less than 75% of the oesophageal circumference

**D** Mucosal breaks that involve at least 5% of the

oesophageal circumference

A relatively novel histologic finding in patients with GERD is thought to be dilated intercellular spaces (DIS). DIS, caused by a loss of intraepithelial cell junctions, has been proposed as one of the earliest signs of acid damage to the oesophagus. This phenomenon allows acid to access sensory nerve endings residing within the intercellular space and possibly causing heartburn in patients with NERD.

**Ambulatory Testing for GERD**

Ambulatory reflux monitoring can provide confirmatory evidence of GERD, particularly in patients with normal endoscopy, typical symptoms. The acid exposure time (AET) is the primary outcome of a 24-hr pH-metry study. Reflux monitoring can be done ‘on’ or ‘off’ PPI therapy in patients with persistent and/or atypical symptoms despite PPI therapy. According to Lyon consensus, in case of unproven GERD, it should be done “off” PPI and in case of proven GERD (LA class C or D), it should be done with double dose of PPI to establish correlation between refractory symptoms and reflux episodes. AET <4% be considered definitively normal (physiological) and >6% be considered definitively abnormal.

The pH monitoring systems are limited to detect only those reflux episodes, which are acidic in nature. There is growing evidence to indicate that non-acid reflux including duodenogastric-esophageal reflux (DGER – bile or alkaline reflux) may have role to play in symptom perception in GERD. Intraluminal multichannel impedance monitoring records reflux events by measuring the change in resistance to current flow between pairs of the impedance electrodes with liquid boluses decreasing impedance while gas boluses increasing impedance. A major advantage of impedance testing is its ability to detect all reflux events irrespective of the pH, thus dramatically improving the sensitivity of reflux episode diagnosis. As non-acid reflux events appear to play a role in GERD symptoms, particularly regurgitation and there is potential for improving the sensitivity of symptom-reflux correlation, impedance monitoring may add to more effective management of GERD symptoms.

The pH-impedance monitoring can detect the number of reflux episodes (acidic, weakly acidic or weakly alkaline). The Lyon GERD Consensus proposes that >80 reflux episodes/24 hrs are definitively abnormal, whereas a number <40 are physiological and intermediate values inconclusive. Clinical application of number of reflux episodes is yet to identify. Both pH monitoring and combined pH-impedance monitoring provide analysis of the temporal association between symptoms and reflux episodes (time window 2 min). The Symptom Index (SI) is the percentage of symptom events preceded by reflux episodes, and the optimal SI threshold for heartburn is 50%. According to Lyon consensus pH-impedance monitoring is the gold standard for detection and characterisation of reflux episodes but is expensive, not widely available and interpretation is time consuming. When reflux monitoring is indicated on PPI, pH-impedance should be performed. When reflux monitoring is indicated off PPI, the choice between catheter-based pH-monitoring, wireless pH monitoring and pH-impedance monitoring is dependent on cost and availability.

The development of a wireless pH capsule monitoring system (BRAVO) offers several advantages over the conventional catheter-based monitoring system; the ability to record over 48 hrs vs 24 hrs and improved tolerability in particular. The ability to monitor for a longer duration has improved the sensitivity of the test in preliminary studies.

**High-Resolution Manometry**

High-resolution manometry (HMR) is used to assess oesophageal peristalsis, to identify alternate major motor defects and to place pH or pH-impedance catheter. HMR also helps to assess esophagogastric junction (EGJ) barrier function and to evaluate EGJ obstruction. Normal study is the most common motility pattern in patient with GERD.

**Novel Imaging Techniques**

The role of novel imaging techniques is based on the premise that the “normal” appearing distal oesophageal mucosa on a conventional white light endoscopy in GERD patients may harbour subtle alterations secondary to contact with refluxed contents.

Narrow band imaging (NBI) is a novel technology that uses spectral narrow band filters (415±15 nm, 540±15 nm) instead of the entire spectrum of light to permit in-vivo visualization of the superficial 170–210 µm of the mucosa. Intrapapillary capillary loops (IPCLs), micro-erosions, columnar islands, rigdge/villous patterns and increased vascularity at the squamocolumnar junction are the early findings of GERD. Literature showed that increased or dilated IPCLs or presence of microerosion had a sensitivity of 92% and specificity of 100% for the diagnosis of GERD.

**Management of GERD**

**Lifestyle Modification**

Control of the GERD symptoms and improve quality of the life is the main goal for the treatment. Mild and intermittent GERD symptoms can be well managed with diet and lifestyle modification. Regular exercise, eating small meals, avoid smoking, weight loss and avoid high fatty meal are the non-pharmacological treatment.

**Pharmacologic Therapy**

Pharmacological therapy is very important in patients with troublesome symptoms with moderate-to-severe GERD. Antacids and prokinetic drugs have very little role to play in the management of GERD. There is little role of alginate in the management of mild GERD symptoms mainly to reduce the use of proton pump inhibitors (PPIs).

**PPIs**

PPI (details in chapter 60) is the most important pharmaco-logical treatment of healing of erosive oesophagitis. PPI inactivates proton pump (H+-K+-ATPase) to suppress both basal and stimulated acid secretions by acetylcholine and histamine. As they need acid to be activated and bind only to the activated proton pumps, they need to be administered 30–60 min before meals to provide the highest efficacy. PPIs are better anti-secretory agents than H2-receptors antagonists (H2RA) due to longer duration of action without any evidence of tachyphylaxis presumably due to the fact that they act at the final step of acid production. However, in 10–30% of GERD patients, symptoms may be refractory to even twice daily dosing of PPIs. This may be, in part, due to a phenomenon called nocturnal acid breakthrough, defined by recovery of gastric acidity to a pH <4.0 for at least 1 continuous hr on a PPI taken twice daily. Given the limitations of PPI therapy in a sub-group of patients, novel agents including potassium-competitive acid blockers (p-CABs) and cholecystokinin receptor type 2 (CCK2) antagonists are being tested in clinical trials. This is further discussed below.

**Novel PPI Formulations**

The enteric-coating on the commonly used PPIs to protect

the acid-labile PPI from acid degradation in the stomach, have the potential disadvantages of delaying PPI absorption. Novel formulations such as lansaprazole orally disintegrating tablet has recently been introduced and greatly improves compliance as it is easy to swallow and can be taken orally with or without water. Also, as it is easy to disperse in water, it provides a less expensive alternative to intravenous PPIs for patients with nasogastric or gastric tubes in ICU or long-term settings. There has been lots of interest lately in

immediate release-omeprazole (IR-omeprazole) formu-lation with its proposed faster onset of action. This formu-lation consists of non-enteric-coated omeprazole mixed with sodium bicarbonate and is available both as a capsule and chewable tablet form. This combination may have synergistic effects as sodium bicarbonate may lead to an early increase in pH besides accelerating and enhancing absorption of omeprazole whose increased bioavailability translates into a profound acid suppression. IR-omeprazole may provide better nocturnal control of acid breakthrough with potential for better control of nighttime symptoms.

**Potassium-competitive Acid Blockers (P-CABs)**

P-CABs are K+ competitive inhibitors of the ATPase. P-CABs have a structural specificity for their target, the K+-binding region of the H+K+ ATPase. P-CABs inhibit H+K+ATPase by binding ionically to the enzyme and thus prevent its activation by the K+ cation. P-CABs are lipophilic weak bases that are stable at low pH (unlike PPIs that have to be enteric coated to avoid acid damage). Vonoprazan is one of the examples of P-CABs.

***Cholecystokinin Receptor Type 2 (CCK2) Antagonists***

Gastrin is a major endocrine regulator of gastric acid secretion and its release stimulates an estimated mean of 90% of postprandial secretion. Gastrin binds to CCK2 receptors that are present on both histamine release enterochromaffin (ECL) cells and acid secreting parietal cells. Gastrin mediates histamine release from ECL cells via activation of CCK2 receptors. The released histamine is a potent stimulant of acid secretion, exerting a direct stimu-latory effect on H2 receptor of the parietal cell. Given the important physiological role of gastrin in the stimulation of gastric acid secretion, selective CCK2 receptor antagonists offer a potential approach to regulate acid production. Five different CCK2 antagonists are being studied. One of the most promising is lorgiumide devazepide, a selective antagonist endowed with good oral bioavailability. After intraduodenal administration, the drug proved to be more potent as an antisecretory compound than either ranitidine or omeprazole with a favourable side effect profile. However, tachyphylaxis and possible delayed mucosal ulcer healing due to blockade of CCK2 receptors are two main concerns. Their major benefit may be to avoid long-term consequences of PP-induced hypergastremina and ECL cell hyperplasia.

**Mechanical Anti-reflux Therapy**

The indications for mechanical or barrier anti-reflux therapy are poorly defined and evolving especially since it is felt that only the group of patients who respond to PPI will benefit

from anti-reflux surgery. Furthermore, as much as 30–40% of the patients who undergo anti-reflux surgery may eventually require PPI. At present, severity of the disease, mechanical incompetence of the LES, presence of hiatal hernia, partial response to PPI in a patient with abnormal acid exposure time, unwillingness to take chronic medications and perhaps, severely symptomatic non-acid reflux may encourage the clinician to offer surgical therapy to a GERD patient.

***Endoscopic Anti-reflux Therapy***

Endoscopic anti-reflux therapy includes implantation and injection devices (Enteryx [Boston Scientific Corp, Natick, MA, USA], Gatekeeper [Medtronic, Minneapolis, MN, USA], Plexiglas microspheres [Artes Medical, San Diego, CA, USA]) and several endoscopic apposition devices (EndoCinch [Bard Medical, Covington, GA USA], NDO Plicator [NDO Surgical, Mansfield, MA, USA]). The currently available popular endoscopic anti-reflux modalities (EARMs) include radiofrequency ablation (RFA), transoral incisionless fundoplication (TIF, EsophyX; EndoGastric Solutions, Redmond, WA, USA), medigus ultrasonic surgical endostapler (MUSE), and anti-reflux mucosectomy (ARMS).

The Stretta system, daycare procedure, delivers radio-frequency energy via a needle balloon catheter system to the LES muscle and gastric cardia. The proposed mechanisms include fibrosis and hypertrophy of the muscularis propria and reduced transient LES relaxations after RFA. Variable results are the most drawback of Stretta procedure. The TIF procedure is a minimally invasive treatment for GERD and follows the principles of anti-reflux surgery. The MUSE (Medigus, Omer, Israel) is an endoscopic stapling device for transoral partial fundoplication. Long-term safety and efficacy data are very limited. Endoscopic full thickness plication (EFTP) device had undergone several modifications to achieve robust anti-reflux valve. The ARMS procedure is based on the mucosal healing after mucosal resection, results in scar formation. This in turn results in shrinkage and remodeling of gastric cardia flap valve; thereby, reducing reflux events. No endoprothesis or no sophisticated device required for ARMS procedure.

***Surgical Anti-reflux Therapy***

The surgical procedure of fundoplication can be classified into either complete (Nissen) or partial (Toupet). Almost 20% of patients will have dysphagia at 3 months after laparoscopic Nissen fundoplication and 5% will continue to have severe dysphagia at 12 months. Other well-described side effects of a complete (Nissen) fundoplication are inability to belch and postprandial bloating replacing the symptoms of GERD with a new constellation of symptoms

commonly referred to as gas-bloat syndrome. To overcome some of these mechanical side effects of a complete fundoplication, Toupet introduced his technique of partial wrap in 1963 and with modifications is applied today as either anterior or posterior partial fundoplication. Due to potential for less dysphagia but more recurrent reflux with partial wrap, it was initially proposed that partial wrap may be offered to the GERD patients with pre-existing esophageal motility disorders. However, subsequent studies indicated that even a partial wrap might have a significant incidence of postoperative dysphagia raising concerns about the presumed advantages and efficacy of the partial wrap procedure. Recently, these two techniques have been compared in randomized controlled trials and suggest that reflux control may be somewhat better after a total fundoplication but at the expense of more dysphagia and the symptom profile of gas-bloat syndrome with its measurable negative impact on quality of life. These differences need to be taken into account prior to recommending a complete vs. partial fundoplication to the patient.

The next issue relates to the open vs laparoscopic approach. The laparoscopic approach has obvious advantages of less surgical scar with potentially faster recovery and improved postoperative quality of life. The open approach may be favoured in those patients with prior abdominal surgeries where extensive intra-abdominal adhesions would be expected, large paraesophageal hernias and extensive esophageal foreshortening mandating a thoracic approach.

Magnetic sphincter augmentation (MSA) is a new antireflux surgical technique for treating GERD, which could physiologically reinforce the LES by magnetic force. MSA (or LINX) devices provide an alternative surgical option for the patients who had failed in medical therapy. This procedure is performed by laparoscopic placement of a small flexible band of interlinked titanium beads with magnetic cores around the LES without altering hiatal or gastric anatomy. The beads separate during swallowing as well as during belching or vomiting. Therefore, adverse events, such as dysphagia, inability to belch and vomiting, are less frequent compared to the traditional surgery.

**Difficult to Treat GERD**

There have been huge advances in the therapy of GERD. Still, there will be a subgroup of patients with symptoms of GERD who may not respond adequately to therapy. Patients who are still symptomatic on adequate acid suppressive therapy may have insufficient acid inhibition, poor compliance, non-acid reflux and/or visceral hypersensitivity. First and foremost, in this group, the diagnosis of GERD should be reevaluated. Further evaluation with pH monitoring may help to clarify the diagnosis although limitations of pH monitoring need to

be considered. Studies suggest that almost 40% of patients may have continued evidence of acid reflux on pH monitoring on once a day PPI compared to 15–18% on twice a day PPI. This suggests that doubling the dose of PPI in patients who have persistent symptoms on once-a-day PPI may be helpful. Another option for patients who are already on twice a day PPI may be to switch PPI as genetic polymorphisms and other unknown factors may affect the efficacy of one PPI over another. In a comparison of the four commonly prescribed PPI, esomeprazole was more effective in 20% of the patients who had inadequate acid suppression with other PPI. Next, the possibility of non-acid reflux needs to be considered. The advent of newer technology such as combined impedance-pH monitoring has helped to diagnose non-acid reflux. In an ongoing multicentre study of refractory GERD patients on twice-a-day PPI, a significant number of the patients had non-acid reflux. PPI may help in the treatment of non-acid reflux by decreasing the volume of gastric secretions but if they are ineffective, then surgical anti-reflux therapy needs to be considered. Although larger studies are needed, initial data suggest that Baclofen may offer a treatment option in patients who complain of reflux symptoms despite acid suppression therapy. The subset of patients who do not respond to doubling the dose of PPI, have a normal pH testing and normal impedance parameters may have the poorly understood disorder of functional heartburn characterized by visceral hypersensitivity. This group has poor symptomatic response to acid suppression and may respond to the institution of selective serotonin uptake inhibitors and tricyclic antidepressants.

**Conclusion**

GERD is one of the most commonly diagnosed disorders in the practice of medicine that can be complicated by impaired quality of life, reflux esophagitis, strictures, Barrett’s oesophagus and last but not the least, adenocarcinoma. There are ethnic and geographic differences in GERD and its complications highlighting environmental or genetic influences on aetiology and disease pathogenesis.

Among South Asian ethnicities, Indians may have a higher

predisposition to complications such as Barrett’s oeso-phagus, albeit at a much lower rate compared to western countries.

The three main phenomena that have been implicated in the causation of GERD are transient lower oesophageal relaxations, hypotensive LES pressures and the mechanical disruption of EGJ with significant contribution of hiatal hernia. Although histology may be relatively inaccurate for the diagnosis of GERD, evaluation for the presence of dilated intercellular spaces may improve its yield.

Endoscopic presence of erosive oesophagitis and Barrett’s oesophagus has a high positive predictive value for the

diagnosis of GERD.

Ambulatory pH monitoring with impedance may be considered the current gold standard for GERD diagnosis. Novel imaging methods such as high-resolution endoscopy and narrow band imaging may aid confirmation of GERD by visualizing details not seen with conventional endoscopy, but further research is needed. The most effective therapy for GERD at present time is proton pump inhibitors (PPIs). However, a subset of patients may suffer from inadequate control due to phenomena such as nocturnal acid break-through and imperfect acid control. These patients may benefit from the newer acid suppressive agents such as potassium competitive blockers and CCK2 antagonists. The latter has potential for preventing hypergastrinemia due to acid suppression by PPIs. Early enthusiasm for endoscopic anti-reflux therapy has led to cautious optimism due to risk of complications including death and limited efficacy. Surgical anti-reflux therapy may lead to significant symp-tomatic improvement in refractory GERD patients with large hiatal hernia and a high symptom burden. Laparoscopic approaches are equally effective as open surgical fundoplication, but almost one-third of post reflux surgery patients may eventually require anti-reflux medications. Refractory or difficult to treat GERD may occur due to insufficient acid inhibition, poor compliance, non-acid reflux and/or visceral hypersensitivity and presents a challenge to the clinician. Options include switching the PPI, addition of medications such as Baclofen and surgical intervention for appropriately selected patients.

**Further Reading**

1 El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastroesophageal reflux disease: a systematic review. *Gut* 2014;63:871–80.

2. Rosemurgy A, Paul H, Madison L, et al. A single institution’s experience and journey with over 1000 laparoscopic fundoplications for gastroesophageal reflux disease. *Am Surg* 2012;78:917–25.

3. Fass R. Therapeutic options for refractory gastro-esophageal reflux disease. *J Gastroenterol Hepatol* 2012; 27:3–7.

4. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol* 2007;102:668–85.

5. Prakash Gyawali, Peter J Kahrilas, Edoardo Savarino, et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018;67:1351–62.

6. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–28.

7. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017;29:1–15.

8. Zaheer Nabi, D Nageshwar Reddy. Endoscopic management of gastroesophageal reflux disease: revisited. *Clin Endosc* 2016;49:408–16.

9. Rouphael C, Padival R, Sanaka MR, et al. *Curr Treat Options Gastroenterol* 2018;16:58–71.

**Chapter 40.**

**Peptic Ulcer Disease**

**Introduction**

Peptic ulcer diseases (PUD), gastric ulcer and duodenal ulcer are defects in the gastric or duodenal mucosa that extend through the muscularis mucosa. Peptic ulcers were thought to be caused by a variety of factors such as smoking, stress and non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin. Therapy was directed primarily against lowering acid production in the stomach to permit healing of ulcerations. However, the discovery and characterization of intragastric infection by Warren and Marshall’s seminal paper in 1983, called *Helicobacter pylori* (*H. pylori*) has revolutionized our concepts of pathogenesis and ulcer therapy. *H. pylori* infection and NSAID use account for most cases of PUD. The incidence of duodenal ulcers has been decreasing over the past 3–4 decades. Although the rate of simple gastric ulcer is in decline, the incidence of complicated gastric ulcer and hospitalization has remained stable, partly due to the concomitant use of aspirin and other NSAID in an aging population.

**Aetiology**

Peptic ulcer disease may be due to any of the following:

1. *H. pylori* infection

2. Drugs

3. Lifestyle factors

4. Severe physiologic stress

5. Hypersecretory states (uncommon)

6. Genetic factors

***H. pylori* infection**

*H. pylori* infection remains an important cause of duodenal and gastric ulcers. The association of *H. pylori* with duodenal ulcer is strong and consistent; it is not specific, as *H. pylori* is also found in many patients without ulcer disease.

**Drugs**

NSAID use is a common cause of PUD. These drugs disrupt the mucosal permeability barrier, rendering the mucosa vulnerable to injury. As many as 30% of adults taking NSAIDs develop GI adverse effects. Factors associated with an increased risk of duodenal ulcers in the setting of NSAID use include advanced age, female sex, history of previous PUD, high doses or combinations of NSAIDs, long-term NSAID use, concomitant use of anticoagulants and severe comorbid illnesses. Most evidence now supports the assertion that *H. pylori* and NSAIDs are synergistic with respect to the development of PUD. Corticosteroids alone do not increase the risk for PUD.

**Lifestyle Factors**

Tobacco use is a risk factor for duodenal ulcers is not conclusive. Support for a pathogenic role for smoking comes from the finding that smoking may accelerate gastric emptying and decrease pancreatic bicarbonate production. Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis, but its association in PUD is incon-clusive.

**Severe Physiologic Stress**

Stressful conditions include burns, CNS trauma, surgery and severe medical illness may cause PUD. Serious systemic illness, sepsis, hypotension, respiratory failure and multiple traumatic injuries increase the risk for secondary (stress) ulceration. Cushing ulcers are associated with a brain tumour or injury and typically are single, deep ulcers that are prone to perforation. Extensive burns are associated with Curling ulcers.

**Hypersecretory States**

The following are among hypersecretory states that may, uncommonly, cause PUD:

1. Gastrinoma (Zollinger-Ellison syndrome) or multiple endocrine neoplasia type I (MEN-I)

2. Antral G cell hyperplasia

3. Systemic mastocytosis

4. Basophilic leukaemias

5. Cystic fibrosis

6. Short bowel syndrome

7. Hyperparathyroidism

**Genetics**

More than 20% of patients have a family history of duodenal ulcers, compared with only 5–10% in the control groups. In addition, weak associations have been observed between duodenal ulcers and blood type O. Furthermore, patients who

do not secrete ABO antigens in their saliva and gastric juices are known to be at higher risk.

**Clinical Features**

Epigastric pain is the most common symptom of both gastric and duodenal ulcers. It is characterized by a gnawing or burning sensation and occurs after meals – classically, shortly after meals with gastric ulcer and 2–3 hrs afterward with duodenal ulcer. Food or antacids relieve the pain of duodenal ulcers but provide minimal relief of gastric ulcer pain. Duodenal ulcer pain often awakens the patient at night. About 50–80% of patients with duodenal ulcers experience nightly pain, as opposed to only 30–40% of patients with gastric ulcers and 20–40% of patients with nonulcer dyspepsia (NUD). Pain with radiation to the back is suggestive of a posterior penetrating gastric ulcer complicated by pancreatitis.

Alarm features that warrant urgent gastroenterology referral are bleeding or anaemia, early satiety, unexplained weight loss, progressive dysphagia, recurrent vomiting and family history of GI cancer. In uncomplicated PUD, the clinical findings are few and nonspecific and include epigastric tenderness or sometimes right upper quadrant tenderness.

**Investigations**

**Routine Biochemistry**

Routine biochemistry is usually normal in uncomplicated PUD.

**Upper GI Endoscopy**

Upper GI endoscopy is highly sensitive for the diagnosis of gastric and duodenal ulcers, allows for biopsies and cytologic brushings in the setting of a gastric ulcer to differentiate a benign ulcer from a malignant lesion, and allows for the detection of *H. pylori* infection with antral biopsies for a rapid urease test and/or histopathology in patients with PUD.

Gastric ulcers appear as discrete mucosal lesions with a punched-out smooth ulcer base, which often is filled with whitish fibrinoid exudate. Ulcers tend to be solitary and well circumscribed and usually are 0.5–2.5 cm in diameter. Most gastric ulcers tend to occur at the junction of the fundus and antrum, along the lesser curvature. Benign ulcers tend to have a smooth, regular, rounded edge with a flat smooth base and surrounding mucosa that shows radiating folds. Malignant ulcers usually have irregular heaped-up or overhanging margins. The ulcerated mass often protrudes into the lumen, and the folds surrounding the ulcer crater are often nodular and irregular.

More than 95% of duodenal ulcers are found in the first part of the duodenum; most are less than 1 cm in diameter.

Duodenal ulcers are characterized by the presence of a well-demarcated break in the mucosa that may extend into the muscularis propria of the duodenum.

Endoscopic biopsy from the gastric ulceration is very important to confirm the neoplastic nature of the ulcer. Single biopsy offers 70% accuracy in diagnosing gastric cancer, but 7 biopsy samples obtained from the base and ulcer margins increase the sensitivity to 99%.

**Barium Study**

An upper GI series is not as sensitive as endoscopy for establishing a diagnosis of small ulcers (<0.5 cm). It also does not allow for obtaining a biopsy. Thus, barium study is replaced by upper GI endoscopy.

***H. pylori* Testing**

*H. pylori* test in is mandatory in all patients with peptic ulcers. Invasive tests needs upper GI endoscopy include a rapid urease test, histopathology and culture. Rapid urease tests are considered the endoscopic diagnostic test of choice. The presence of *H. pylori* in gastric mucosal biopsy specimens is detected by testing for the bacterial product urease.

Non-invasive tests includes urea breath test, fecal antigen test and antibody assessment (immunoglobulin G [IgG]).

*In rapid urease test (RUT),* one or more gastric biopsy specimens are placed in the rapid urease test kit. If *H. pylori* are present, bacterial urease converts urea to ammonia, which changes the pH, resulting in a colour change.

Several non-invasive tests like urea breath tests, stool antigen test and serological tests. Urea breath tests (UBT) detect active *H. pylori* infection by testing for the enzymatic activity of bacterial urease. In the presence of urease produced by *H. pylori,* labelled carbon dioxide (heavy isotope, carbon-13, or radioactive isotope, carbon-14) is produced in the stomach, absorbed into the bloodstream, diffused into the lungs and exhaled.

**Serum Gastrin Level**

A fasting serum gastrin level should be obtained in certain cases to screen for Zollinger-Ellison syndrome. Patient needs to discontinue the proton pump inhibitor at least for 5 days before fasting serum gastrin level. Certain conditions need measurement of serum gastrin level:

1. Patients with multiple ulcers

2. Post bulbar ulcer

3. Strong family history of PUD

4. Peptic ulcer associated with diarrhoea, steatorrhoea or weight loss

5. Peptic ulcer not associated with *H. pylori* infection or NSAID use

6. Peptic ulcer associated with hypercalcaemia or renal stones

7. Ulcer refractory to medical therapy

8. Ulcer recurring after surgery

**Complications**

1. Ulcer healing lead to fibrosis causing stricture formation

2. Perforation

3. Bleeding

4. *H. pylori* infection is associated with gastric lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma.

5. Malignancy should be strongly considered in the case of a persistent non-healing gastric ulcer.

**Management**

Treatment of peptic ulcers varies depending on the cause and clinical presentation. Most patients with PUD are treated successfully with eradication of *H. pylori* infection and/or avoidance of NSAIDs, along with the appropriate use of proton pump inhibitor. Endoscopy is required to document healing of gastric ulcers and to rule out gastric cancer. This usually is performed 6–8 weeks after the initial diagnosis of PUD. Documentation of *H. pylori* cure with a non-invasive test, such as the urea breath test, is appropriate in patients with complicated ulcers.

**Acid Suppression**

Acid suppression is the general pharmacologic principle of medical management of uncomplicated and complicated mainly bleeding PUD. Concomitant *H. pylori* infection in the setting of bleeding peptic ulcers should be eradicated, as this lowers the rate of rebleeding.

Two classes of acid-suppressing medications currently in use are histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). Both classes are available in intravenous and oral preparations. Examples of H2RAs include ranitidine, cimetidine, famotidine, roxatidine and nizatidine. Examples of PPIs include omeprazole, panto-prazole, lansoprazole, esomeprazole and rabeprazole.

Details of acid suppression and endotherapy for bleeding PUD are described in Chapter 8 and 60, respectively.

***Helicobacter pylori* Infection**

Around half of the population in the world are infected with *H. pylori* infection. Majority are asymptomatic. The exact route of this bacterium’s transmission is unclear; oral–oral or fecal–oral route is proposed route of transmission. Once *H. pylori* colonized in the antrum and body of the stomach, it leads to many complications like gastritis, gastric ulcer, duodenal ulcer, dyspeptic symptoms, gastric cancer and

gastric mucosa-associated lymphoid tissue (MALT) B-cell

lymphoma. Ischaemic heart disease, neurodegenerative disease, iron-deficiency anaemia and thrombocytopenia are the non-gastric complications of *H. pylori* infection. Eradication of *H. pylori* significantly reduces the risk of gastric cancer development if given early (before the stage of gastric atrophy, intestinal metaplasia and dysplasia). “Test and treat” is the most important strategy in the management.

Bacterial virulence factors like cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are associated with gastric epithelial cell apoptosis and the development of severe gastric complications. Cag is an oncogenic protein and responsible for gastric cancer, whereas Vac is an endotoxin leads to host cell vacuolation and cell death. Urease, a potent virulence factor, promotes tumour growth and metastatic dissemination and plays important role in the progression of gastric cancer.

Non-invasiveness and high sensitivity of the urea breath test makes it the best approach for the screening of *H. pylori* infection. The Maastricht V/Florence consensus report recommended using non-invasive methods over endoscopic procedures for the diagnosis of *H. pylori* infection in patients with dyspeptic symptoms while the American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology suggested the use of upper gastrointestinal endoscopy in patients with dyspeptic symptoms above 60 yrs of age or with strong family history of gastric cancer.

As prevalence of *H. pylori* infection is varied, the treatment guidelines are also variable. The Kyoto global consensus report recommended screening for *H. pylori* gastritis after the age of 12 yrs and treatment for all positive cases even if they are asymptomatic. The Maastricht V/Florence consensus recommended the “test and treat” strategy for patients with dyspeptic symptoms.

Acid inhibition is the integral part of anti-*H. pylori* therapy. Various regimes are available in the literature according to geographical resistance pattern of antibiotics. Standard triple therapy (first-line therapy) with proton-pump inhibitor (PPI), amoxicillin and clarithromycin remains the most commonly prescribed *H. pylori* eradication regimen (only when clarithromycin resistance <15%). If clarithro-mycin resistance >15%, bismuth-based quadruple therapy or levofloxacin-based triple therapy for 10–14 days as first-line therapy. In most of the ASEAN countries, high metronidazole and clarithromycin resistance confers difficulty in achieving the goal of clarithromycin- and metronidazole-based therapy. Sequential therapy –consisting of PPI and amoxicillin for 5–7 days followed by PPI, clarithromycin and metronidazole for a further 5–7 days – is an option for first-line triple therapy. The urea breath test

should be performed following first-line therapy to assess the successful eradication.

Nonbismuth quadruple therapy, also termed “con-comitant,” has been proposed as an alternative to the sequential therapy that is less confusing for the patient and more likely to facilitate compliance with therapy. It involves

using concurrently all three antibiotics with PPI usually for a period of 10–14 days. Hybrid therapy includes a combination of sequential and concomitant therapy. It consists of a standard 14-day sequential regimen but with the amoxicillin continued for the entire period, turning out to be a “concomitant” therapy for the last 7 days. Eradication rate of bismuth-based therapy is around 97% when given for 14 days but it drops to 81% if the duration of therapy reduced to 10 days. Ecabet sodium is another antiulcer drug that has been proposed as an alternative to bismuth. Eradication rate is similar with bismuth and ecabet regimen. Current European Guidelines suggest that rescue therapy be based on antimicrobial susceptibility testing after obtaining biopsy specimens for culture. Rifaximin or rifabutin may be included in rescue therapy. Role of probiotics in the eradication of *H. pylori* infection has received some momentum, but still needs more literature clarification.

**Further Reading**

1. Ramakrishnan K, Salinas RC. Peptic ulcer disease. *Am Fam Physician* 2007;76:1005–12.

2. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102:1808–25.

3. Boparai V, Rajagopalan J, Triadafilopoulos G. Guide to the use of proton pump inhibitors in adult patients. *Drugs* 2008;68:925–47.

4. Malfertheiner P, Megraud F, O’Morain CA, et al. Management of *Helicobacter pylori* infection – the Maastricht IV/Florence Consensus Report. *Gut* 2012;61:646–64.

5. Zullo A, Hassan C, Ridola L, De Francesco V, et al. Standard triple and sequential therapies for *Helicobacter pylori* eradication: an update. *Eur J Intern Med* 2013;24:16–9.

6. Zamani M, Ebrahimtabar F, Zamani V, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2018; 47:868–76.

7. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 2017;153:420–9.

8. Malfertheiner P, Megraud F, O’Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017;66:6–30.

9. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015;64:1353–67.

10. Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 2017;112:212–39.

11. Mahachai V, Vilaichone RK, Pittayanon R, et al. *Helico-bacter pylori* management in ASEAN: the Bangkok consensus report. *J Gastroenterol Hepatol* 2018;33:37–56.

**Chapter 41.**

**Gallstone Disease**

**Introduction**

Gallstone-related conditions are among the most common gastrointestinal disorders requiring hospitalization. Prevalence varies widely among ethnic groups, varying from 30 to 38% in American Indians, Chileans and Swedes to almost nil to under 5% in Bantus and Masai tribe of Africa. In the Western world, the prevalence in general is about 10% whereas that in northern India it is 4–6%. Gallstones are more prevalent in females across all ages and ethnic groups. Cholesterol stones account for 75% of gallstones in Western countries, whereas pigment or bilirubinate stones predominate in Africa and Asia.

**AEtiology and pathogenesis**

Gallstones are divided into two categories: cholesterol stones and pigment stones. Cholesterol stones are predominantly composed of cholesterol monohydrate with small amounts of calcium salts and glycoproteins. Pigmented biliary tract stones are subclassified into black and brown stones based on differences in chemical composition and associated clinical features. Both are composed of calcium bilirubinate. Black stones contain polymers of bilirubinate, whereas brown stones contain monomers of bilirubinate as well as cholesterol and fatty acid salts. Black pigment stones can be caused by chronic haemolysis; brown pigment stones typically develop in obstructed and infected bile ducts. Alpha-glucuronides from infecting bacteria and, to a lesser extent, from biliary mucosal sources deconjugates bilirubin glucuronides.

**Risk Factors and Conditions Associated with Gallstone Formation**

**Cholesterol Stones**

1. Age

2. Female sex

3. Oestrogens

4. Pregnancy

5. Diabetes mellitus

6. Obesity

7. Hypertriglyceridemia

8. Prolonged fasting

9. Rapid weight loss or obesity surgery

10. Ileal disease or resection

**Black Pigment Stones**

1. Chronic haemolysis

2. Cirrhosis of the liver

3. High-protein diet

**Brown Pigment Stones**

1. Biliary infections

2. Foreign bodies (e.g., sutures)

3. Low-protein diet

**Clinical Features**

Gallbladder stones remain asymptomatic in 80% of patients; however, in the remaining they may present with a wide spectrum of clinical presentations, including recurrent biliary colic, acute cholecystitis and chronic cholecystitis. Passage of a gallstone through the common bile duct may lead to acute cholangitis or acute pancreatitis.

**Biliary Colic**

Biliary colic is a visceral pain, which is steady rather than intermittent, usually in the epigastrium and right upper quadrant, increases over a period of 15 min to 1 hr and then remains at plateau for 1 hr or more, and then slowly resolving within 6 hrs. During attacks of biliary colic, patients are restless and may have associated diaphoresis and vomiting. The interval between attacks is highly variable and may be days to years. There is no convincing evidence that ingesting fatty foods precipitates an attack of biliary colic.

**Acute Cholecystitis**

When a biliary colic attack lasts longer than 6 hrs or if localized right upper quadrant tenderness and fever develop, the diagnosis of acute cholecystitis should be entertained. A Murphy sign, the abrupt cessation in inspiration in response to pain on palpation of the right upper quadrant, is a classic finding observed in 60–70% of patients with acute cholecystitis. High fever, haemodynamic instability and peritoneal signs suggest gallbladder perforation, which is a complication in 10% of patients with acute cholecystitis. Ten percent to 15% of patients develop jaundice, which is a symptom that may be caused by gallstone obstruction of the common bile duct, or by Mirizzi’s syndrome, which is an obstruction of the common hepatic duct caused by oedema and inflammation at the origin of the cystic duct.

**Chronic Cholecystitis**

Repeated attacks of biliary pain or acute cholecystitis result in a thickened and fibrotic gallbladder.

**Laboratory Studies**

Most patients with acute cholecystitis exhibit leucocytosis with a left shift. They may also have elevations in amino-transferases, alkaline phosphatase, bilirubin or amylase caused by choledocholithiasis or cystic duct oedema with resulting biliary obstruction. Patients with uncomplicated biliary colic usually have normal biochemical profiles.

**Imaging**

Ultrasound is highly sensitive and specific for diagnosing cholelithiasis. In uncomplicated biliary colic, gallstones may be the only finding. Thickening of the gallbladder wall is a nonspecific finding commonly observed in acute and chronic cholecystitis. Pericholecystic fluid and intramural gas are specific ultrasonography features of acute cholecystitis. Dilation of the intrahepatic or extrahepatic ducts suggests choledocholithiasis; however, ultrasound is insensitive for imaging common bile duct stones. Computed tomography (CT) may be beneficial in evaluating patients with complicated disease (e.g., perforation, gangrene or emphy-sematous gallbladder) as well as common bile duct stone. EUS is one of the excellent modality to evaluate bile duct stone. EUS may identify small stones missed on abdominal ultrasound. MRCP is highly sensitive to identify common bile duct stone.

**Natural History of Asymptomatic Gallstones**

Natural history of “silent” gallstones does not appear to justify treatment with prophylactic cholecystectomy. Most studies, conducted mainly in the 1980s, demonstrated that nearly 80% of patients remain asymptomatic throughout their lives, with only 1–4% progressing to symptoms or develop-ing complications from gallstones annually. Overall, patients developed symptoms or serious complications, such as acute cholecystitis, at a rate of 1–2% per year, with most patients developing symptoms within 5 yrs. The cumulative probability of developing severe complications was lower among patients with asymptomatic gallstones compared with those with mild symptoms after 5, 10, 15 and 20 yrs of follow-up (4 vs 5%, 5 vs 12%, 10 vs 15% and 16 vs 18%, respectively).

**Management**

Once symptoms occur, there is a high risk of recurrent attacks of pain and complications. Laparoscopic cholecystectomy is treatment of choice in patients with symptomatic gallstone disease. Laparoscopic cholecystectomy is favoured because there are fewer wound-related complications, shorter

hospital stays and more rapid recoveries. This may result in 2–3% incidence of bile duct injuries. Open cholecystectomy is preferred in extensive scarring from prior abdominal surgery exists, exploration of the common bile duct is planned, or visualization by laparoscopy is inadequate.

Most patients with truly asymptomatic gallstones are currently advised no surgical treatment. In patients who are morbidly obese or who have had a heart and lung transplant, complications of gallstone disease carry a high morbidity, and prophylactic cholecystectomy may be indicated. Prophylactic cholecystectomy in an asymptomatic diabetic patient with gallstones does not appear warranted.

Dissolution therapy with chenodeoxycholic acid or ursodeoxycholic acid should be reserved for patients who are at high risk of surgery. Small (<1.5 cm in diameter) non-calcified stones that float on oral cholecystography are suitable for dissolution. Candidate patients should demonstrate adequate gallbladder filling and emptying by oral cholecystography. Dissolution often requires longer than 6 months of therapy. Response rates range from 60 to 70%. There are frequent recurrences after therapy is discontinued.

Extracorporeal shock wave lithotripsy (EWSL) is 90% successful in achieving stone fragmentation and clearance of solitary, small, radiolucent stones, usually in combination with gallstone dissolution therapy in the form of cheno-deoxycholic acid or ursodeoxycholic acid but clearance may take months and recurrence is inevitable. Hence, EWSL is at present restricted to CBD stones only in those high surgical risk patients who cannot undergo interventions like endoscopic or surgical treatment (see below).

Most patients also require associated. It may take months of extracorporeal shock-wave lithotripsy to clear the gallbladder of stones, thus not advocated in management of gallstone disease.

**Diabetes and asymptomatic gallstone**

In the past, the management of diabetic patients with asymptomatic gallstones emphasized early cholecystectomy. The argument for prophylactic cholecystectomy was based on the assumption that these patients had diabetic autonomic neuropathy that masked the pain and signs associated with acute cholecystitis, and thus they presented with advanced disease and had more complications.

Landau and colleagues found diabetics to have higher rates of infected bile, gangrene, gallbladder perforation and surgical mortality than nondiabetics in the setting of acute cholecystitis (21 vs 9%). More recent evidence demon-strated that the prevalence and natural history of asymp-tomatic gallstones in diabetic patients are roughly the same as those reported for nondiabetic patients.

**Choledocholithiasis**

Most bile duct stones are cholesterol stones that have migrated from the gallbladder. Ten percent to 15% of patients who undergo cholecystectomy have concomitant bile duct stones, and 1–4% exhibit residual postoperative choledo-cholithiasis, even after the common bile duct is explored. Conversely, more than 80–90% of patients with choledoc-holithiasis have gallbladder stones. The prevalence of choledocholithiasis and intrahepatic stones is higher in Asian countries. These populations have higher incidences of pigment stones, which usually are formed de novo in the bile ducts.

**Risk Factors for Bile Duct Stones**

Most bile duct stones originate in the gallbladder, some stones form de novo in the bile ducts. Any process that increases the concentration of unconjugated bilirubin in bile or increases bile stasis leads to brown stone formation. Other potential risk factors include periampullary diverticula, ampullary stenosis and foreign material in the bile ducts.

The classic Charcot triad of right upper quadrant pain, fever and jaundice may be present in only 50–75% of patients with acute cholangitis. Ten percent of episodes are marked by a fulminant course with haemodynamic instability. Reynolds’s pentad refers to the constellation of the Charcot triad plus hypotension and confusion.

**Laboratory Studies**

Majority of patients demonstrate neutrophilic leucocytosis. Most symptomatic patients have hyperbilirubinemia; the bilirubin level is in the range of 2–14 mg/dL. Liver enzyme level shows moderate elevation of AST and ALT, whereas marked elevation in alkaline phosphatase and GGT.

**Imaging**

Helical CT has sensitivity and specificity of 80–85% in detecting bile duct stones. Endoscopic retrograde cholan-giopancreatography (ERCP) is the procedure of choice for evaluating patients with suspected choledocholithiasis. ERCP has the advantage of facilitating therapeutic sphincterotomy and stone extraction using either balloon or basket. Endoscopic ultrasound can detect 95% or more of common bile duct stones. The diagnostic accuracy of EUS and MRCP for the detection of CBDSs has been widely investigated (sensitivity 97% vs 90% and specificity 87% vs. 92 % for EUS and MRCP, respectively). Normal LFTs and ultrasonography indicate a low risk of CBDSs and no further revaluations are recommended, unless the patient continues to have symptoms that suggest CBDSs. Common bile duct stones (CBDs), even if asymptomatic, require therapy because of the high complication rate.

**Endoscopic Management of Bile Duct Stone**

The most recent meta-analysis of nine RCTs indicated that antibiotic prophylaxis could reduce bacteraemia and may prevent cholangitis and septicaemia in patients undergoing elective ERCP. A critical step to obtain successful stone extraction is to provide an adequate exit for the stones that are to be removed by endoscopic sphincterotomy alone, endoscopic papillary balloon dilation alone or a combination of both. The use of primary papillary balloon dilation without endoscopic sphincterotomy is considered mainly in patients with coagulopathy. The appropriate length of endoscopic sphincterotomy should be adjusted according to the papillary anatomy and stone size. Most bile duct stones measure 8–10 mm in diameter and can be extracted after sphinc-terotomy using standard accessories like the Dormia basket or the balloon with equal success. Endoscopic sphincterotomy with stone extraction has success rates of 80–90% in the treatment of CBDSs.

“Difficult” biliary stones are defined according to their diameter (> 1.5 cm), number, unusual shape (barrel-shaped), or location (intrahepatic, cystic duct) or because of anatomical factors (narrowing of the bile duct distal to the stone, sigmoid-shaped CBD, stone impaction, shorter length of the distal CBD or acute distal CBD angulations <135°). Multiple procedures and additional interventional techniques (large-balloon dilation, mechanical lithotripsy, cholan-gioscopy-assisted electrohydraulic/laser lithotripsy or ESWL) may be required to remove “difficult” CBDs. The use of endoscopic papillary large-balloon dilation (EPLBD) after endoscopic sphincterotomy has become widespread for the management of difficult CDBSs. Endoscopic sphincterotomy + EPLBD reduces the need for mechanical lithotripsy by about 30–50% in comparison with endoscopic sphincterotomy alone. Major adverse events are mainly pancreatitis, bleeding and perforation. EPLBD is performed with a dilation balloon diameter that ranges from 12 to 20 mm. The vast majority of studies have reported dilation duration of 10–180 sec from the disappearance of the waist.

Mechanical lithotripsy is the simplest available method of fragmenting CBDSs. It consists of entrapping the stone within a reinforced basket and then crushing it by closing the basket against a metal spiral sheath. Two techniques of mechanical lithotripsy are used: out of the scope (OTS) and through the scope (TTS). The OTS technique represents a “salvage” procedure to be performed when a standard basket engages a large stone and becomes impacted in the papilla, whereas the TTS technique is preferred in elective cases. Mechanical lithotripsy has been reported to be an effective and safe technique, but multiple sessions may be required. The reported success rates range between 76% and 91%. Stone impaction, stone size >30 mm and stone to CBD

diameter ratio >1 were significant predictors of mechanical lithotripsy failure. The most common and feared complications of mechanical lithotripsy are entrapment of the basket, a broken basket, a traction wire fracture, or a broken handle. These complications are usually treated by other types of lithotripsy (OTS, ESWL or cholangioscopy-assisted lithotripsy), sphincterotomy extension or stenting.

**Shock Wave Lithotripsy**

Extracorporeal shock wave lithotripsy (ESWL) uses electrohydraulic or electromagnetic energy to generate shock waves that then travel through the soft tissues of the body to fragment CBDSs. ESWL is a complex and technically demanding procedure. A nasobiliary drain is inserted to allow fluoroscopic identification and targeting of CBDSs and to perform continuous irrigation of the bile duct with saline during ESWL. In addition, multiple ESWL sessions and subsequent ERCP procedures to extract stone fragments are required. Ductal clearance rates of 70–90% have been reported with ESWL.

Intraductal shock wave lithotripsy represents an alternative method to fragment bile stones and allow their removal. There are two methods of generating shock waves in a fluid, using either a bipolar probe capable of generating a spark in the case of electrohydraulic lithotripsy (EHL) or a pulsed dye laser system in the case of laser lithotripsy. Both EHL and laser lithotripsy are preferably performed under direct visualization with cholangioscopic guidance. There are three major techniques for cholangioscopy: (i) a dual-operator dedicated mother – baby cholangioscopic (MBC) system; (ii) a single-operator catheter-based cholangioscopic system (SOC); and (iii) direct use of an ultraslim endoscope or slim gastroscope (direct peroral cholangioscopy [DPOC]).

**Stents and Nasobiliary Drains**

This is a good palliative measure in elderly and high-risk patients with non-extractable bile duct stones. A stent is placed in such a way that one limb is above the stone and the other in the duodenum. Double pigtail stents are often preferred although the straight 10 Fr stents placed into the intrahepatic ducts have been reported to be favorable. A nasobiliary tube can be placed temporarily if stones cannot be extracted endoscopically. This prevents stone impaction, allows drainage, allows repeated cholangiography assessment of the common bile duct and enables accurate focusing for ECSWL.

**Surgical Management**

The surgical treatment of CBDSs can be performed during both laparoscopic and open cholecystectomy. It offers the valuable opportunity to definitively treat patients with

combined cholecystolithiasis and choledocholithiasis in a one-stage procedure.

**Bile duct stone management in altered anatomy**

The endoscopic management of bile duct stones in patients with altered upper GI anatomy presents a significant challenge. Patients with Billroth II gastrectomy, the ‘upside-down’ (5 o’clock) orientation of the papilla is approached from the afferent limb. It requires a significant alteration in sphincterotomy technique. Successful outcomes can be achieved by using sphincterotomes that have been modified to alter the orientation of the cutting wire or by using conventional sphincterotomes that can be rotated. Roux-en-Y gastric bypass procedure is increasing in number due to bariatric surgery. Removal of CBDs is very challenging. Conventional per-oral retrograde approach using enteroscopes with either a single or double balloon, or a spiral overtube is used to reach the papilla. Procedure is very challenging in view of narrow working channel and long length of enteroscopes. Alternate way is to perform large gastrostomy through which a duodenoscope can be passed. Recently, EUS- guided placement of a self-expanding lumen-apposing metal stent has been described.

**Post-cholecystectomy Syndrome**

After cholecystectomy, 20–40% of patients experience abdominal discomfort and 2–10% have debilitating pain. Patients who do not have gallstones confirmed on surgical pathological examination are more likely to remain symp-tomatic after cholecystectomy. Most of these patients have functional abdominal pain, but a small percentage of patients with the post-cholecystectomy syndrome have symptoms originating from the biliary tract. Possible causes include retained common bile duct stones, postoperative bile duct strictures, biliary tumours and sphincter of Oddi (SO) dysfunction.

**Management of bile duct stone in pregnant women**

ERCP in pregnant women seems to be a relatively safe examination throughout the whole gestation. EUS and MRCP are highly accurate for the diagnosis of biliary obstruction; thus ERCP should only be performed for therapeutic purposes. With respect to the potential harm related to X-rays, keep radiation exposure as low as possible. ERCP is best carried out during the second trimester of pregnancy. Radiation should be avoided in first trimester (the phase of fetal organogenesis), and, in the third trimester (close topographic proximity of the fetus to the path of the X-rays).

There is various techniques o f non-radiation ERCP (NR-ERCP) like aspiration of bile through the cannulation catheter to confirm biliary cannulation, ultrasound guidance, peroral cholangioscopy, or a two-stage procedures consisting of first biliary stenting followed by stone extraction after parturition.

**Cholangitis**

Acute cholangitis is a morbid condition characterized by acute inflammation and infection in the bile duct. It usually occurs in association with obstruction of the biliary tree. The clinical severity can range from mild disease to a potentially life-threatening state accompanied by septic shock and multiorgan dysfunction. Because of the propensity for rapid deterioration among patients with untreated acute cholangitis, expeditious diagnosis and therapy are essential to good patient outcome. The recent publication of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis has brought an evidence-based approach to the definition, diagnosis and management of this condition. Failure of biliary drainage is a strong determinant of mortality, particularly in patients with severe cholangitis.

Mechanisms postulated to help maintain the normal sterility of the biliary tract include: (1) an intact sphincter of Oddi that prevents reflux of duodenal contents into the common bile duct, (2) unimpeded *efflux* of bile from the common bile duct, (3) the presence of immunoglobulin A in bile and (4) the bacteriostatic properties of bile salts. When one or more of these defenses is breached – or if a foreign body is present in the biliary tract, where it can serve as a nidus for infection – cholangitis may ensue. The presence of a foreign body such as a stone, fluke or stent provides a protective niche for bacteria such as *Escherichia coli,* which secrete -glucuronidase. This enzyme deconjugates bilirubin glucuronide and the resultant poorly soluble unconjugated bilirubin precipitates in bile, adding to the foreign body load and leading to brown pigment microstones. Eventually the stage of contamination may evolve to frank infection, and repeated bouts of such infection. In 1877, Jean Charcot described the hallmarks of acute cholangitis: fever, jaundice and right upper quadrant abdominal pain. All three features of this eponymous triad are present in only about 50% of patients with acute cholangitis (range in reports is from 15 to 75%). Jaundice is the most common symptom, present in 90% of patients, with fever and abdominal pain being less prevalent, present in 66%. Reynold’s pentad, described by Reynold and Dargon in 1959, denotes the presence of mental status derangements and hypotension, in addition to features of Charcot’s triad, and is suggestive of severe disease and systemic sepsis. It is present in only about 5% of patients.

Acute cholangitis is a clinical diagnosis that is based on the presence of the clinical features discussed earlier, together with supportive findings revealed by laboratory tests and radiographic studies. Because acute cholangitis can present without abdominal pain, particularly in elderly patients, absence of pain or of any of the individual symptoms and signs discussed earlier does not rule out this diagnosis.

Therapy for acute cholangitis consists of three main components: (a) *resuscitation,* (b) *antibiotics,* and (c) *biliary drainage (endoscopic, radiological or surgical).* Resuscitation with administration of intravenous fluids and correction of electrolyte abnormalities should be initiated without delay. Given that urgent interventional or surgical procedures are likely to be required, attention should be directed to identifying and correcting coagulopathies that may exist (e.g., those resulting from vitamin K deficiency or sepsis-induced thrombocytopenia). Vigilant monitoring to ensure adequacy of resuscitation and early recognition of clinical deterioration, such as shock or mental status abnormalities, is essential. High-risk patients with significant comorbidities are best monitored in a dedicated intensive care unit, where invasive monitoring and inotropic support can be instituted.

**Further Reading**

1. Attili AF, De Santis A, Capri R, et al. The natural history of gallstones: The GREPCO experience. The GREPCO Group. *Hepatology* 1995;21:655–60.

2. Tandon RK. Studies on pathogenesis of gallstones in India. *Ann Natl Acad Med Sci* (India) 1989;25:213–22.

3. Haldestam I, Enell EL, Kullman E, et al. Development of symptoms and complications in individuals with asymptomatic gallstones. *Br J Surg* 2004;91:734–8.

4. Moody FG, Amerson JR, Berci G, et al. Lithotripsy for bile duct stones. *Am J Surg* 1989;158:241–7.

5. Higuchi T, Kon Y. Endoscopic mechanical lithotripsy for the treatment of common bile duct stones: experience with the improved double sheath basket catheter. *Endoscopy* 1987;9:216–7.

6. Mayumi T, Okamoto K, Takada T, et al. Tokyo Guidelines 2018: updated Tokyo Guidelines for the management of acute cholangitis/acute cholecystitis. *J Hepato-biliary Pancreat Sci* 2018;25:96–100.

7. Earl Williams, Ian Beckingham, Ghassan El Sayed, et al. Updated guideline on the management of common bile duct stones (CBDS). *Gut* 2017;66:765–82.

8. Manes G, Paspatis G, Aabakken L, Anderloni A, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2019;51:472–91.

9. Testoni PA, Mariani A, Aabakken L, Arvanitakis M, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2016;48:657–83.

**Chapter 42.**

**Acute Pancreatitis**

**Introduction**

Acute pancreatitis (AP) is a disorder of varied presentations, aetiology, obscure pathogenesis and varied clinical outcomes. Keeping this mind, physicians have felt the need to device a classification system capable of providing uniformity in reporting and assisting the clinical management of these patients. In 1992 physicians around the world gathered and devised a classification called the Atlanta classification, which has recently been revised in 2012.

**aEtiology**

AP has multiple aetiological factors – gall stones (45%) and alcohol (35%) are statistically the most important causes.

The other causes have been briefly described below.

1. **Obstruction**: Obstruction can be caused by common bile duct stone. The gall stone migrates into the common bile duct (CBD) and obstructs the ampulla, which causes obstruction of the pancreatic duct (PD), which causes reflux of noxious bile into the PD causing infection and inflammation of the pancreas. Ampullary and pancreatic tumours are another cause of obstruction. Rarer causes include pancreas divisum, choledochocele and hypertensive sphincter of Oddi.

2. **Drugs and toxins**: Alcoholic pancreatitis is undoubtedly the commonest toxin causing debilitating disease. There is relaxation of the sphincter of Oddi, which results in reflux of the duodenal contents into the PD leading to spasm of the sphincter of Oddi. There is increased permeability of the PD and sudden release of large amounts of enzymes that are inappropriately activated. Alcohol increases the synthesis of digestive and lysosomal enzymes by pancreatic acinar cells. There is overstimulation of cholecystokinin with increased protein concentration in the pancreatic juices, which obstructs the small ductules and alcohol or any one of its metabolites directly injures acinar cells resulting in AP. Many other drugs have been implicated to cause AP but the drugs commonly used in clinical practice are azathioprine, metronidazole, estrogens, furosemide tetracycline and ranitidine.

3. **Metabolic**: Hypertriglyceridemia is a rare but a well-recognized cause of AP. A triglyceride level of more than 1000 mg/dL is needed to precipitate an attack of AP.

Hypercalcaemia from any cause may be associated with AP.

4. **Infections**: HIV and antiretroviral drugs are both associated with AP. These cause a direct toxic effect on the acinar cells of the pancreas. Other common infections like CMV, TB, mumps, rubella and hepatitis A & B can also precipitate AP.

5. **Trauma**: Posttraumatic AP due to blunt and penetrating injuries carries a high mortality. Iatrogenic pancreatitis resulting from endoscopic retrograde cholangio- pancreatography (ERCP, 2%) is a known entity and may at times pose a serious hazard.

6. Other uncommon causes include inherited conditions, vascular abnormalities like SLE and miscellaneous conditions like Reye’s syndrome, Crohn’s disease, post CABG and renal dialysis.

**Pathophysiology**

The pancreas secretes a number of digestive enzymes, which are secreted as inactive proenzymes or zymogens. When activated enzymes come in contact with tissues outside their usual milieu, they have the potential to produce inflammation, necrosis and cellular death. This is normally prevented by the storage of inactive pancreatic zymogens and enzyme activators in separate cytosol granules. Once the integrity of this protective compartmentalization is lost, autodigestion due to enzymatic activation occurs, initiating a self-perpetuating inflammatory reaction. Activated enzymes, which include proteases such as trypsin, chymotrypsin and elastase, can in turn activate proenzymes in the inflammatory and complement cascades. Lipase produces fat necrosis and liberates phospholipid remnants. Inflammation and necrosis is not confined to the pancreatic and peripancreatic area, but can occur in various organ systems, leading to multiple organ dysfunction and death. Sepsis frequently complicates necrotizing pancreatitis. Systemic toxicity is related to the release of several mediators, including arachidonic acid metabolites, interleukin-1 and other cytokines.

**Clinical features**

Clinical assessment is initially directed towards establishing a diagnosis and determining the severity and prognosis of acute pancreatitis. Further diagnostic evaluation is then necessary to identify the presence of pancreatic necrosis and

pancreatic and peripancreatic infection. The timing and nature of surgical intervention in some of these patients is indeed a matter of fine judgment based on clinical features, results of diagnostic tests and experience.

Abdominal pain and vomiting are invariably present. Unlike the pain of a perforated peptic ulcer, the severity of which is maximal almost from the start, the pain of acute pancreatitis often builds up to a crescendo over a matter of hours. The pain is classically initially felt in the upper abdomen. It is, however, often poorly localized, and may be felt all over the abdomen, as also in the back. Rarely, it is experienced more in the back than the abdomen also pain may be felt in the left hypochondriac region only which is associated with tail pancreatitis.

Low-grade fever is often present. Abdominal distension and tenderness on palpation are present, but guarding and rigidity denoting peritonitis, are late in developing and may be absent to start with. Localized ileus may cause gastric dilatation which worsens vomiting. Localized effect of inflammation on the distal transverse colon leads to distension of the loop of the transverse colon with the “colon cut off” sign on X-ray of the abdomen. Ecchymosis of the flanks (Grey-Turner’s sign), and of the umbilicus (Cullen’s sign), have been described, but are rarely observed. These signs reflect bleeding into the pancreatic bed or retroperitoneal space. Subcutaneous fat necrosis may be appreciated as erythematous skin nodules on the abdominal wall, buttocks, scalp and over joints. Xanthomas may be seen with hypertriglyceridemia.

Disorientation, drowsiness and coma may be present due to toxic effects of pancreatic enzymes or with hypoxemia and/or hypotension. Tetany due to hypocalcaemia is rarely seen. Sudden loss of vision can occur due to blockage of the retinal artery. Fundus examination may show haemorrhages (Purtscher’s retinopathy) and cotton wool deposits around the macular and optic space. Polyarteritis and thrombophlebitis are rare manifestations.

Some physical findings point to a specific cause of AP-hepatomegaly, spider angioma and thickening of palmar sheaths favour alcoholic pancreatitis. Parotid pain and swelling is feature of mumps. Band keratopathy occurs in hypercalcaemia. All patients with severe pancreatitis show circulatory changes of hypovolaemia, characterized by tachycardia, hypotension, cold peripheries and a falling urine output. Hypovolaemia is due to transudation of fluid into the retroperitoneal space, peripancreatic and extra-pancreatic tissues, to sequestration of fluid in the ileum and to ascites. In fact, the diagnosis of acute pancreatitis should be always considered in any patient with abdominal pain and a compromised circulation. Peripancreatic fluid collections occur in up to 50% of patients. Pseudocysts are better defined

collections of fluid within the lesser sac, and occur in 10–15% of patients. Pseudocysts can compress the stomach and duodenum. Pseudocysts can leak into the peritoneal cavity or track into the retroperitoneal space, pleural cavity or even rarely into the pericardial space. Necrosis of a part of the inflamed pancreas is termed as acute necrotizing pancreatitis. If volume replacement has been adequate, necrotizing pancreatitis is characterized by clinical features of the systemic inflammatory response syndrome and is associated with a hyperdynamic circulation, tachycardia, tachypnea, hypotension and fever.

Initial studies suggest that SIRS can reliably predict the severity of pancreatitis and has the added advantage that it can be applied easily at the bedside every day. In one validation study, mortality rates were 25, 8 and 0 percent in those with persistent SIRS from admission, SIRS at admission but not persistent, and no SIRS, respectively. When SIRS is present and persistent, there is an increased risk that the pancreatitis will be complicated by persistent organ failure, and the patient should be treated as if he has severe acute pancreatitis. Pulmonary complications are an intrinsic feature of almost every patient with severe necrotizing pancreatitis. Tachypnea is invariably present. Hypoxia may occur without significant changes in an X-ray of the chest. Raised diaphragms, basal atelectasis are commonly observed. Pleural effusions (usually left sided) are frequent.

**Diagnosis**

The diagnosis of acute pancreatitis requires two of the following three features:

I. Abdominal pain consistent with acute pancreatitis.

II. Serum amylase or lipase activity at least three times greater than the upper limit of normal.

III. Characteristic findings on contrast enhanced computed tomography (CECT) or transabdominal sonography.

**Pancreatic Enzymes**

1. **Serum amylase** – The pancreas accounts for 40–45% of serum amylase, hence in pancreatic disease increase in serum pancreatic [P] isoamylase is specific and sensitive in cases of AP in comparison to other serum markers. However, the total serum amylase is most frequently ordered to diagnose AP as it is cheap easily available.

It rises in the first few hours of the disease and remains elevated up to day 5 in uncomplicated cases.

2. **Serum lipase** – The sensitivity of lipase for the diagnosis of AP is similar to that of serum amylase and is between 85% and 100%. Serum lipase always is elevated on the first day of the illness and remains elevated longer than serum amylase.

Other pancreatic enzymes include phospholipase A, trypsin, carboxylester lipase, carboxypeptidase A, co-lipase elastase, ribonuclease and phospholipase A2. None or alone in combination are better than serum amylase and serum lipase. These are also not routinely available. Another potential marker of AP is trypsinogen activation peptide (TAP). This is a 5-amino acid peptide that is cleaved from trypsinogen to produce active trypsin. As activation of trypsin is the early event in AP, TAP may be useful in detection of early AP. Elevated urine TAP also may predict severity of AP.

Some other non-specific markers are C-reactive protein, neutrophil elastase, complement levels, tumour necrosis factor and interlukin-6. These are markers of inflammation and necrosis and may predict severity and outcome of the disease.

**Hemoconcentration** – AP results in significant third space losses, resulting in hemoconcentration and a high haematocrit. Studies evaluating the haematocrit as a predictor of the severity of AP have produced variable results. The discrepancies may be due to differences in values chosen as a cutoff and the time that they were obtained. Despite these differences, it appears that a normal or low haematocrit at admission and during the first 24 hrs is generally associated with a milder clinical course.

Multiple other serum markers have been studied for predicting the severity pancreatitis including: urinary trypsinogen activation peptide (TAP), procalcitonin, polymorphonuclear elastase, pancreatic-associated protein, amylase, lipase, serum glucose, serum calcium, procarbo-xypeptidase-B, carboxypeptidase B activation peptide, serum trypsinogen-2,phospholipase A-2, serum amyloid protein-A, substance P, antithrombin III, platelet activating factor, interleukins 1, 6 and 8, tumour necrosis factor- or soluble tumour necrosis factor receptor and various genetic polymorphisms. Tests for most of these markers are not widely available and their test characteristics are incompletely understood. Exceptions are a dipstick test for procalcitonin, an ELISA test for urine TAP and a test for urine anionic trypsinogen, which are likely to become commercially available. IL-6, 8, 1, all have a sensitivity and specificity around 74–90% within the first few hours of the illness.

Interleukin-1 (IL-1) has a positive predicted value (PPV) of around 88% for necrosis. Procalcitonin is the most rapid general acute phase reactant. In a validation study, the procalcitonin strip test had an accuracy of 86% for predic-ting severe AP. TAP is cleaved from the amino-terminal end of trypsinogen when trypsin is activated. TAP is the most studied activation peptide in AP. A European multicentre study found a sensitivity of 58% and specificity of 73% with urinary TAP within 24 hrs of symptom onset.

**Radiological diagnosis**

1. ***Chest radiographs*** – A pleural effusion and/or pulmonary infiltrates during the first 24 hrs may be associated with necrosis and organ failure.

2. ***CT scan abdomen*** – A CT scan is probably the most frequently used radiological investigation when severe AP is suspected **(Table 42.1)**. It is used to look for pancreatic necrosis and extrapancreatic inflammation. Intravenous contrast-enhanced CT distinguishes between oedematous and necrotizing pancreatitis. CT is more accurate than ultrasonography for the diagnosis of severe pancreatic necrosis (90 vs 73% in one report). After assessment of the patient, a contrast-enhanced CT scan is indicated in patients who are deteriorating or have severe pancreatitis determined clinically and by the APACHE II score. A CT scan is not required on the first day unless there are other diagnoses being considered. A retrospective analysis of the performance of several CT scoring systems for the severity of acute pancreatitis found that none were statistically superior to the APACHE II or BISAP scoring systems In addition, it takes time for pancreatic necrosis to develop, and treatment is unlikely to be altered on the basis of CT findings on day 1.

**Point (A)**

A. Normal pancreas 0

B. Pancreatic enlargement 1

C. Pancreatic or peripancreatic fat inflammation 2

D. Single peripancreatic fluid collection 3

E. 2 fluid collections and/or retroperitoneal air 4

Degree of pancreatic necrosis based on contrast CT findings

**Points (B)**

A. No pancreatic necrosis 0

B. Up to 30% of the gland 2

C. 30–50% of the gland 4

D. >50% of the gland 6

**CT severity index (CTSI) A+B**

Mild pancreatitis 0–2

Moderate pancreatitis 3–6

Severe pancreatitis 7–10

3. ***MRI and MRCP*** – Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are being used increasingly to diagnose AP and to assess its severity. MRI appears to be comparable to CT, if not better, in providing precise information regarding the severity of the disease. MRI is as effective as CT in demonstrating the presence and extent of pancreatic necrosis and fluid collections, and is probably superior for indicating the suitability of such collections for nonsurgical drainage. MRI/MRCP is helpful prior to

ERCP in delineating the anatomy and detecting low CBD stones. It is also helpful in cases of pancreas divisum.

MRI can characterize the “pancreatic necrosis” seen on CT as necrotic pancreatic parenchyma, peripancreatic necrotic fluid collections or haemorrhagic foci. A study found that MRI was reliable for staging the severity of AP and predicting prognosis with fewer contraindications than CT. MRI can also detect pancreatic duct disruption, which can sometimes occur early in the course of AP.

**Scoring Systems to Assess Severity of Disease**

There are various scores use to assess severity of AP. A simplified scoring system known as the Bedside Index of Severity in Acute Pancreatitis (BISAP, **Table 42.2**) was developed based on data from 177 U.S hospitals and more than 17,000 cases of acute pancreatitis.

n BUN >25 mg/dL

n Impaired mental status (Glasgow Coma Scale Score <15)

n SIRS - SIRS is defined as

Two or more of the following:

- Temperature of <36 or >38°C

- Respiratory rate >20 breaths/min or PaCO2 <32 mmHg

- Pulse >90 beats/min

- WBC <4000 or >12,000 cells/mm3

n Age >60 yrs

n Pleural effusion detected on imaging

The above score is to be calculated within 24 hrs. One point is given to each criterion. A score >3 calculated within 24 hrs of presentation denotes severe disease with increased risk of complications.

**Harmless Acute Pancreatitis Score**

The harmless acute pancreatitis score can typically be calculated within 30 min of admission and takes into account three parameters: lack of rebound tenderness or guarding, normal haematocrit and normal serum creatinine.

Presumably patients were considered likely to have a harmless course if none of the three parameters were present, though this was not clearly defined in the study.

**Ranson’s Criteria**

Score based on Ranson’s criteria is one of the earliest scoring systems for severity in AP. Ranson’s criteria consist of 11 parameters **(Table 42.3)**. Five of the factors are assessed at admission and six are assessed during the next 48 hrs, later modification for biliary pancreatitis included only 10 points. Mortality increases with an increasing score. Using the 11 components, mortality was 0–3% when the score was <3, 11–15% when the score was 3 and 40 percent when the score was 6. Although the system continues to be used,

a meta-analysis of 110 studies found that Ranson’s score was a poor predictor of severity of AP.

**0 hrs**

Age >55

White blood cell count >16,000/mm3

Blood glucose >200 mg/dL

(11.1 mmol/L)

Lactate dehydrogenase >350 U/L

Aspartate aminotransferase >250 U/L

(AST)

**48 hrs**

Haematocrit Fall by >10%

Blood urea nitrogen Increase by >5 mg/dL (1.8 mmol/L) despite fluids

Serum calcium <8 mg/dL (2 mmol/L)

pO2 <60 mmHg

Base deficit >4 MEq/L

Fluid sequestration >6000 mL

**AGA GUIDELINES**

The American Gastroenterological Association (AGA) has issued guidelines for assessing the severity of pancreatitis.

The AGA recommends:

1. Prediction of severe disease be performed using the APACHE III system (using a cutoff of 8).

2. Those with actual or predicted severe disease and those with other severe comorbid conditions should be considered for triage to an intensive care or intermediate medical care unit.

3. In patients with predicted severe disease (i.e., APACHE III score of 8) and those with evidence of organ failure during the initial 72 hrs, rapid-bolus CT should be performed after 72 hrs of illness to assess the degree of pancreatic necrosis. CT should be used selectively based on clinical features in patients who do not meet these criteria.

4. Laboratory tests can be used as an adjunct to clinical judgment and the APACHE III score. A serum C-reactive protein level of >150 mg/L at 48 hrs is preferred.

**Revised definitions of morphological features in AP**

1. **Interstitial oedematous pancreatitis**

n Acute inflammation of the pancreatic parenchyma and peri-pancreatic tissues, but without recognizable tissue necrosis.

n Pancreatic parenchyma enhancement by intravenous contrast agent.

n No findings of peripancreatic necrosis.

2. **Necrotising pancreatitis**

n Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.

n Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or presence of findings of peripancreatic necrosis (see below - ANC and WON).

3. **Acute peripancreatic fluid collection (APFC)**

n Peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripan-creatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial oedematous pancreatitis and without the features of a pseudocyst. -Occurs in the setting of interstitial oedematous pancreatitis.

n Homogeneous collection with fluid density.

n Confined by normal peripancreatic fascial planes.

n No definable wall encapsulating the collection adjacent to the pancreas (no intrapancreatic extension).

4. **Pancreatic pseudocyst**

n An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis to mature. Well circumscribed, usually round or oval.

n Homogeneous fluid density; No non-liquid component. Well-defined wall, completely encapsulated.

n Maturation usually requires >4 weeks after onset of acute pancreatitis.

5. **Acute necrotic collection (ANC)**

n A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peri-pancreatic tissues. Occurs only in the setting of acute necrotizing pancreatitis.

n Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course).

n No definable wall encapsulating the collection.

n Location – intrapancreatic and/or extrapancreatic.

6. **WON (walled-off necrosis)**

n A mature, encapsulated collection of pancreatic and/or peri-pancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotizing pancreatitis.

n Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous).

n Well-defined wall, that is, completely encapsulated.

n Location – intrapancreatic and/or extrapancreatic.

n Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis.

**Grades of severity**

**Mild Acute Pancreatitis**

1. No organ failure

2. No local or systemic complications

3. Mortality rare

**Moderately Severe Acute Pancreatitis**

1. Organ failure that resolves within 48 hrs (transient organ failure) and/or local or systemic complications without persistent organ failure.

2. Mortality is far less than severe acute pancreatitis.

**Severe Acute Pancreatitis**

1. Persistent organ failure (>48 hrs)

2. Single organ failure

3. Multiple organ failure

4. Mortality is extremely high especially if there is infected necrosis

**Management**

Management includes:

1. Careful monitoring of the patient

2. Relief of pain

3. Correction of haemodynamic defects - Chiefly correction of volume depletion and electrolyte abnormalities. It is essential to maintain adequate oxygen transport and tissue perfusion to important organ systems during the period of acute illness, and during resolution of the inflammatory process within the pancreas.

4. Correction of metabolic abnormalities.

5. Control of pancreatic enzyme secretion as far as possible.

6. Support to all other organ systems, particularly the respiratory and renal systems.

7. Nutritional support.

8. Use of antibiotics.

9. Treatment of local complications arising from acute pancreatitis.

1. **Careful monitoring of the patient**: In critically ill patients, full haemodynamic monitoring is of great value, and should include heart rate, arterial blood pressure, ECG, central venous pressure and hourly urine output. In patients with large volume deficits or in those who are haemodynamically unstable, or have sepsis or pulmonary complications, a central line may be necessary.

Frequent examination of the CBC, blood chemistry and serum electrolytes are necessary to detect complications, to evaluate the function of various organ systems and to judge the adequacy of treatment. ABG may be helpful in those patients who have respiratory complications. Serial ultrasounds and CT scans are of great importance in evaluating retroperitoneal complications.

2. **Relief of pain**: Pain can be excruciating in the early phase. Tramadol 100 mg intravenously is preferred to morphine. Buprenorphine 150 g diluted in 10–20 mL of normal saline and given slowly 8 hourly via an epidural catheter, is also effective in relieving pancreatic pain but chances of hypotension is high. Epidural analgesia has shown to reduce respiratory complications.

3. **Fluid and electrolyte restitution and correction of haemodynamic defects**: Volume replacement is of crucial importance. Acute severe pancreatitis is in effect of a massive retroperitoneal burn with an ongoing loss of fluid into the retroperitoneum, peritoneal cavity and into the gut. Volume requirements vary. In severe cases, it may be >8–10 L within a period of 24 hrs. The adequacy of fluid replacement in severe cases should be judged carefully and clinically, and by monitoring the central venous pressure.

The latter should be kept between 12 and 15 mmHg. Fluids used for volume replacement include both colloids and isotonic crystalloids.

Potassium replacement is also invariably necessary. Blood transfusions may be necessary to counter retroperitoneal haemorrhage produced by proteolytic enzyme extravasation. Hypoalbuminemia when present should be treated by intravenous infusions of albumin. Successful fluid resuscitation should result in warm peripheries, a good pulse volume, a normal arterial blood pressure, a good urine output and an improved mixed venous oxygen tension (PvO2).

If the patient is still hypotensive despite adequate fluid replacement, inotropic support is mandatory. Dopamine 10–15 ìg/kg/min in a slow intravenous infusion, offers good cardiovascular support. Dobutamine may be preferred to dopamine in patients who are already vasoconstricted. Both these drugs can be used for inotropic support. It is important to maximise oxygen delivery or transport, in the hope that perfusion improves and oxygen uptake and

oxygen utilization by tissues are increased. Evaluation of organ perfusion is difficult. Perfusion of tissues may be inadequate even in the presence of a normal arterial blood pressure. A low PvO2 (<35 mmHg) and/or the presence of lactic acid acidosis, are additional pointers to hypoperfusion.

4. **Correction of metabolic abnormalities**: Metabolic acidosis, hyperglycaemia, hypocalcaemia and hypomag-nesaemia must be recognized and treated. Restoration of fluid volume, arterial blood pressure and perfusion, generally suffice to correct the metabolic acidosis.

5. **Control of pancreatic enzyme secretion**: There is no definite way of reducing pancreatic enzyme secretion in acute pancreatitis. Nasogastric suction is advisable in severe cases; it is absolutely indicated in the presence of ileus and continuous vomiting. It decreases the risk of aspiration, and may perhaps help in reducing pancreatic secretions. We also routinely use a proton pump inhibitor intravenously to help reduce gastric acid secretion. This decreases the chances of bleeding from acute erosions, and may perhaps also help to reduce pancreatic secretions. Somatostatin in an intravenous bolus dose of 500 g, followed by an infusion of 250 g over 4 hrs, has also been shown to suppress pancreatic secretion. However, its high cost precludes its use for many patients in our part of the world.

6. **Support to other organ systems**

***Respiratory Support***

Patients with severe tachypnea with a respiratory rate > 30/min, or who have a PaO2 <60 mmHg despite getting oxygen at 6–8 L/min through nasal prongs or a face mask, need to be intubated and kept on ventilator support. Mechanical ventilation ensures a high PaO2 and maximum oxygen saturation of arterial blood. The evolution of acute lung injury and ARDS requires expert care till such time as the complication resolves.

***Renal Support***

Renal function may deteriorate despite adequate hemodynamic resuscitation. A low-dose dopamine infusion to enhance urine output is recommended in those with a low urine output. In patients with increasing azotemia, temporary haemodialysis or haemofiltration should be carried out till renal function returns.

7. **Nutritional support**

All oral feeds or nutrients are stopped in severe pancreatitis as pancreatic exocrine secretion is stimulated by intragastric and intraduodenal stimuli. The first priority is the restitution of fluid and electrolyte loss and restoration of haemodynamic stability. Once this is achieved patients are started on nutritional support. The recent

trend is to use total enteral nutrition (TEN) through a naso-jejunal tube. It is suggested that early use of the gut maintains mucosal integrity and prevents translocation of intestinal bacteria into the pancreatic bed, thereby reducing the incidence of pancreatic infection, an important cause of morbidity and mortality in this disease.

Enteral nutrition may be impossible in the presence of fulminating disease associated with vomiting, distension, ileus, peritonitis and severe sepsis. In these patients, nutritional support with caloric intake outlined above should be given by total parenteral nutrition. Intravenous lipid emulsions are not harmful in patients with severe pancreatitis. Nosocomial sepsis through central catheter-related infections are a grave potential danger in patients on parenteral nutrition.

Vitamins, minerals, calcium, magnesium, antioxidants also need to be given for nutritional support.

Criteria for starting oral feeds are: (i) absence of abdominal pain; (ii) reduction of amylase and lipase to normal levels; (iii) absence of complications like pancreatic fistulas; (iv) resolution of ileus with return of bowel sounds.

8. **Antibiotics**: A gram-negative infection in and around the retroperitoneal necrotic pancreatic area, invariably supervenes in patients with fulminant pancreatitis. In our protocol, we use a third-generation cephalosporin, metronidazole and either ciprofloxacin or an aminoglycosides from the very start of the illness. Imepenam or meropenam are antibiotics with a good penetration within pancreatic tissue and are often used in combination with metronidazole.

9. **Critical care management of complications of pancreatitis**

The complications that should be anticipated are: (a) pancreatic necrosis; (b) infected necrosis, pancreatic abscess and peripancreatic suppuration; (c) pseudocyst formation. Rarer complications include (d) enteric fistulae and (e) catastrophic bleeds.

**Pancreatic Necrosis**

Patchy devitalization with necrosis of the pancreatic gland occurs from within a few days to a few weeks of the onset of acute inflammation. The clinical picture is one of persistent low-grade fever, abdominal pain and leukocytosis. The diagnosis is made on a CT scan, which shows local areas of non-enhancement. It may be impossible to determine whether the necrotic area is infected for not. Therefore a CT-guided needle aspiration with microbiological examination of the aspirate is mandatory. The growth of aerobic and/or anaerobic organisms signifies infection. A negative culture, however, does not always exclude the presence of infection in a

necrotic area. Surgery should not be done if the patient has only a low-grade fever, the CT findings are not suggestive of an infected necrosis or abscess, and if a CT-guided aspiration of the necrotic is sterile.

**Infected Pancreatic and Peripancreatic Necrosis, Pancreatic Abscess**

Contamination of the necrotic pancreas by bacteria (presumably from the transverse colon) leads to infected pancreatic necrosis. Liquefaction of the necrotic areas produces an abscess, which can be generally made out on a CT scan. CT-guided needle aspiration is positive for bacteria on gram’s stain and/or a culture. The clinical course in patients with retroperitoneal sepsis can be rapidly downhill, with spiking fever, leukocytosis, tachycardia and tachypnea.

***Surgical Debridement of Infected Pancreatic Necrosis***

The mortality in patients from infected pancreatic necrosis is 15–40%. Death in the majority of these patients is due to fulminant sepsis with progressive multiple organ dysfunction syndrome. Surgery in fulminant necrotizing pancreatitis should be reserved only for pancreatic sepsis. Persistent gall stone pancreatitis can be effectively dealt with by endoscopic sphincterotomy and is no longer an indication for surgery.

Currently, experience of several surgeons in the field of pancreatic surgery has led to the following guidelines for surgical debridement in pancreatic sepsis.

1. Surgery should not be performed within the first 7 days of the onset of fulminating pancreatitis – death is almost inevitable.

2. The longer the surgery is delayed the less the surgical mortality. Those operated upon within 15 days of the onset of pancreatitis suffer over twice the mortality compared to those operated on later. Of late, placement of wide-bore percutaneous drainage for pancreatic suppuration thereby delaying surgery to around 28 days is being advocated. Antibiotics, nutritional support and support to all organ systems is mandatory during this period.

3. Rapidly progressive MODS with features of severe sepsis may, however, force the surgeon to an earlier intervention. The details of surgical procedures are beyond the scope of this book.

**Pancreatic Pseudocyst**

Fluid collections within and around the lesser sac are easily picked up by ultrasound and CT examinations of the abdomen. When sufficiently large, these collections can be palpated per abdomen. Diagnosis of a pancreatic pseudocyst does not necessitate treatment unless the cyst is infected, bleeds or ruptures into the peritoneal cavity or bowel. Repeated percutaneous aspirations of the pseudocyst may,

however, be necessary. Definitive surgery, even for a large pseudo-cyst, should be delayed preferably for at least 6 weeks, by which time the patient is stable, and the cyst wall thick enough to allow anastomosis between the cyst and the gut (Chapter 33).

**Enteric Fistulae**

These occur during the phase of severe retroperitoneal inflammation associated with fulminant pancreatitis. The retroperitoneal inflammation can cause thrombosis of vessels supplying the gut; the middle colic vessels supplying the transverse colon are particularly vulnerable. Necrosis of the colonic wall leads to colonic fistula. Gastric, duodenal and small bowel perforation and fistulae can also occur. Awareness of a possibility of enteric fistulae as a major hazard of acute pancreatitis allows a quicker diagnosis and planned surgical treatment.

**Catastrophic Bleeding**

Severe bleeding occurs when pancreatic and peripancreatic inflammation destroys vessel walls within the retroperitoneal space or causes erosion of the splenic or other large vessels. Surgical control of bleeding may be virtually impossible in the midst of inflamed distorted tissue planes. Embolization of the vessels employing angiographic techniques to identify the bleeding vessels is the treatment of choice. Ischaemic necrosis of the transverse colon can also cause bleeds into the large bowel.

**Further Reading**

1. Adarsh Shah, Moustafa Mourad, Simon Bramhall**.** Acute pancreatitis: current perspectives on diagnosis and management. *J Inflamm Res* 2018;11:77–85.

2. Whitcomb DC. Acute pancreatitis. *N Engl J Med* 2006; 354:2142–50.

3. Toouli J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. *J Gastroenterol Hepatol* 2002;17:515–39.

4. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. *World J Gastroenterol* 2009;15:1427–30.

5. Ahmed T Chatila, Mohammad Bilal, Praveen Guturu. Evaluation and management of acute pancreatitis. *World J Clin Cases* 2019;7:1006–20.

6. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. *Lancet* 2008;371:143–52.

7. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. *World J Gastroenterol* 2009;15:1427–30.

8. Seth D Crockett, Sachin Wani, Timothy Gardner. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology* 2018;154:1096–101.

**Chapter 43.**

**Hepatitis B**

**Introduction**

Hepatitis B virus (HBV) belongs to the family of hepadnaviruses. Hepatitis B virus is 50–100 times more infectious than the human immunodeficiency virus (HIV). The complete virion or Dane particle is 42 nm in diameter. It consists of an envelope composed of virus-encoded proteins and host-derived lipid components and a core particle consisting of the nucleocapsid protein, the viral genome and the polymerase protein.

The HBV genome is a circular partially double-stranded DNA of approximately 3200 base pairs in length. There are four open reading frames (ORFs) encoding the envelope (pre-S/S), core (precore/core), polymerase, and X protein. The pre-S/S ORF is divided into pre-S1, Pre-S2 and S regions that encode the large (L), middle (M) and small (S) envelope proteins, respectively. The precore/core ORF consists of two regions that encode a precore polypeptide, which is post-translationally modified into soluble proteins, the hepatitis B e antigen (HBeAg) and the core protein (HBcAg). The HBX protein has been implicated in hepatocarinogenesis.

The replication cycle of HBV begins with attachment of the virion onto the hepatocyte membrane through an entry receptor. Inside the hepatocyte nucleus, synthesis of the plus strand HBV DNA is completed and the viral genome is converted into a covalently closed circular DNA (cccDNA). The likelihood of spontaneous viral clearance in patients with chronic HBV infection is very low because of the presence of extrahepatic reservoirs of HBV, the integration of HBV DNA into the host genome, and the presence of an intracellular conversion pathway whereby newly replicated HBV DNA reenters the hepatocyte nuclei and is used to amplify covalently closed circular HBV DNA (cccDNA). This intracellular pathway enables the establishment of a pool of transcriptional templates in the hepatocyte without the need for multiple rounds of reinfection.

**Epidemiology**

HBV infection is a worldwide health problem. Globally, 257 million people are living with HBV infection (Hepatitis B surface antigen-positive). The lifetime risk of complications, including hepatocellular Carcinoma (HCC) and cirrhosis in chronic HBV patients is 15–40%. Every year, 1 million people die because of HBV-related liver failure, cirrhosis, and HCC.

The prevalence of HBV carriers varies from 0.1–2% in low prevalence areas (USA and Canada, Western Europe, Australia, and New Zealand) to 3–5% in intermediate prevalence areas (Mediterranean countries, Japan, Central Asia, Middle East, and Latin and South America) and 10–20% in high prevalence areas (Southeast Asia, China and sub-Saharan Africa). HBVs can survive outside the body for prolonged periods. The rate of progression from acute to chronic HBV infection is approximately 90% in the case of patients with a perinatally acquired infection, 20–50% in the case of patients with infections acquired between the age of 1 and 5 years, and less than 5% in the case of adults. Perinatal infection is the predominant mode of transmission in high prevalence areas. Horizontal transmission, particularly in early childhood, accounts for most cases of chronic HBV infection in intermediate prevalence areas, whereas transmission via unprotected sexual intercourse and intravenous drug use are the major routes of spread in low prevalence areas.

A total of 80–90% of infants and 30–50% of children infected during the first year of life and before the age of 6 yrs, respectively, develop chronic infections. About 2.7 million people with HBV infection are also infected with HIV. Similarly, 1.7–3.5 million patients with an HIV infection are co-infected with HBV. In addition, an estimated 5 to 10% of HBV patients are also co-infected by hepatitis delta virus (HDV).

**Clinical Features**

Infection with HBV has a wide spectrum of manifestations including subclinical hepatitis, anicteric hepatitis, icteric hepatitis and fulminant hepatitis during the acute phase; and asymptomatic carrier state, chronic hepatitis, cirrhosis and HCC during the chronic phase.

**Acute Hepatitis**

Approximately 70% of patients with acute HBV infection have subclinical or anicteric hepatitis, whereas 30% become icteric. Acute liver failure develops in approximately 0.1–0.5% of patients. The incubation period is 50–150 days. A serum sickness-like syndrome may develop during the prodromal period. This is followed by constitutional symptoms such as low-grade fever, malaise, anorexia, nausea and vomiting, and pain in the right upper quadrant of the abdomen or mid-epigastric pain. Jaundice usually appears as the constitutional symptoms begin to subside.

Prothrombin time, which reflects hepatic synthetic function, is the best indicator of prognosis. In patients who recover, normalization of aminotransferases usually occurs within 1–4 months, followed by normalization of bilirubin levels. Persistent HBsAg infection, which lasts for more than 6 months, indicates progression to chronic infection.

**Chronic Hepatitis**

Many patients are asymptomatic, while others may have non- specific symptoms such as fatigue and mild right upper quadrant discomfort. Physical examination may be normal or there may be stigmata of chronic liver disease.

**Extrahepatic Manifestations**

Extrahepatic manifestations occur in 10–20% of patients with chronic HBV infection. Approximately 10–50% of patients with polyarteritis nodosa are HBsAg-positive. Vasculitis associated with HBV may affect large-, medium- and small-sized vessels in multiple organs including cardiovascular, gastrointestinal, neurologic and dermatologic systems. The course is highly variable and the mortality rate is high.

Hepatitis B virus-related glomerulonephritis, most commonly membranous, glomerulonephritis, is more often found in children. Approximately 30–60% of children with HBV-related membranous glomerulonephritis undergo spontaneous remission. In adults, the course of HBV-related glomerulonephritis may be progressive and response to interferon is poor.

Other extrahepatic manifestations including essential mixed cryoglobulinemia and aplastic anemia have also been reported.

**Natural course of HBV infection**

The natural course of chronic HBV infection is determined by the interplay of viral replication and the host immune response, and it can be divided into five phases.

**Phase 1: HBeAg-positive Chronic HBV Infection (previously known as immune tolerant phase)**

In patients with perinatally acquired HBV infection, the initial phase is characterized by high levels of HBV replication. The patients are HBeAg-positive and show high levels of HBV DNA in the serum, normal alanine amino transferase (ALT) levels, and minimal changes on liver biopsy. A mild degree of liver injury despite high levels of HBV replication is believed to be due to immune tolerance to HBV. During the immune tolerant phase, which lasts one to three decades, the rate of spontaneous HBeAg clearance is very low. The cumulative rate of spontaneous HBeAg clearance is estimated to be approximately 2% during the

first 3 years and only 15% after 20 years of infection. In a majority of patients, because of the low risk of progression of liver disease and the poor response to the existing anti-viral agents, current guidelines do not recommend therapy but close monitoring of the patients by measuring the ALT

and HBV DNA levels once in every 3–6 months.

**Phase 2 HBeAg-positive Chronic Hepatitis HBV (previously known as immune clearance phase)**

In patients with HBV infection acquired in their childhood or in adult patients with HBV infection, the immune tolerant phase is short-lived or absent. This phase is characterized by the presence of HBeAg, high levels of serum HBV DNA, and active liver disease (elevated ALT and necorinflammation on liver biopsy). In patients with perinatally acquired HBV infection, transition from the immune tolerant to the immune clearance phase usually occurs during the second to the fourth decades of life. Most patients with HBV infection acquired during their childhood or adult patients with HBV infection are already in the immune clearance phase at presentation. During this phase, spontaneous HBeAg clearance occurs at an annual rate of 10–20%.

An important outcome of the immune clearance phase is HBeAg to anti-HBe seroconversion. The rates of spontaneous HBeAg seroconversion are higher in older patients and in patients with high ALT levels; further, these rates are higher in patients with HBV genotype B infection than in those with HBV genotype C infection.

**Phase 3 HBeAg-negative Chronic HBV Infection (previously known as inactive carrier phase)**

This phase is characterized by the absence of HBeAg, presence of anti-HBe, persistently normal ALT levels, and low or undetectable serum HBV DNA (usually < 103 IU/mL). Liver biopsy generally shows mild hepatitis and minimal fibrosis. The inactive carrier phase may persist indefinitely, in which case the prognosis is generally favourable. The annual rate of HBsAg clearance has been estimated to be 0.5–2%. HBsAg clearance is generally accompanied by undetectable serum HBV DNA, normalization of ALT, and improved liver histology. Some inactive carriers have reactivation of HBV replication later in life. Reactivation may occur spontaneously or as a result of immunosuppression.

**Phase 4 HBeAg-negative Chronic Hepatitis B (previously known as the reactivation phase)**

This phase is characterized by the absence of HBeAg, presence of anti-HBe, presence of HBV DNA in the serum, elevated ALT levels and chronic inflammation with or without fibrosis on biopsy. Patients in this phase are usually

older and have more advanced liver disease because this is a later phase in the course of chronic HBV infection.

Fluctuating course is the hallmark of this phase.

**Phase 5 HBsAg-negative (previously known as latent/occult hepatitis B virus infection)**

Occult HBV infection is defined as the detection of HBV DNA in persons who are HBsAg-negative. HBV DNA is more often detected in the liver than in the serum. Patients in the HBsAg-negative phase generally have excellent prognosis if HBsAg is lost before the development of advanced fibrosis or cirrhosis. However, if patients develop cirrhosis before the loss of HBsAg, these patients remain at risk of HCC and they should be carefully monitored.

**Diagnosis**

The diagnosis of hepatitis B depends on serologic assays for hepatitis B-associated antigens and antibodies followed by viral assay.

**Hepatitis B Surface Antigen and Antibody**

HBsAg is the hallmark of HBV infection. It is usually detectable 1–10 weeks after an acute exposure to HBV and approximately 2–6 weeks before the onset of clinical symptoms. Most patients who recover from acute hepatitis B clear HBsAg in 4–6 months. The presence of HBsAg in the serum for more than 6 months implies chronic infection.

Anti-HBs is a neutralizing antibody that confers protective immunity to in patients with HBV infection. Recovery from acute hepatitis B is indicated by the disappearance of HBsAg and the development of anti-HBs antibodies. Some patients are positive for both HBsAg and anti-HBs antibody. These patients should be considered as carriers because the anti-HBs antibodies are usually not capable of neutralizing the circulating virus.

**Hepatitis B Core Antigen and Antibody**

HBcAg is an intracellular antigen and is not detected in the serum. Immunoglobulin M (IgM) anti-HBc is the first antibody to develop during an acute HBV infection. It is usually detectable within 1 month after the appearance of HBsAg. The anti-HBc antibody is the only marker of HBV infection that is detectable during the window period between the disappearance of HBsAg and the detection of anti-HBs antibodies. The presence of IgM anti-HBc usually indicates a recent HBV infection.

Immunoglobulin G (IgG) anti-HBc antibodies (measured as total anti-HBc) are found in individuals who recover from hepatitis B. Isolated presence of anti-HBc antibodies in the absence of HBsAg and anti-HBs antibodies can be detected

in approximately 1% of blood donors in low prevalence

areas and in up to 20% of blood donors in endemic areas. This situation usually reflects recovery from acute hepatitis B or after loss of HBsAg at a late stage of chronic infection. Transmission of HBV infection has been reported in blood and organ donors with isolated anti-HBc.

**Hepatitis Be Antigen and Antibody**

HBeAg is a marker of HBV replication and infection. The presence of HBeAg is usually associated with the detection of HBV DNA in the serum and a high risk of transmission of infection. During acute HBV infection, HBeAg is rapidly cleared, before the disappearance of HBsAg. However, in patients with chronic HBV infection, HBeAg may persist for years to decades. Seroconversion from HBeAg to anti-HBe is usually associated with a decrease in serum HBV DNA to a low level and remission of liver disease. However, HBeAg-negative and anti-HBe-positive patients may continue to have active liver disease and moderate levels of HBV DNA in the serum.

**Serum HBV DNA assays**

Sensitive quantitative assays for determining the levels of HBV DNA in the serum have been developed to assess the level of HBV replication. The branched DNA (bDNA) assay can detect HBV DNA levels up to 2000 copies/mL. Polymerase chain reaction (PCR) assays are even more sensitive with detection limits of 50 copies/mL. In patients with acute hepatitis B, HBV DNA appears in the serum at an early stage and may precede the detection of HBsAg. In patients with HBeAg-positive chronic hepatitis, serum HBV DNA levels are usually much higher than 100,000 copies/mL (median level is 109). In patients with HBeAg-negative chronic hepatitis B, serum HBV DNA levels are usually lower (median level is 107). In inactive HBsAg carriers, serum HBV DNA levels are typically low (median 103). Measurement of the serum HBV DNA level is necessary for the diagnosis and to assess response to antiviral therapy.

**QUANTITATIVE HBsAg**

The desire to assess covalently closed circular DNA (cccDNA) inside hepatocytes led to development of reproducible, automated and standardized (IU/mL) assays to quantify HBsAg. Quantitative HBsAg (qHBsAg) reflects cccDNA and intrahepatic DNA levels; in addition, it measures HBsAg that arises from integrated DNA, thereby reducing its specificity as a biomarker for viral replication. The levels of HBsAg are generally higher in HBeAg-positive patients than HBeAg-negative patients. In HBeAg-negative patients, low levels of qHBsAg (<1000 IU/mL) and HBV DNA (<2000 IU/mL) suggest inactive chronic hepatitis B. For peg-interferon (IFN) treatment of HBeAg-positive patients,

qHBsAg helps predict response and provides a stopping rule.

A previous study showed that qHBsAg level <1500 IU/mL at week 12 resulted in a likelihood of 57% for HBeAg seroconversion and 18% for HBsAg loss. Treatment of More than >1 log reduction in qHBsAg, in HBeAg-negative patients on nucleos(t)ide analog (NA) therapy, is associated with an increased loss of HBsAg. Level of qHBsAg <100 IU/mL, after 3 years of consolidation therapy, is associated with sustainable response following discontinuation of NA.

**Testing for Viral Resistance**

Testing for viral resistance in treatment-naïve patients is not recommended. Resistance testing can be useful in patients with past treatment experience, those with persistent viremia on NA therapy, or those who experience virological breakthrough during treatment. Current assays typically required an HBV DNA level > 1000 IU/mL.

**Liver Histology**

Liver biopsy is seldom indicated in acute hepatitis B. Histologic changes include lobular disarray, acidophilic degeneration of hepatocytes, focal lobular necrosis, cholestasis and portal inflammation. Bridging necrosis may be present in patients with severe hepatitis. Liver biopsy is useful in assessing the severity of liver disease and in predicting the prognosis. The most common features include portal inflammation and periportal necrosis. Periportal necrosis may be severe, which causes disruption of the limiting plate (piecemeal necrosis or interface hepatitis). As the liver disease progresses, fibrosis, and eventually, cirrhosis develop. A third form of liver injury, chronic lobular hepatitis (CLH), which is characterized by spotty necrosis and inflammation within the lobules with mild portal inflammation, is seen during exacerbations of chronic hepatitis B. Liver biopsy should be considered in patients with persistent borderline normal or slightly elevated ALT levels, particularly in patients over the age of 40, who have been infected with HBV from a young age. Patients with moderate-to-severe inflammation (A3 or higher) and/or fibrosis (F2 or higher) can be candidates for antiviral therapy. Non-invasive methods like elastography are more accurate than serum fibrosis panels (e.g., aspartate aminotransferase (AST) to platelet ratio index or FIB-4) in predicting significant or advanced fibrosis, but overestimate fibrosis if necorinflammation is high or the levels of liver enzymes are elevated.

**Hepatitis B virus genotypes**

Hepatitis B virus can be classified into ten genotypes designated A to J. The geographic distribution of HBV genotypes is summarized in **Table 43.1**.

**HBV genotypes Distribution areas**

A Northwest Europe, North America,

Central Africa

B China, Japan, Indonesia, Vietnam

C China, Japan ,East Asia, Korea, Vietnam

D Mediterranean basin, Middle East, India

E Africa

F American natives

G United states, France

H Mexico, Latin America

I Vietnam, Laos

J Japan

Studies in Asia where genotypes B and C are predominant found that genotypes B is associated with HBeAg seroconversion at an earlier age, more sustained remission after seroconversion, less hepatic necrosis, a slower rate of progression to cirrhosis and a lower rate of HCC development compared with genotypes C. HBV genotype B is also associated with slower rate of progression to cirrhosis and HCC. HBV genotype may also affect the response to IFN therapy. Genotype A (vs B-D) is associated with significantly higher rates of HBeAg and HBsAg loss with IFN therapy. Genotype C or F is associated with higher incidence of HCC in Alaska populations.

**Screening for HCC**

The annual risk of HCC in patients with HBV infection is >0.2% per year. Thus, All HBsAg-positive patients with cirrhosis should be screened with US examination with or without AFP every 6 months. There is no strong evidence to recommend HCC surveillance in children except in children with cirrhosis or with a first-degree family member with HCC.

**Prognosis**

Morbidity and mortality in chronic hepatitis B are linked to evolution to cirrhosis or HCC. The 5-year cumulative incidence of hepatic decompensation is approximately 20%.

The 5-year probability of survival being approximately 80–86% in patients with compensated cirrhosis. Patients with decompensated cirrhosis have a poor prognosis (14–35% probability of survival at 5 years). The risk of HCC is highest for patients with cirrhosis and usually arises in the clinical setting of compensated cirrhosis which may be silent clinically. The annual incidence of HCC in HBV carrier ranges between 0.2% and 0.6%, but it reaches 2% when hepatic cirrhosis is established.

**Special Patient Groups**

***Paediatric Patients***

Infants infected perinatally are usually asymptomatic but have a high rate (90%) of progression to chronic infection. Infection with HBV has been estimated to account for 10–25% of all cases of patients with childhood acute hepatitis. The acute illness is usually mild. Recovery with HBsAg to anti-HBs seroconversion occurs in >80% of children infected after the age of 1 year. Children with perinatally acquired chronic HBV infection are usually asymptomatic with normal ALT values, despite high serum HBV DNA levels. In contrast, 15–30% of children with childhood acquired chronic HBV infection are symptomatic with elevated ALT levels and chronic hepatitis on liver biopsies. Progression of chronic hepatitis to cirrhosis is rare in children, but some studies have reported cases of childhood HCC.

***Alcoholic Patients***

Alcoholic patients with HBV infection have an accelerated liver damage and an increased risk of progression to cirrhosis and HCC. Antiviral treatment should be initiated according to the standard protocol.

**Co-infection with Hepatitis C Virus**

In HBV/HCV-coinfected patients, the viral activity responsible for liver disease can be determined by measuring HCV-RNA and HBV-DNA levels. If HCV RNA is detectable, treatment for HCV infection should be undertaken. If HBV DNA is detectable, treatment is determined by the levels of HBV DNA and ALT. Importantly, treatment of one virus may lead to changes in the activity of the other virus, and thus, monitoring during and after treatment is necessary to assess viral activity. Most patients who are chronically infected with both HCV and HBV have detectable serum HCV RNA levels but not HBV DNA levels, which indicate that HBV replication is suppressed by HCV.

**Co-infection with HIV**

All patients with HBV and HIV coinfection should be administered antiretroviral therapy (ARVT), regardless of CD4 count. The ARVT regimen should include 2 drugs

acting against HBV. Specifically, the backbone of the ARVT regimen should be tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine. TAF-emtricitabine–inclusive regimens require dose adjustment if creatinine clearance is <50 mL/min, and TDF-

emtricitabine–inclusive regimens are not recommended in patients with a creatinine clearance of <30 mL/min.

**Co-infection with Hepatitis Delta Virus**

Hepatitis delta virus (HDV) is a sub-viral agent that is

dependent for its life cycle on HBV. Transmission of HDV can occur either co-infection or superinfection with HBV infection, leads to severe complications. Hepatitis D is generally the dominant virus over hepatitis B. Pegylated interferon alpha therapy is currently best available treatment with 20% response.

**Pregnancy**

All pregnant women should be screened for HBsAg. Hepatitis B immunoglobulin (HBIG) and HBV vaccine should be administered to their newborns <12 hrs after delivery. A proportion of women (around 25%) have hepatitis flares with or without HBeAg seroconversion within the first months after delivery because of rapid decrease in cortisol level. Vaccination against HBV is both safe and efficacious during pregnancy. Chronic HBV infection does not usually affect the outcome of pregnancy unless the mother has cirrhosis or advanced liver disease. Women who meet standard indications for HBV therapy should be treated. Women without standard indications but who have HBV DNA >200,000 IU/mL in the second trimester should consider treatment to prevent mother-to-child transmission. TDF is safe and effective first-line treatment owing to its antiviral potency and concerns for resistance with the other antiviral agents. According to Association for the Study of Liver Diseases (AASLD) guidelines, antiviral therapy given for the prevention of mother-to-child transmission should be discontinued at the time of delivery or up to 4 weeks postpartum. Breastfeeding is not prohibited.

**Treatment**

The main goal of treatment of chronic hepatitis B is to prevent cirrhosis, hepatic decompensation and HCC. Parameters used to assess response include normalization of serum ALT levels, serum HBV DNA level, loss of HBeAg with or without detection of anti- HBe (for HBeAg-positive patients), loss of HBeAg and improvement in histopathological findings in the liver.

Currently, there are eight approved treatments for hepatitis B: standard and pegylated INF-, and six NUCs (Nucleoside/nucleotide analogue), namely lamivudine, adefovir, entecavir, telbivudine, TDF and TAF. Antiviral treatment suppresses but does not eradicate HBV; in the absence of loss of HBsAg, most patients require long-term treatment. Antiviral treatment can reverse liver fibrosis and decrease but not eliminate the risk of HCC. Head-to-head comparisons of some antiviral therapies fail to show superiority of one therapy over another in achieving risk reduction in liver-related complications. However, in recommending peg-IFN, tenofovir, and entecavir as

preferred therapies, the most important factor considered was the lack of development of resistance with long-term use.

IFNs are administered for predefined durations while NUCs are usually administered until a specific endpoint is achieved. HBeAg seroconversion frequently occurs a few

months after cessation of IFN treatment. Viral relapse is inevitable if NUCs are withdrawn before achieving the therapeutic endpoint. For HBeAg-positive patients, virus suppression can be sustained in 50–90% patients if NUC treatment is discontinued after HBeAg seroconversion is achieved and at least 6 months of consolidation therapy is administered. For HBeAg-negative patients, relapse is frequent even when HBV DNA levels have been suppressed to undetectable levels for more than a year.

**Interferon**

Interferons (INFs) are of two types, standard and pegylated. The attachment of polyethylene glycol to a protein (pegylation) reduces its renal clearance and decreases immunogenicity of the protein, which results in an increase in the half-life of the pegylated protein. Compared to NUC therapy, INF therapy has a finite duration of treatment, selection of resistant mutants is absent, and this therapy has a more durable response. However, some patients experience side effects with INF therapy. Furthermore, INFs cannot be used in patients with decompensated disease. The main role of INFs is in the treatment of young patients with well-compensated liver disease who do not wish to be on long-term treatment or are planning to be pregnant within the next two to three years. In addition, INF is an attractive option for patients with HBV genotype A infection. IFNs have antiviral, antiproliferative, and immunomodulatory effects. Standard IFN is administered as a subcutaneous injection. The recommended dose for an adult is 5MU daily or 10MU thrice weekly and for children is 6MU/m2 thrice weekly to a maximum of 10MU. In the era of PEG-INFs, it is not of much use. Dosage of PEG-INF-2a (pegylated with a branched 40 kD PEG chain) is 180 µg subcutaneously once a week for 48 weeks and dosage of PEG-INF-2b (pegylated with a branched 120 kD PEG chain) is 1.5 µg/kg per week for 48 weeks.

**Nucleoside Analogue**

**Lamivudine**

Lamivudine is cheaper than the other oral agents. It is safe during the pregnancy. While lamivudine shows a more rapid and potent viral suppression than adefovir, entecavir, telbivudine and tenofovir are superior to lamivudine in suppressing viral replication. The main disadvantage of lamivudine is the high rate of drug resistance. The most

common mutation affects the YMDD motif of the HBV DNA polymerase (methionine to valine or isoleucine M204V/I).

Genotypic resistance can be detected in 14–32% of HBeAg-positive patients after 1year of lamivudine treatment and increases with the duration of treatment to 60–70% after 5 yrs of treatment. The role of lamivudine in the care of HBV is diminishing with the availability of new therapies, which are associated with lower rates of drug resistance. Lamivudine may still have a role in patients with concomitant infection with HIV

**Adefovir**

Adefovir is used against lamivudine-resistant HBV and has a lower rate of drug resistance than lamivudine. However, virus suppression is slow at the approved dose and up to 25% of patients experience minimal or no viral suppression. Adefovir at high doses has been associated with nephrotoxicity. At the approved dose of 10 mg daily, a reversible increase in serum creatinine has been reported in 3–9% of patients after 4–5 years of treatment. Adefovir resistance was not detected after 1 year of treatment, but the rate of drug resistance has been reported to be as high as 29% after 5 years of treatment. With the approval of tenofovir, which is more potent, the role of adefovir is rapidly diminishing and is not currently recommended.

**Entecavir**

Entecavir has potent antiviral activity and a low rate of drug resistance. Entecavir has a more important role in the primary treatment of HBV than in patients with lamivudine-resistant HBV. In addition, entecavir can be used in patients with decompensated cirrhosis because of its potent antiviral activity and a low rate of drug resistance. Resistance to entecavir is rare among nucleoside-naïve patients (approximately 1% with up to 5 years of treatment). Resistance has been observed in up to 50% of lamivudine-resistant patients after 5 years of treatment.

**Telbivudine**

Telbivudine appears to have slightly more potent antiviral effects than with lamivudine and adefovir, but it selects for the same resistant mutants as lamivudine and is more expensive. Thus, its role in primary therapy is limited.

**Tenofovir**

Tenofovir (TDF) has more potent antiviral activity than adefovir and is effective in suppressing wild-type as well as lamivudine-resistant HBV. TDF may be used as first-line treatment in treatment-naive patients, and in patients with lamivudine, telbivudine or entecavir resistance, preferably as additional treatment in these patients. Preliminary data

indicate that resistance to tenofovir is rare after up to 8 years of treatment. In patients who have been previously exposed to lamivudine, TDF is a better drug than entecavir in patients previously exposed to NA.

**Tenofovir Alafenamide**

Tenofovir alafenamide (TAF), a new tenofovir prodrug, is as effective as TDF in the treatment of HBV infection with an improved renal and bone safety. Antiviral efficacy of 25 mg of TAF is equal to 300 mg of TDF. The active metabolites of TAF achieve 7.6 times higher intracellular concentration in peripheral blood mononuclear cells.

Entecavir, tenofovir, and TAF are potent HBV inhibitors with a high barrier to resistance. Thus, they can be effectively used as first-line monotherapy. All NAs except, TAF require dose adjustment in individuals with a creatinine clearance <50 mL/min.

Duration of therapy for NUCs-based therapy is variable and influenced by HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis and/or decomp-ensation. The period of consolidation therapy generally involves treatment of persistently normal ALT levels and undetectable serum HBV-DNA levels for at least 12 months. Currently, whether a longer duration of consolidation would further reduce rates of virological relapse remains to be clarified. Thus, an alternative approach involves treatment until clearance of HBsAg is confirmed. Patients in whom antiviral therapy is discontinued should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, seroconversion, and clinical decompensation.

**Indications for Treatment**

Patients should be considered for treatment when they have HBV DNA levels above 2000IU/mL serum ALT levels above the upper limit of normal (ULN), and liver disease assessed by liver biopsy(or non-invasive markers once validated in HBV-infected patients) showing moderate to severe active necorinflammation and/or at least moderate fibrosis using a standardized scoring system. In addition, indications for treatment include age, health status, family history of HCC or cirrhosis, and extrahepatic manifestations.

1. **Phase 1**: HBeAg-positive patients under 30 yrs of age with persistently normal ALT levels and a high HBV DNA level, without any evidence of liver disease and without a family history of HCC or cirrhosis do not require immediate liver biopsy or therapy. Follow-up at least every 3–6 months is mandatory. Liver biopsy or even therapy should be considered in such patients over 30 years of age and/or those with a family history of HCC or cirrhosis.

2. **Phase 3**: HBeAg-negative patients with persistently normal ALT levels(ALT determinations at least every 3

months for at least 1 year) and HBV DNA levels above 2000 but below 20, 000 IU/ml, without any evidence of liver disease, do not require immediate liver biopsy or

therapy.

3. **Phase 2 and Phase 4**: HBeAg-positive and HBeAg-negative patients with ALT levels twice the ULN and serum HBV DNA levels above 20,000 IU/ml for HBeAg-positive and >2000 IU/mL for HBeAg-negative individuals may start treatment even without a liver biopsy.

Patients with compensated cirrhosis and detectable HBV DNA in the serum must be considered for treatment even if ALT levels are normal.

Patients with decompensated cirrhosis and detectable HBV DNA in the serum require urgent antiviral treatment with NUCs. Significant clinical improvement can be associated with control of viral replication.

**Ideal End Points of Therapy**

In HBeAg-positive and HBeAg-negative patients, the ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs.

**Various Definitions**

n HBV reactivation: Loss of HBV immune control in HBsAg-positive, anti-HBc–positive or HBsAg-negative, anti-HBc–positive patients receiving immunosuppressive therapy for a concomitant medical condition; a rise in HBV DNA compared to baseline (or an absolute level of HBV DNA when a baseline is unavailable); and reverse seroconversion (seroreversion) from HBsAg negative to HBsAg positive for HBsAg-negative, anti-HBc-positive patients.

n HBeAg clearance: Loss of HBeAg in a person who was previously HBeAg positive

n HBeAg seroconversion: Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative.

n HBeAg seroreversion: Reappearance of HBeAg in a person who was previously HBeAg negative

n *Biochemical response* is defined as normalization of ALT levels.

n *Serological response* for *HBsAg* applies only to patients with HBeAg-positive CHB and is defined as HBeAg loss and seroconversion to anti-HBe.

n *Serological response for HBsAg* applies to all CHB patients and is defined as HBsAg loss and development on anti-HBs.

n *Histological response* is defined as decrease in necroinflammatory activity (by >2 points in HAI or Ishaks system) without worsening in fibrosis compared to pre-treatment histological findings.

n *Functional cure* is loss of HBsAg with acquisition of anti-HBs.

n *Completed cure* is like functional cure, but with the physical elimination of cccDNA.

n *Virological breakthrough* is defined as a 1-log10 (10-fold) increase in serum HBV DNA from nadir during treatment in a patient who had an initial virological response.

***Finite-duration treatment with PEG-IFN***: Most studies performed thus far indicate that patients be treated with peg-IFN for a duration of 48 weeks. The HBeAg seroconversion rates after a 48-week treatment were 20–31% and HBV-DNA suppression after discontinuation of treatment was <2000 IU/mL in 65% of persons who achieved HBeAg to anti-HBe seroconversion. The combination of peg-IFN and NAs has not yielded higher rates of serological or virological responses after treatment discontinuation and thus is not recommended.

***Finite-duration treatment with a NA***: Finite-duration treatment with a NAs is possible only with HBeAg-positive CHB infection. Treatment should be started with the most potent agent with the highest barrier to resistance (tenofovir or entecavir) to rapidly reduce levels of viraemia to undetectable levels and avoid breakthroughs due to HBV resistance. Once anti-HBe seroconversion occurs after administration of NAs, treatment should be prolonged for an additional 12 months; a sustained response (persistence of anti-HBe seroconversion) after treatment discontinuation can be expected in 40–80% of these patients.

***Long-term treatment with NAs***: This strategy is necessary for patients, who are not expected or fail to achieve a virological response after treatment discontinuation and require extended therapy, i.e., for HBeAg-positive patients who do not develop anti-HBe seroconversion and HBeAg-negative patients. In addition, long-term treatment with NAs is recommended in patients with cirrhosis irrespective of their HBeAg status or anti-HBe seroconversion after treatment. The most potent drugs with the low resistance profile, such as tenofovir, TAF, or entecavir, should be used as first-line monotherapy.

**Treatment Monitoring**

**Finite Therapy with PEG-IFN**

In patients treated with PEG-IFN, complete blood counts and serum ALT levels should be monitored monthly and TSH levels should be monitored every 3 months. All patients should be monitored for safety through 12 months of treatment. HBeAg and anti-HBe antibodies and serum HBV

DNA levels should be examined at 6 and 12 months during

treatment and at 6 and 12 months after treatment. Sustained anti-HBe seroconversion and normalization of ALT levels and serum HBV DNA levels below 2000 IU/mL after treatment discontinuation is the desired outcome. For HBeAg-negative patients, serum HBV DNA levels should be measured at 6 and 12 months during treatment and at 6 and 12 months after treatment. A sustained virological response with HBV DNA levels <2000 IU/mL after treatment discontinuation is the desired outcome. Quantitative HBsAg (qHBsAg) helps predict response and provides a stopping rule. A qHBsAg level <1,500 IU/mL at week 12 resulted in a 57% likelihood for HBeAg seroconversion and 18% for HBsAg clearance.

**Finite Treatment with NUCs in HBeAg-positive Patients**

HBeAg and anti-HBe antibodies should be examined every 6 months. HBV DNA levels should be measured using a sensitive PCR assay every 3–6 months during treatment. Suppression of HBV DNA to undetectable levels on real-time PCR and subsequent anti-HBe seroconversion is associated with biochemical and histological responses. HBsAg clearance is not observed frequently during or after treatment with NUCs.

**Long-term Therapy with NUCs**

NUCs are cleared by the kidneys, and appropriate dose adjustments are recommended for patients with creatinine clearance <50 mL/min. Therefore, the serum creatinine levels and estimated creatinine clearance should be examined in all patients before commencing treatment with NAs. High renal risk includes one or more of the following factors: decompensated cirrhosis, creatinine clearance < 60mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs and solid organ transplantation. The nephrotoxic potential seems to be higher for nucleotide analogues, particularly adefovir. The frequency of renal monitoring can be every 3 months during the first year and every 6 months. Closer renal monitoring is required in patients who develop creatinine clearance < 60mL/min or serum phosphate levels <2 mg/dL.

***Prediction of Response in HBeAg-positive Patients***

For HBeAg-positive patients, the likelihood of response to lamivudine, adefovir, telbivudine, entecavir, interferon and probably tenofovir depends on the degree of increase in the levels of serum aminotransferases. Typically, treatment with any of these drugs does not result in higher rates of HBeAg seroconversion than no treatment in those who have a serum ALT levels d”2 times the ULN.

***Prediction of Response in HBeAg-negative Patients***

For HBeAg-negative patients, prediction of response is less precise. Because of the need for long-term treatment, therapy is recommended only for those with persistent or intermittent elevation in ALT levels and/or substantial histological abnormalities (moderate/severe inflammation or bridging fibrosis/cirrhosis). Interferon, entecavir or tenofovir are generally preferred because long-term treatment with lamivudine or telbivudine is associated with diminishing response due to selection of drug-resistant mutants.

**Treatment Failure**

*1. Primary non-response*: Primary non-response is rarely observed with entecavir or tenofovir, telbivudine or lamivudine.

Primary non-response seems to be more frequent with adefovir (approximately 10–20%). In NA(s)-naive patients with primary non-response to adefovir, a rapid switch to tenofovir or entecavir is recommended.

*2. Partial virological response*: Partial virological response may be obtained with all available NAs. It is always important to check for compliance.

In patients receiving lamivudine or telbivudine with a partial virological response at week 24 or in patients receiving adefovir with a partial response at week 48, switching to a more potent drug (entecavir or tenofovir), preferentially the one not showing cross-resistance, is recommended.

The optimal management of patients with partial virological response using entecavir or tenofovir is currently debatable. Patients with declining serum HBV DNA levels may continue treatment with the same agent (entecavir or tenofovir) given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both these agents.

3. *Virological breakthrough*: Virological breakthrough in compliant patients is related to the development of HBV drug resistance. The rates of resistance at 5 yrs in NA-naive patients are <1.5% and 0% for entecavir and tenofovir, respectively; thus, virological breakthroughs in NA-naive patients receiving entecavir or tenofovir are usually because of poor drug compliance.

In case of resistance, an appropriate rescue therapy should be initiated with the most effective antiviral agent

that does not share cross-resistance to minimize the risk of inducing multiple drug-resistant strains.

In patients with resistance to lamivudine, most experts, based on the current evidence, suggest that switching to tenofovir is as effective as adding tenofovir to lamivudine. In patients with adefovir resistance, a switch to entecavir or tenofovir or tenofovir plus emtricitabine is an option.

The efficacy of tenofovir monotherapy has been reported to be suboptimal in patients with high serum HBV DNA levels because of virological breakthroughs associated with adefovir resistance. In patients with telbivudine resistance, a switch to or add-on tenofovir are the preferred options.

n *Lamivudine resistance*: Switch to tenofovir

n *Adefovir resistance*: Switch to entecavir or tenofovir. If the patient has previous lamivudine resistance, switch to tenofovir and add a NA.

n *Telbivudine resistance*: Switch to or add tenofovir

n *Entecavir resistance*: Switch to or add tenofovir

4. *Failed previous interferon therapy* – Patients who failed to respond to previous interferon therapy can be treated with lamivudine, adefovir, telbivudine, entecavir or tenofovir with the expectation of a response similar to that in treatment-naive patients. Because most patients require a long duration of treatment, entecavir or tenofovir is preferred.

**Pre-emptive Therapy Before Immunosuppressive Therapy or Chemotherapy**

Previous studies showed that HBV reactivation from anticancer therapies occurs in 41–53% of HBsAg-positive, anti-HBc-positive patients and in 8–18% of HBsAg-negative, anti-HBc–positive patients. All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc before the initiation of treatment. Vaccination of HBV-seronegative patients is highly recommended. Higher vaccine doses may be required to achieve anti-HBs response in immunocompromised patients. HBsAg-positive, anti-HBc-positive patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy. Serum ALT levels, HBV DNA levels and HBsAg levels should be carefully monitored in HBsAg-negative and anti-HBc-positive patients with the intent for on demand therapy, except for patients receiving anti-CD20 antibody therapy (e.g., rituximab) or in those undergoing stem cell transplantation for whom anti-HBV prophylaxis is recommended. Anti-HBV drugs with a high resistance barrier (entecavir, TDF or TAF) are preferred over low-barrier agents. Once started, anti-HBV prophylaxis should continue during immunosuppressive therapy and should last for at least 6 months (or for at least 12 months in patients receiving anti-CD20 therapies) after completion of immunosuppressive therapy.

The criteria for HBV reactivation include the following: (a) an increase in HBV DNA levels compared to baseline levels (or an absolute level of HBV DNA when a baseline is unavailable) and (b) reverse seroconversion (seroreversion) from HBsAg negative to HBsAg positive

for HBsAg-negative and anti-HBc–positive patients. Following HBV reactivation, a hepatitis flare demonstrated by ALT elevation can occur.

**Dialysis and Renal Transplant Patients**

Patients with renal disease should be screened for HBV infection. Although vaccine responsiveness is impaired, HBV seronegative patients should be vaccinated. Renal function should be monitored during antiviral treatment. Unexpected deterioration of renal function during antiviral treatment may necessitate a change of treatment or further changes in the dose. Hypertension and coexisting diabetes mellitus should be optimally controlled.

PEG-IFN should be avoided in patients undergoing a renal transplant because of the risk of rejection. Every HBsAg-positive patient who undergoes renal transplantation and receives immunosuppressive agents should receive anti-HBV prophylaxis with a NUC.

**Hepatitis B Immune Globulin (HBIG)**

Hepatitis B Immune globulin (HBIG) is a hyperimmune serum globulin with a high hepatitis b surface antibody titer. It is effective in preventing infection if given before or within hours of exposure. HBV vaccine should always be given with HBIG. HBIG is used to prevent HBV reinfection in patients who undergo liver transplantation for HBV-related liver disease, but its role has been greatly reduced with the use of potent NAs with high barriers to resistance. A single dose of HBIG (0.06 mL/kg or 5.0 mL for adults) should be given as soon as possible after exposure and within 24 hrs if possible.

**Hepatitis B vaccination**

There are two types of HBV vaccines, namely, plasma-derived and recombinant. Plasma vaccines have been largely replaced by recombinant vaccines because of concerns about the transmission of blood-borne infections. Recombinant vaccines may be derived from yeast or mammalian cells. HBV vaccines have an excellent safety record.

3-dose series (10 µg for an individual<10 years of age and 20 µg for person >10 years of age) at 0, 1 and 6 months intramuscular preferably in the deltoid region as injections given in the buttocks have resulted in lower seroconversion rates than expected.

1. A rapid schedule of day 0, 1 month and 2 months with an additional dose at 12 months, and a very rapid schedule of day 0, day 7 and day 21 with a booster dose at 12 months, has been proposed.

2. A protective immune response defined as anti-HBs titer> 10 mIU/mL is achieved in 90–95% of vaccine recipients, and 50–70% of non-responders respond to the second course of three doses of vaccine.

3. For patients on haemodialysis, use special formulations of the vaccine (40 µg/mL) or two 1 mL 20 µg doses given at one site. Dose schedule should be 0, 1, 2 and 6 months.

Double dose (40 µg) and four doses give a better seroprotection rate (73–92%) than that achieved with the conventional 3 dose schedule (45–67%). For hemodialysis patients, the need for booster doses should be assessed by annual testing for antibodies to hepatitis B surface antigen (anti-HBs). A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.

Sexual and household contact with persons infected with HBV who are negative for HBsAg and anti-HBs should receive HBV vaccination. Newborns of HBV-infected mothers should receive HBIG and HBV vaccine at delivery and complete the recommended vaccination series. Infants of HBsAg-positive mothers should undergo testing after vaccination at 9–15 months of age.

**Further Reading**

1. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016;63:261–83.

2. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva, Switzerland: World Health Organization; 2015.

3. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004;11:97–107.

4. Raimondo G, Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. *J Hepatol* 2007;46:160–70.

5. Ganem D, Prince AM. Hepatitis B virus infection-natural history and clinical consequences. *N Engl J Med* 2004; 350:1118–29.

6. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001;34:617–24.

7. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336:1106–10.

8. Bengsch B, Chang KM. Evolution in our understanding of hepatitis B virus virology and immunology. *Clin Liver Dis* 2016;20:629–44.

9. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007;45:1056–75.

10. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HL, Chan HL. The role of quantitative hepatitis B surface antigen revisited. *J Hepatol* 2017;66:398–411.

11. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358–80.

12. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014;11:209–19.

13. Miquel M, Nunez O, Trapero-Marugan M, Diaz-Sanchez A, Jimenez M, Arenas J, Canos AP. Efficacy and safety of entecavir

and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice. *Ann Hepatol* 2013;12:205–12.

14. Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. *Aliment Pharmacol Ther* 2012;35:674–89.

**Chapter 44.**

**Hepatitis C**

**Introduction**

Hepatitis C is an infection caused by an RNA virus referred to hepatitis C virus (HCV) that attacks the liver and leads to inflammation. HCV is a double stranded RNA virus belonging to the family Flaviviridae. Without treatment, most of the acute HCV infections progress to chronic hepatitis with variable progression to cirrhosis and HCC. Alcohol and the metabolic syndrome are the main cofactors influencing the progression to advanced liver disease and HCC. Each year, about a third of liver transplantations are performed because of complications associated with the HCV infection, like decompensated cirrhosis or HCC.

**Epidemiology**

The World Health Organization (WHO) estimates that about 3% of the world’s population has been infected with HCV and that there are more than 170 million who carry the virus as chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer. HCV is transmitted by parenteral contact with blood or blood products. Recognized routes of infection include transfusion of blood or blood products, injection drug use, needle stick or other forms of contaminated injury among healthcare workers, maternal-infant transmission and sexual spread. Maternal-infant transmission may occur if mother is seropositive with very high HCV RNA. This occurs in approximately 5% of infants, although the risk appears to be increased by the presence of co-infection with the human immunodeficiency virus (HIV) in the mother, presumably because the serum levels of HCV RNA are higher in mothers with HIV co-infection. The risk of acquiring HCV with needle stick injury appears very low. Sexual transmission of HCV has been well documented to occur but the exact frequency of this occurrence is not evident. There are seven genotypes (genotype 1–7) and numerous subtypes of HCV. Genotypes 1 and 3 are the most common cause of infections (46% and 30%, respectively). Genotypes 2, 4 and 6 are responsible for a total 22.8% of all cases; genotype 5 comprises the remaining <1%. Genotype 1 is more common in North America and Europe. Genotype 3 is more common in south Asia. Genotype 4 is common in Central Africa and Middle East, genotype 5 is in southern Africa. HCV subtypes – specifically 1a, 1b, 2a, and 3a – are widely distributed across the globe and account for a large proportion of HCV infections in high-income countries. These so-called “epidemic subtypes.” The identification of Genotype of virus is important for treatment and follow-up. HIV–HCV coinfection is important in the West.

**Transmission**

Major route for transmission for HCV is mainly percutaneous. But the exact pattern of how it happens varies from region to region in the world. IDU is the major source of infection in the affluent world, whereas blood and blood product related transmission still remains an important source in the developing countries, lacking stringent implementation of blood screening measures prior to transfusion. High-risk sexual behavior and maternal-fetal transmission has been implicated in nearly 5% of the patients; also coinfection of human immunodeficiency virus (HIV) type 1 leads to increased risk of transmission of HCV via both these routes.

**Pathogenesis**

HCV is thought to be a non-cytopathic virus and liver damage is probably immune mediated. Cytotoxic T lymphocytes (CTLs) are thought to be particularly important in pathogenesis as they recognized viral antigens on cell surfaces in conjunctions with major histocompatibility complex (MHC) class I proteins and lyses infected target cells. Progression of liver disease due to HCV is marked by progressive increases in hepatic fibrosis associated with activation of hepatic stellate cells, presumably through cytokine mediators produced as part of the immune response to HCV. In the natural history of disease it is the prolonged hepatocellular damage and subsequent fibrosis leading to clinical cirrhosis and liver cancer resulting in mortality.

**Clinical Features**

Most patients with either acute or chronic hepatitis C are asymptomatic. The vast majority of patients present clinically in chronic hepatitis and hence all discussion refers to chronic hepatitis C unless specified otherwise. Most symptoms if present are non-specific. In clinical practices some patients for the first time present as liver cancer.

**Generalized Symptoms**

The correlation of symptoms to hepatitis C is not established and clear. Most frequently seen are fatigue, sleep disturbances, nausea, diarrhea, myalgia, arthralgia, weakness and weight loss. Depression and anxiety are also common. HCV infection has also been shown to be associated with cognitive impairment.

**Extrahepatic manifestations**

Around 40% patients with hepatitis C have extrahepatic manifestations. These include:

1. Autoimmune disorders such as thyroiditis and presence of auto antibodies

2. Skin conditions such as porphyria cutanea tarda and lichen planus

3. Haematologic diseases like essential mixed cryoglobulinemia and lymphoma

4. Renal disease like membranoproliferative glomerulonephritis

5. Diabetes mellitus

**Natural course of HCV infection**

Majority of patients who get HCV do not clear the virus. Progression at a variable rate to chronic inflammation, fibrosis and hepatocellular carcinoma occurs. Risk of chronic infection is 50–85% **(Fig. 44.1)**. HCV because of its tendency to rapid mutation creates multiple populations in the same host and can escape immune detection.

**Host predictors of risk**

1. Interleukin – 28 B (IL 28 B) Gene favourable allele (C / C) is associated with higher rates of clearance as opposed

to unfavourable (T/ T allele). Whites are likelier to have the favourable allele than blacks.

2. Specific HLA – DRB 1 and DQB 1 alleles

3. Neutralising antibodies to HCV structural proteins.

4. Host neutralising responses to viral entry

5. HCV specific CD 4 response

6. White patients with low viral levels during acute infection are less prone to chronic illness.

7. Female sex: lesser chance to progression

8. Childhood infection: children are somewhat less prone.

9. Symptomatic acute infection may help to clear the infection.

**Risk of progression to cirrhosis**

The natural history of HCV is difficult to delineate because of long course and variability of individual responses

In a review, the prevalence of cirrhosis 20 years after infection was 16%. Progression to cirrhosis after development of advanced fibrosis is high and tends to be faster.

**HCC**

In the USA, HCV is responsible for one-third of HCC cases. The risk has been estimated to be 0–3% per year in those with cirrhosis. In contrast to hepatitis B, HCC occurs in HCV patients who progressed to cirrhosis.

**Survival**

Mortality is increased due to HCV. In 2007 it was 4.6 per 100,000 patients per year in USA. Most deaths occurred in age group of 45–65 years. Majority of deaths are attributable to liver causes and mortality increases with disease

progression. However, non-liver related causes like metabolic syndrome and diabetes also contribute to death.

**Factors associated with disease progression**

1. ***Liver histology***

It is the best predictor of future disease progression in HCV is baseline inflammation and fibrosis on biopsy as follows:

n Patients with mild inflammation and fibrosis had only 1–2% risk of progressing to cirrhosis.

n Patients with moderate chronic hepatitis had 4–6% risk of developing cirrhosis.

n Majority patients with severe inflammation and bridging fibrosis developed cirrhosis within 10 yrs.

n Moderate to severe steatosis on biopsy is associated with rapid progression of fibrosis.

n Stainable iron in hepatocytes predicts progression

2. ***Host factors***

n Demographic factors

- Gender: Male sex is associated with faster progression

- Age; acquisition of HCV after age 40–55 may be associated with more rapid progression while children have decreased risk.

- Race/ethnicity: Progression is slower in blacks compared to others

- Co morbidities:

i) HIV coinfected have accelerated rate of progress

ii) HBV infection leads to more severe liver disease

iii) Diabetes mellitus: Many studies have shown increased risk of fibrosis to cirrhosis in patients with DM and insulin resistance

iv) Obesity leads to steatosis and increased risk of fibrosis

v) Vitamin D deficiency. A vitamin D level of <10 ng/mL was associated with advanced with fibrosis

n Behavioural factors

- Alcohol use: Has a negative impact on cirrhosis risk

- Regular coffee consumption is associated with decreased rate of progression

- Daily marijuana use leads to more rapid fibrosis progression

- Dietary cholesterol has a negative impact while statin use has a positive impact

**Diagnosis**

Testing for chronic HCV infection is done in patients with elevated amino transferases or other clinical evidence of liver disease. Diagnosis of chronic HCV infection is made in patients with reactive HCV antibody and a positive molecular

test that detects the presence of HCV RNA. Presence of anti-HCV antibody is proof of infection (present or past) and must be complimented by detection of HCV RNA, its quantification and genomic testing. False negative test for antibody is seen in immunocompromised patients like hemodialysis, transplant recipients and HIV. In real time practice, anti-HCV positive and HCV RNA positive indicates active infection.

**Diagnostic tests**

**Standard Immuno Assay Testing**

Most labs detect anti-HCV antibodies in serum and plasma using an immune assay, which employs an enzymatic reaction (EIA or ELISA) or light emission (chemiluminiscence). Latest generation EIAs are very sensitive and specific and can detect antibodies as early as 8 weeks and generally by 2–6 months. Rapid immune assay tests are available for use on venous blood, finger stick blood, serum, plasma and oral fluid with accuracy similar to standard assays with results obtainable in 30 min. Recombinant immune blot assay (RIBA) has higher specificity. Anti-HCV positive patient should be tested with HCV RNA quantitative and genotype assessment. Anti-HCV antibody-positive, HCV RNA-negative individuals should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance. HCV core antigen in serum or plasma is a marker of HCV replication that can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable.

**RNA detection methods**

**Quantitative**

These are polymerase chain reaction (PCR); transcription mediated amplification (TMA) and branched DNA testing (bDNA). Real-time PCR methods detect upwards of 15 IU/mL. TMA can detect levels of 10 IU/mL. Branched DNA (bDNA) testing has a lower limit of 615 international units IU/mL.

**Qualitative**

These are used to detect low levels of HCVRNA and give results as positive or negative. They are used to confirm cure of the disease. Amplicor PCR assay and Versant TMA assay are examples.

**Genotype**

The genotype testing has practical utility of drug selection and predicting relapse and resistance. The HCV genotype and genotype 1 subtype (1a or 1b) must be assessed prior to treatment initiation to determine the choice of therapy and its duration, among other parameters. Treatment with new pangenotypic regimens can be initiated without knowledge

of the genotype and subtype in areas where genotype determination is not available. Testing for HCV resistance prior to treatment is not recommended.

**Treatment**

The treatment of hepatitis C has dramatically changed for the better in the last decade or so to the extent that it is now a curable disease. Cure is defined as sustained virological response or SVR when virus is undetectable 12 weeks after end of treatment. Treatment must be considered without delay in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; patients with clinically significant extra-hepatic manifestations. Fibrosis stage must be assessed by non-invasive methods (fibroscan, ARFI, FIB-4 or APRI) initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies. Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score >18–20 will benefit from transplantation first and antiviral treatment after transplantation, because the probability of significant improvement in liver function and delisting is low. However, patients with a MELD score <18–20 with a waiting time before transplantation expected to be more than 6 months can be treated for their HCV infection. In patients with advanced fibrosis (F3) or compensated cirrhosis (F4), Hcc surveillance is mandatory following SVR.

The first therapeutic agent was interferon injection which was given three times a week. It was supplanted by pegylated interferon or peg-interferon given weekly along with ribavirin. In 2011, the first direct acting antivirals (DAAs) were introduced- Boceprevir and Telaprevir. There is now a great shift in the treatment of all genotypes with the new directly acting antiviral drugs and now is the standard of care with cure rates close to 100%.

“Treatment-naive” patients is defined as patients who have never been treated for their HCV infection and ‘‘treatment-experienced‘” patients is defined as patients who were previously treated with pegylated IFN- and ribavirin; or pegylated IFN-, ribavirin and sofosbuvir; or sofosbuvir and ribavirin.

**Directly acting antivirals (DAA)**

Hepatitis C has many non-structural (NS) proteins which are targeted by drugs. They include NS3/NS4A complex protein, NS4B, NS5A which regulates replication and NS5B which is RNA- dependent RNA polymerase. Therefore the classes of drugs available are as follows:

1. NS3/NS4A inhibitors (protease Inhibitors, **previr**): Glecaprevir, Grazoprevir, Paritaprevir, Simeprevir, Voxilaprevir

2. NS5A inhibitors (**asvir**): Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, Pibrentasvir, Velpatasvir

3. NS5B inhibitors (Polymerase Inhibitors, **buvir**): Nucleot(s) ide inhibitors- sofosbuvir, non-nucleotide- Dasabuvir

*Evaluation for following conditions that might affect therapy*:

1. Renal function – Sofosbuvir has renal clearance

2. CBC and differential count

3. Concurrent alcohol and drug use

4. Extrahepatic manifestations of HCV

5. HIV co-infection

6. HBV/HDV co-infection

7. Presence of severe co-morbidity

8. Potential for drug interactions

9. Pregnancy test and contraception plan

10. Psychiatric history

11. Presence autoimmune disorders

12. Thyroid function, glucose, fundoscopy

**Precautions with Anti-HCV Agents**

***Direct-acting Antivirals***

1. Drug-drug interactions (DDI) should be kept in mind.

2. Sofosbuvir containing regimens should be avoided in severe renal impairment.

3. Certain regimes are to be avoided in decompensated cirrhosis.

**Ribavirin**

Ribavirin was the main stay in the treatment in chronic HCV infection 5 yrs back in combination with pegylated interferon. The adverse effect of ribavirin is haemolysis, which becomes of significance in anemia, renal disease and coronary artery disease. It is also contraindicated in pregnancy. In recent era, majority of the treatment regimes are ribavirin free, interferon free.

**Sofosbuvir**

Sofosbuvir the drug that has changed the entire treatment protocols given 400 mg daily with very high antiviral response. The drug is excreted through kidney. The majority of the sofosbuvir dose recovered in urine is the dephosphorylation-derived nucleoside metabolite GS-007 (78%).

Thus, Sofosbuvir is contraindicated patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) or with end-stage renal disease. Sofosbuvir-based regimens are contraindicated in patients who are being treated with the anti-arrhythmic amiodarone because of the risk of life-threatening arrhythmias. Phenytoin, Carbamazepine and Rifampicin potentially reduce the therapeutic level of

Sofosbuvir. Sofosbuvir has high barrier of genetic

resistance.

**Sofosbuvir and ledipasvir**

It is available as fixed-dose combination (400 mg + 90 mg PO daily). Biliary excretion is the major route of elimination of ledipasvir. NS5A inhibitors have low barrier of genetic resistance. No dose adjustment is required for patients with mild or moderate renal impairment, but no dose recommendation can currently be given for patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) or with end-stage renal disease. Fatigue and head ache are the most common side effects of this combination. Ledipasvir solubility decreases as pH increases, drugs that increase gastric pH (antacids, H2-receptorantagonists, proton pump inhibitors) are likely to decrease concentrations of ledipasvir. Real-world data have suggested slightly reduced SVR rates in patients only receiving high-dose proton pump inhibitors.

**Sofosbuvir and Velpatasvir**

It is available as fixed-dose combination (400 mg + 100 mg PO daily, pangenotypic). Biliary excretion is the major route of elimination of Velpatasvir. In HIV-HCV coinfected patients, sofosbuvir/velpatasvir may be given with most antiretrovirals, the exceptions being the inducing drugs efavirenz, etravirine and nevirapine. Efavirenz causes a 50% decrease in velpatasvir exposure. Currently this combination is used across all genotypes and it is suggested that these drugs can be prescribed even without Genotype testing.

**Daclatasvir**

Daclatasvir (60 mg PO daily) is one of the pangenotypic NS4A inhibitors with major route of excretion is biliary system. Although it is pangenotypic, it is approved in the treatment of genotype 3 with Sofosbuvir with/without Ribavirin.

**Sofosbuvir, Velpatasvir and Voxilaprevir**

It is available as fixed-dose combination (400 mg + 100 mg + 100 mg PO daily, pangenotypic). The combination of sofosbuvir, velpatasvir and Voxilaprevir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in those with severe hepatic impairment (Child-Pugh C). Headache, diarrhoea and nausea were the most commonly reported adverse events.

**Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir**

Paritaprevir is a protease inhibitor, which is metabolised primarily by CYP3A4 and is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. This enables once daily administration and a lower dose than would be required without ritonavir. Ombitasvir is an NS5A

inhibitor given in a fixed-dose combination with paritaprevir/ritonavir. The recommended dose of this combination is two tablets of ritonavir/paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase administered in 250 mg tablets twice daily, in combination with ritonavir/paritaprevir/ ombitasvir in genotype 1 patients. Fatigue and nausea are the most common side effects. It is contraindicated in severe hepatic impairment.

**Grazoprevir and Elbasvir**

It is available as fixed-dose combination (100 mg + 50 mg PO daily). No dose adjustment is required in patients with mild, moderate or severe renal impairment (including patients on haemodialysis or peritoneal dialysis).

**Glecaprevir and Pibrentasvir**

It is available as fixed-dose combination (100 mg + 40 mg PO daily, pangenotypic). Biliary excretion is the major route of elimination. It is not contraindicated in end-stage renal disease.

**Treatment of genotype 1 HCV infection**

The treatment of chronic HCV infection has evolved constantly and rapidly over the last decade. Many professional societies of Hepatology have issued guidelines based on their region and experiences. The treatment described here is as per AASLD and IDSA and can be accessed at www.hcvguidelines.org.

**Treatment-naive Patients**

1. Ledipasvir-Sofosbuvir: this is available as a fixed dose combination and is given for 8 weeks in those without cirrhosis and viral loads <6 MU/mL. In those with cirrhosis or viral load >6 MU / ml or with negative predictors like male sex, obesity and black race. It is given for 12 weeks.

2. Sofosbuvir-Velpatasvir given for 12 weeks.

3. Glecaprevir-Pibrentasvir for 8 weeks in those without cirrhosis; 12 weeks in cirrhotic.

4. Elbasvir-Grazoprevir with or without Ribavirin for 12–16 weeks.

5. Ombitasvir-Paritaprevir-Ritonavir + Daclatasvir + Ribavirin 12–24 weeks.

6. Simeprevir + Sofosbuvir or Daclatasvir +Sofosbuvir can be given if above drugs are not available.

**Treatment Experienced Patients**

***Prior Peginterferon and Ribavirin Failure***

1. Same regimens as above are given.

2. Ledipasvir-Sofosbuvir is combined with ribavirin.

3. Ombitasvir based regimens are not given in decompensated cirrhosis patient.

***Prior Protease Inhibitor Failures***

1. These are those who have been on Simeprevir, Telaprevir and Boceprevir.

2. Sofosbuvir-Velpatasvir for 12 weeks.

3. Ledipasvir - Sofosbuvir for 12 weeks and with Ribavirin if cirrhosis patient.

4. Elbasvir-Grazoprevir for 12–16 weeks.

**Prior Sofosbuvir Failure (no NS5A Exposure)**

These are patients who have been given Sofosbuvir plus interferon ± ribavirin

1. Glecaprevir-Pibrentasvir for 8–12 weeks.

2. Sofosbuvir-Velpatasvir –Voxilaprevir 12 weeks in genotype 1A and without Voxilaprevir in genotype 1B

***Prior Failure with NS5A Regimens***

These patients are given Sofosbuvir + Velpatasvir + Voxilaprevir for 12 weeks

**Treatment of genotype 2 patients**

**No Prior DAA Exposure**

For those who have had no treatment or failed treatment with peg interferon and ribavirin the following are suggested.

1. Sofosbuvir-Velpatasvir for 12 weeks

2. Glecaprevir-Pibrentasvir for 8 weeks if no cirrhosis for 12 weeks if compensated cirrhosis

3. Daclatasvir-Sofosbuvir for 12–24 weeks is recommended for patients who have no access to above

**Prior DAA Failure**

***Prior Sofosbuvir (without NS5A)***

1. Glecaprevir-Pibrentasvir 8 weeks if no cirrhosis and 12 weeks if compensated cirrhosis

2. Sofosbuvir-Velpatasvir for 12 weeks

3. Daclatasvir-Sofosbuvir with or without ribavirin for 24 weeks

**Prior Sofosbuvir plus NS5A Inhibitor**

1. Sofosbuvir – Velpatasvir-Voxilaprevir for 12 weeks

2. Sofosbuvir-Velpatasvir-Ribavirin for 24 weeks

**Treatment of genotype 3**

**Treatment Naive**

***No Cirrhosis***

1. Glecaprevir-Pibrentasvir for 8 weeks

2. Sofosbuvir-Velpatasvir for 12 weeks

3. Daclatasvir-Sofosbuvir for 12 weeks

***Cirrhotic***

1. Glecaprevir-Pibrentasvir for 12 weeks

2. Sofosbuvir-Velpatasvir for 12 weeks if Y93H variant is absent

3. Sofosbuvir-Velpatasvir- Voxilaprevir if Y93H variant present

4. Daclatasvir -Sofosbuvir for 24 weeks

**Prior Interferon/Ribavirin Failure**

***No Cirrhosis***

1. Sofosbuvir-Velpatasvir for 12 weeks if Y93H absent

2. Sofosbuvir-Velpatasvir - Voxilaprevir for 12 weeks if Y93H variant is present

3. Glecaprevir - Pibrentasvir for 16 weeks

***Cirrhosis***

1. Glecaprevir - Velpatasvir for 16 weeks

2. Sofosbuvir-Velpatasvir-Voxilaprevir for 12 weeks

3. Daclatasvir-Sofosbuvir ± Ribavirin for 24 weeks

***Prior DAA failure***

1. Sofosbuvir-Velpatasvir-Voxilaprevir for 12 weeks

2. With Ribavirin if compensated cirrhosis

**Treatment of genotype 4**

The highest prevalence of HCV is seen in Egypt – 15% and majority of the cases (90%) are genotype 4. It is also the main strain in Central and West Africa.

**Regimens**

1. Ledipasvir-Sofosbuvir for 12 weeks

2. Sofosbuvir-Velpatasvir for 12 weeks

3. Glecaprevir – Pibrentasvir for 8 weeks in patients without cirrhosis and 12 weeks in patients with cirrhosis. Can be given in renal impairment but contraindicated in decompensated (B or C) cirrhosis.

4. Elbasvir-Grazoprevir is given for 12 weeks routinely and for 16 weeks in those who have failed peginterferon plus ribavirin. Safe in renal impairment but contraindicated in child’s B & C cirrhosis.

5. Ombitasvir-Paritaprevir-Ritonavir plus Ribavirin given for 12 weeks.

6. Sofosbuvir plus Ribavirin for 24 weeks.

**Treatment of genotype 5**

Genotype 5 is most commonly seen in South Africa. Data on its treatment is limited. The options are Ledipasvir – Sofosbuvir or Sofosbuvir-Velpatasvir for 12 weeks or Glecaprevir – Pibrentasvir for 8 weeks in non-cirrhotic and 12 weeks in compensated cirrhotic.

**Treatment of genotype 6**

The regimens are Ledipasvir – Sofosbuvir or Sofosbuvir-Velpatasvir for 12 weeks of Glecaprevir-Pibrentasvir for 8 to 12 weeks.

**Treatment of HCV in renal impaired patients**

End-stage renal disease patients have an increased prevalence of HCV infection, an increased risk for progressive liver disease and reduced graft and patient survival after kidney transplantation. Current DAAs can be safely given in those with mild to moderate renal impairment, i.e., GFR >30 mL/min. Elbasvir-Grazoprevir and Glecaprevir-Pibrentasvir are recommended for severe renal disease or ESRD. Exceptions to these regimens are similar to naive genotype 1 patients. Treatment success has also been shown with various dual and triple regimens.

**Treatment of HIV–HCV co-infection**

More than 2 million people have HIV and hepatitis C co-infection, which translates to 6.2% of people living with globally. Co-infection is not surprising considering that roots of transmission are similar with highest prevalence seen in intravenous drug users. Also important is that HCV infection in HIV patients leads to accelerated liver disease progression and shortened life span after decompensation of cirrhosis. It is now possible to get a cure of HCV in co-infected patients due to highly effective directly acting antivirals.

In those HIV patients not on ART, ART should be started regardless of CD4 count and anti-HCV therapy can be started 4–6 weeks later. It may be possible to delay ART in those with CD4 count >500 cells/cmm and finish anti-HCV therapy.

In those already in ART, anti-HCV regiment may be started provided there is no drug interaction between the two or a switch may be made in the ART and anti-HCV therapy started 4–6 weeks after the switch.

The drugs and regimens used in co-infected patients for HCV are the same as for mono-infected patients. Therefore, in general the recommendations for drugs and regimens for various genotypes are similar for co-infected patients as mono-infected patients.

The main concern starting anti-HCV therapy is drugs interactions with ART drugs. For this reason, help of HIV specialist and official drug notifications should be kept in mind.

**HCV infection in liver transplant candidates and recipients**

As mentioned above, the introduction of highly effective oral drugs has totally changed the prognosis of patients and cure

is now possible. Also more patients of hepatitis C are being

transplanted and multiple considerations are involved in deciding to treat before or after transplant. Antiviral treatment before transplant are advised in: (a) patients with Childs A or B cirrhosis with MELD<20, (b) patients with access to living donors. Antiviral therapy is postponed to after transplant if: (a) patients have high MELD (>27) or severe portal hypertension or (b) patients have severe renal disease and decompensated disease. Pre-transplant regimen is as discussed above with the caveat that protease-inhibitors regimens should not be used.

The prognosis of patients with viremia who are transplanted but not treated is not good. 20–40% will develop progressive liver disease with around half of them developing cirrhosis within 5 yrs. A small percentage will develop severe recurrence called fibrosing cholestatic HCV. Therefore recipients who have not been treated should be evaluated and treated within 3 months after transplant. In patients without cirrhosis Glecaprevir -Pibrentasvir or sofosbuvir-velpatasvir for 12 weeks is given. Ledipasvir-sofosbuvir plus ribavirin is an option for genotypes 1, 4, 5 or 6. Sofosbuvir-Daclatasvir plus ribavirin is an option for genotype 2 or 3. In compensated cirrhosis, ledipasvir-sofosbuvir with ribavirin is given for 12 weeks with sofosbuvir-velpatasvir or Glecaprevir-Pibrentasvir as options. For Genotype 2 or 3 patients, daclatasvir-sofosbuvir plus ribavirin in low dose for 12 weeks is recommended. Sofosbuvir-velpatasvir or Glecaprevir-Pibrentasvir can also be considered. In decompensated cirrhotic patients, ledipasvir-sofosbuvir with low dose ribavirin is suggested for 12 wks in genotypes 1, 4, 5 and 6. For genotypes 2 and 3 Daclatasvir-sofosbuvir is the choice.

**Treatment of HCV-HBV coinfection**

In co-infection with HCV-HBV, HCV is the main driver for the inflammation and HBV DNA is usually low. Patients with HBV-HCV coinfection should be treated with the same anti-HCV regimens, following the same protocols as HCV monoinfected patients. There is a potential but unpredictable risk of HBV reactivation following HCV clearance. Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped. In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue therapy should be initiated if HBs antigen and/or HBV DNA are present.

**Further Reading**

1. Vladimir Alexei Morozov, Sylvie Lagaye. Hepatitis C virus: Morphogenesis, infection and therapy. *World J Hepatol*  2018;10:186–212.

2. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; 2:161–176

3. Younossi ZM. Hepatitis C infection: a systemic disease. *Clin Liver Dis* 2017;21:449–53.

4. Kamili S, Drobeniuc J, Araujo AC, et al. Laboratory diagnostics for hepatitis C virus infection. *Clin Infect Dis 012*; 55:S43–S48.

5. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology* 2016;151:70–86.

6. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017;66:153–94.

7. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med* 2015;373:2599–607.

8. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med* 2017;377:1448–55.

9. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. *Journal of Hepatology* 2018:69:j 461–511.

10. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD-IDSA HCV Guidance Panel. *Clin Infect Dis* 2018;67:1477–92.

**Chapter 45.**

**Non-alcoholic Fatty Liver Diseases**

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized cause for liver-related morbidity and mortality. NAFLD is characterized by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction >5.6% assessed by proton magnetic resonance spectroscopy. Sometimes, NAFLD views as a hepatic manifestation of metabolic syndrome. NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption  30 g for men and  20 g for women.

**Epidemiology**

Exact prevalence of NAFLD is very difficult to decide, as liver enzymes are normal in 80% patients of fatty liver and ultrasonography lacks sensitivity for milder steatosis. Recent metaanalysis of 85 studies covering 22 countries suggested a global NAFLD prevalence of 25.24%. The frequency of NAFLD was lowest in Africa (13.48%) and greatest in the Middle East (31.79%) and South America (30.45%). Another recent meta-analysis from Asia including 237 studies found the prevalence of NAFLD in general population to be 29.62% (95% CI: 28.1–31.1) with increasing prevalence in last 20 years. The prevalence of NAFLD in general population of India varies from 9 to 53% with lower prevalence in rural areas. In the United States and Europe, NAFLD is closely associated with obesity and insulin resistance, whereas in Southeast Asia, NAFLD can often be seen in the setting of a lower body mass index (BMI) and is labeled as ‘Lean NAFLD/NASH.’ Even though Asians and Indian patients with NAFLD have lower BMI than their Western counterparts, they have a high percentage of total body fat, higher visceral fat and insulin resistance in comparison to white Caucasians and African Americans.

Most of the cases occur in 4–6th decades of life; even childhood NASH is known (around 3% of children and 22–52% of obese children). NAFLD is more common among men than women. Although the exact relationship between ethnicity and NAFLD remains unresolved, of US-based studies reported that NAFLD prevalence was highest in Hispanic populations (22.9%), followed by White (14.4%) and then African American population (13.0%). Polymorphisms in genes such as the *PNPLA3* gene may be responsible for differences in the prevalence of NAFLD among different ethnic groups.

**Obesity and metabolic syndrome**

Because of the high prevalence of NAFLD in patients with metabolic syndrome (MS), it is considered as a hepatic component of MS. Obesity is strongly associated with development of fatty liver disease. Around 80–85% of patients with NAFLD have either overweight or obesity with higher prevalence in those with NASH and normal BMI (Lean NAFLD) in around 15–20% of patients. Vice versa, data in obese patients undergoing bariatric surgery also reveal higher prevalence of NAFLD/NASH. Another strong association of NAFLD is type 2 diabetes mellitus (T2DM) and dyslipidemia. Around 22% of patients with NAFLD have T2DM at presentation, whereas around 43% of NASH patients have T2DM. Around 69% of patients with NAFLD have dyslipidemia, whereas around 72% of NASH patients have dyslipidemia. As highlighted earlier, lower BMI observed in NAFLD patients of Asian origin (lean NAFLD) may reflect differences in fat distribution between the subcutaneous and visceral compartments for individuals of different ethnic origin.

Recent data has highlighted a bidirectional link between NAFLD and MS with not only higher prevalence of NAFLD in patients with MS but also a higher risk of developing type 2 diabetes mellitus and MS in patients with NAFLD (without these risk factors at base line) on long-term follow-up.

**Genetics and NAFLD**

Other than environment factors, inter-individual and inter-ethnic differences and difference in the severity and progression of liver disease among patients with NAFLD suggest the involvement of genetic and epigenetic factors in their pathogenesis. The most widely studied genetic risk factor for NAFLD is the Patatin-like phospholipase domain-containing protein 3 (*PNPLA3)*gene encoding adiponutrin

(involved in lipogenesis and lipolysis in hepatocytes and adipocytes). Several studies have shown association of both NAFLD with I148M PNPLA3 variant. In addition to the higher prevalence of hepatic steatosis, the I148M PNPLA3 variant is also associated with severity of liver disease and risk of hepatocellular carcinoma. Transmembrane 6 superfamily 2 (TM6SF2), regulator of liver fat metabolism is the other genetic variant shown to be significantly associated with hepatic steatosis and cirrhosis in patients with NAFLD

**Various Nomenclature of fatty liver disease**

***Nonalcoholic Fatty Liver Disease (NAFLD)***: Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and NASH-related cirrhosis and NASH-related HCC.

***Nonalcoholic Fatty Liver (NAFL)***: Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.

***Nonalcoholic Steatohepatitis (NASH)***: Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer.

***NASH Cirrhosis***: Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis

***Cryptogenic Cirrhosis***: Presence of cirrhosis with no obvious aetiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome.

***NASH related HCC***: Presence of HCC with presence or history of metabolic risk factors (obesity, diabetes mellitus etc.) and exclusion of other aetiologies.

***NAFLD Activity Score (NAS)****:* An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials.

**Pathogenesis**

Both environmental and genetic factors play an important role in the pathogenesis of NAFLD and NASH. A “two-hit” theory which was proposed several years ago is now considered outdated. NAFLD is a multi-factorial disease resulting from

a complex interaction of environmental “hits” like insulin resistance, small intestinal bacterial overgrowth (SIBO), endotoxemia, oxidative stress, cytokines, apoptosis and a

genetic background. A high-calorie diet, often coupled with a sedentary behaviour, contributes to the development of NAFLD, both directly and via weight gain. Dietary excess of saturated fats and refined carbohydrates has been associated with NAFLD and a high fructose intake may increase the risk of NASH.

Development and progression of NAFLD are strongly associated with insulin resistance (IR) and metabolic syndrome (MetS) components, particularly abdominal obesity and T2DM. Overall, around 55–98% of patients with NAFLD in India have been shown to have insulin resistance as assessed by homeostasis model assessment for insulin resistance (HOMA –IR) or insulin tolerance test (ITT). Insulin resistance is also common in so called ‘Lean’ patients with NAFLD. NAFLD will invariably develop when the rate of hepatic triglyceride flowing to the liver via the bloodstream or synthesized within the liver exceeds the rate of hepatic triglyceride oxidation and VLDL secretion into the bloodstream. Approximately 60% of hepatic lipids derives from increased peripheral lipolysis of triglycerides (due to adipose tissue IR and failure to adequately suppress peripheral triglyceride lipolysis), while dietary fats and sugars contribute approximately 35–40%. The contribution of de novo lipogenesis (DNL, excess of carbohydrate mainly fructose converts into fatty acid) to liver fat content is less than 5% in healthy subjects.

Toxic lipids can determine cell injury through a variety of mechanisms, including increased oxidative stress and mitochondrial dysfunction. Saturated fatty acids are increased in NASH and induce inflammation and hepatocytes apoptosis by activating Jun N-terminal kinase (JNK) and mitochondrial pathways. Free cholesterol is a prominent mechanism for NASH development and progression.

As mentioned earlier, polymorphisms in the patatin like phospholipase domain containing 3 (PNPLA3) genes have been accepted universally to be involved in causing increased risk of NAFLD and NASH. Recently, it has been shown that PNPLA3 mutation impaired lipolysis which leads to further fat accumulation in the liver. Data in Asian Indians also suggest the role of apolipoprotein C3 (APOC3) and cluster of differentiation (CD14), a co-receptor of toll like receptor 4 gene polymorphisms but in contrast to the West, iron overload and HFE gene mutations are probably not involved in the pathogenesis of Indian patients with NAFLD/NASH. JNK, an activator of inflammation and apoptosis implicated in NAFLD progression, is one of the major mediators of endoplasmic reticulum (ER) stress. Chronic inflammation is a key factor in NASH pathogenesis. Kupffer cell activation

occurs at an early stage, and precedes the recruitment of other cells. Hepatocytes death is a strong trigger of inflammation and fibrosis, through signaling pathways that include tumour

necrosis factor (TNF)-related apoptosis-inducing ligand receptor, Fas and TNF receptor, and promote the expression of several cytokines and chemokines. TGF-â and chemokines such as CCL2 and CCL5 may induce hepatic stellate cell activation, triggering fibrogenesis. Besides resident and infiltrating macrophages, the role of other inflammatory cells, such as neutrophils, lymphocytes, NK cells and dendritic cells is actively being evaluated. The NOD-like receptors (NLR), which participate in the assembly of inflammasomes, play a major role in NASH pathogenesis. Activation of the inflammasome is induced by TLRs together with signals linked to cellular damage, e.g., uric acid, reactive oxygen species or adenosine triphosphate, and results in the secretion of mature IL-1 and IL-18. Different nuclear receptors have been implicated in the pathogenesis of NASH and development of fibrosis. Importantly, these proteins may be targeted by drugs already present in the clinical arena. The receptors on which more information has accumulated include the nuclear farnesoid X receptor (FXR), the peroxisome proliferator-activated receptor (PPAR)-gamma and the PPAR-alpha. Agonists of these nuclear receptors improve hepatic steatosis, inflammation and fibrosis. A role of dysbiosis in the development of obesity and NAFLD has been demonstrated in both animal and human studies. Gut microbiota can trigger different signaling pathways, which eventually lead to an increased deposition of peripheral fat.

**Clinical Features**

NAFLD is a heterogeneous disease. Its clinical features are non-specific and similar to other chronic liver diseases.

Majority of the patients (48–100%) with NAFLD are asymptomatic and detected incidentally during routine laboratory check-ups or during investigations for diseases like hypertension, diabetes, obesity, atherosclerosis or gallstone disease.

In these patients, NAFLD becomes evident because of ALT elevation or sonographic evidence of fatty liver. Among symptomatic individuals, fatigue (< 10%), malaise and right upper quadrant discomfort (30–40%) are the most common symptoms; in others, symptoms are due to advanced liver disease like nausea, anorexia, itching, gastrointestinal bleeding, ascites, anasarca, encephalopathy or jaundice.

On physical examination, parameters of obesity by measuring BMI, waist circumference and waist: hip ratio. Hepatomegaly in found in around 50–75% (difficult to define due to abdominal obesity) and stigmata of chronic liver disease (palmar erythema and spider naevi being most common) and signs of portal hypertension (splenomegaly, ascites, abdominal wall veins, varices) in minority of patients. Jaundice and muscle wasting are late. Acanthosis nigricans

(especially in children) and lipomatosis or xantholasma (suggestive of dyslipidemia) may be seen.

**Investigations**

Most common laboratory abnormality is moderate elevation (1.5–5 times upper limit of normal) in transaminases levels (in 50–90% cases). ALT levels are usually higher than AST levels, but AST levels are greater in presence of cirrhosis. Prolonged prothrombin time, hypoalbuminemia and hyperbilirubinemia represent advanced liver disease. There is no correlation between ALT values and degree of fibrosis or steatosis or clinical presentation. ALT values more than 10-fold seldom occur; in a suspected NAFLD patient, this may suggest co-existing viral hepatitis A or E or alternate etiology. Normal ALT values do not rule out presence of NASH or advanced disease. Gamma-glutamyl-transferase and alkaline phosphatase may be variably elevated in up to 30% cases. It is also important to exclude other secondary causes of hepatic steatosis and raised transaminases (if present) with appropriate history of alcohol, history of intake of steatogenic drugs (corticosteroids, amiodarone, metho-trexate, etc), history of gastric bypass and total parental nutrition. Certain liver diseases like chronic hepatitis C, Wilson’s disease and hepatic tuberculosis can cause hepatic steatosis and need exclusion by appropriate history and investigations. As mentioned earlier, liver enzymes have poor correlation with histological severity and it is not appropriate to make the diagnosis of NASH just based on the elevated liver enzymes. Moreover, the elevation of transaminases in patients with NAFLFD may be because of concomitant illness like chronic hepatitis B and C, autoimmune hepatitis, celiac disease and hemochromatosis, all of which need exclusion by appropriate investigations. In patients of NASH, ANA may be positive (low-titer < 1:320) in 10–25% cases. Features of iron overload like elevated serum ferritin [40–58%] and transferrin (11–22%) is not common in Indian patients with NAFLD.

All patients with NAFLD should be assessed for the prevalence of metabolic syndrome based on history or investigations. Metabolic syndrome can be assessed by various criteria and include detailed anthropometry (height, weight, BMI, waist circumference for the assessment of overweight and central and overall obesity), assessment for hypertension, impaired glucose tolerance/diabetes mellitus, serum triglycerides and high density lipoprotein (HDL). Prevalence of metabolic syndrome not only helps in making the diagnosis of NAFLD but also helps in assessing the severity of liver disease (more likely to have NASH) and helping in taking a decision regarding performing a liver biopsy ( to establish the diagnosis of NASH). Assessment

of severity of NAFLD should be first done non-invasively (detailed later). Since the natural history of NAFL and NASH is entirely different, it is very important to predict NASH non-invasively in all patients with NAFLD and then to subject those suspected of NASH to a liver biopsy (detailed later).

**Role of Imaging**

Imaging with either ultrasonography or CT or MRI scan is useful in excluding focal liver disease or biliary tract disease. They have poor sensitivity in detecting fatty liver and cannot differentiate steatosis, steatohepatitis or steatohepatitis with fibrosis. They can diagnose fatty liver with high sensitivity, only when total liver fat is more than 33%. Ultrasonography has better sensitivity to detect fatty liver, but cannot differentiate diffuse fibrosis from diffuse fatty liver. Hyperechoic echotexture, vascular blurring, deep attenuation and increased echotexture compared to kidneys are common sonographic features. CT scan and MRI are better in evaluation of focal fatty deposition and have higher specificity to define fatty liver. MR spectroscopy has been shown to be effective for quantifying liver fat. Role of MR-elastography (MRE) in diagnosis and progression of NAFLD is promising, but not easily available. For MRE, results are approximately one third the values of transient elastography, with values less than 2.9 kPa denoting normal liver and more than 5.2 kPa indicating presence of cirrhosis.

**Non-invasive Assessment of Steatohepatitis and Advanced Fibrosis in NAFLD**

Many non-invasive methods have been identified to assess the severity of fibrosis in patients with NAFLD; these include the NAFLD Fibrosis Score, Enhanced Liver Fibrosis (ELF) panel and transient elastography. Commonly used algorithms include the AST to Platelet Ratio Index (APRI), NAFLD fibrosis score (NFS) and FIB-4.

AST to platelet ratio index – The APRI (cutoff value 0.5–1.5) is based on the AST level and platelet count. APRI = (AST elevation/platelet count) x 100. For predicting cirrhosis (F4), an APRI cutoff of 1.0 had a sensitivity of 76% and a specificity of 72%.

AST/ALT ratio – The AST/ALT ratio is approximately 0.8 in normal subjects. Some studies have suggested that a ratio >1 suggests the presence of cirrhosis.

The NAFLD Fibrosis Score is based on six readily available variables (age, BMI, hyperglycaemia, platelet count, albumin, AST/ALT ratio) and it is calculated using the published formula (*http://nafldscore.com*). Sensitivity and specificity is around 90% and 97%, respectively. These tests

classify patients into fibrosis risk categories defined as high-risk fibrosis (F2–F4) from minimal or no fibrosis (F0–F1).

**FIB-4 index –** The FIB-4 index (cutoff value 1.3–2.67) combines biochemical values (platelet count, ALT and AST) and age. The BARD score takes into account BMI, the AST/ALT ratio, and the presence of diabetes mellitus.

Second-line noninvasive tests include the serum Enhanced Liver Fibrosis Score (ELF), *FibroScan*transient elastography (TE) or Acoustic Radiation Force Impulse (ARFI) elastography. Second-line tests are used in patients with intermediate risk of fibrosis.

The ELF panel consists of plasma levels of three matrix turnover proteins (hyaluronic acid, TIMP-1 and PIIINP) had 80% sensitivity and 90% specificity for detecting advanced fibrosis.

The cutoff for advanced fibrosis ( F3) is  9.8 for serum ELF measurements.

TE is a widely used modality that can be performed in the clinic and provides a reading of liver stiffness. TE relies on the principle that the speed of wave conduction is linked to tissue stiffness, which reflects the degree of liver fibrosis. TE accurately diagnoses cirrhosis (fibrosis stage 4 [F4]) and is useful for distinguishing advanced fibrosis (ie, fibrosis stage 2 [F2] or greater) from minimal or no fibrosis (fibrosis stage 1 [F1] or fibrosis stage 0 [F0]). The published cutoff of significant fibrosis is > 8 kPa for *FibroScan*. Cutoffs for ARFI vary according to the device manufacturer.

Circulating levels of cytokeratin-18 (CK18) fragments have been investigated extensively as novel biomarkers for the presence of steatohepatitis in patients with NAFLD with sensitivity of 78% and specificity of 87%.

**Role of Liver Biopsy**

Liver biopsy is the only available method for definitive diagnosis, for exclusion of the alternative diagnoses, for differentiating steatohepatitis from steatosis and for defining grading and staging of the disease (presence of fibrosis), and thus defining prognosis and progression of the disease. A diagnosis of NAFLD is relatively straightforward and requires the presence of steatosis in 5% of hepatocytes in the absence of excessive alcohol consumption and hepatitis C infection. Diagnosing NASH requires a liver biopsy, and the diagnosis depends on the presence of hepatic steatosis with both ballooning and lobular inflammation. Commonly used scoring systems for evaluating the severity of NAFLD include the NAFLD Activity Score, which evaluates and assigns scores to 4 domains: steatosis (0–3), lobular inflammation (0–3), hepatocyte ballooning (0–2), and liver fibrosis (0–4) **(Table 45.1)**.

Metavir fibrosis score is described below:

n F0: No fibrosis

n F1: Portal fibrosis without septa

n F2: Few septa

n F3: Numerous septa without cirrhosis

n F4: Cirrhosis

**Alcohol Consumption & NAFLD**

By definition, NAFLD indicates the lack of any evidence of ongoing or recent consumption of significant quantities of alcohol. A thorough history of alcohol consumption should be taken. The European Association for the Study of the Liver defines excessive alcohol consumption as a daily intake of alcohol  20 g for women and  30 g for men. Although NAFLD and excessive alcohol consumption can coexist, it remains problematic to make the diagnosis of NAFLD or NASH with confidence in the setting of increased alcohol intake.

**Natural History and Prognosis**

Top three leading causes of death in patients with NAFLD are cardiovascular disease, extrahepatic neoplasm and liver

disease. Patients with steatosis without inflammation (F0-F2), mortality is more with extrahepatic cause. As fibrosis score progress (F3-F4), mortality is more due to liver disease. Large scale studies are lacking. Simple hepatic steatosis is generally believed to have benign long-term prognosis and rarely progress to cirrhosis (3–4% over 8-year follow-up). A meta-analysis of 11 observational studies in 411 patients with NAFLD and paired biopsies reported that the rate of fibrosis progression is approximately 1 fibrosis stage per 14 years in those with nonalcoholic fatty liver compared with 7 years in NASH.

Once cirrhosis develops, patients with NASH cirrhosis in CTP class B and C behave almost same as HCV-related cirrhosis: complications due to portal hypertension are seen in around 30% and liver-related deaths in 20% whereas in CTP class A the occurrence of decompensation is less in patients with NASH cirrhosis in comparison to HCV cirrhosis.

More than 20% of liver transplant are done for biopsy-proven NASH, most of these cases are labeled as cryptogenic cirrhosis Even though the occurrence of HCC is less common in patients with NASH cirrhosis in comparison to virus associated cirrhosis, HCC has also been reported in patients with NAFLD in the absence of cirrhosis, which suggests multiple mechanisms of hepatocarcinogenesis in the context of NAFLD.

**Management**

The management of patients with NAFLD consists of treating liver disease as well as the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance and T2DM. Management of NAFLD consist of life style modifications and pharmacotherapy.

**Lifestyle Modifications**

Lifestyle modifications may reduce aminotransferases and improve hepatic steatosis when measured either by ultrasound or MR imaging and spectroscopy.

Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity; combination of dietary restriction and exercise has been shown to be better than either modality alone. Weight loss of  3% appears necessary to improve steatosis, but a greater weight loss of  5%,  7% and 10% may be needed to improve ballooning/necroinflammation, NASH resolution and hepatic fibrosis respectively. Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown.

**Control of Morbid obesity and Diabetes**

For morbidly obese NAFLD patients, more aggressive management strategies can be considered like drug (Orlistat:

inhibitor of gastric and pancreatic lipase) or surgery (proximal gastric bypass is better than vertical-banded gastroplasty or jejunoileal bypass), But this should be weighed against morbidity and mortality associated with interventions and risk of developing liver failure due to rapid severe weight loss (>1.6 kg/week). Bariatric surgery if otherwise indicated in patients with obesity has been shown to improve hepatic steatosis and inflammation but is not indicated primarily for the treatment of NAFLD/NASH. In diabetic patients, hemoglobin A1c should remain below 7%. Optimal control of hyperlipidemia and diabetes is needed.

**Target- Metabolism and oxidative stress**

**Antioxidants** - The fat-soluble antioxidant vitamin E has been shown to be superior to placebo in achieving histological response and resolution of NASH in trial of Pioglitazone, Vitamin E, or placebo for non-alcoholic Steatohepatitis (PIVENS). The TONIC trail also demonstrated increased resolution of NASH with Vitamin E. Vitamin E (800 IU) is currently recommended as first line off-label pharmacotherapy for NASH. Recent retrospective data has even shown the efficacy of vitamin E in NASH related cirrhosis with reduction in decompensation and requirement of liver transplantation. Cysteamine, reactive oxygen species scavengers was shown to improve levels of ALT in small pilot study in children. Omga-3 fatty acid did not to improve NASH histology.

**Lipid-lowering agents** - Rosuvastatin (10 mg/day) showing some promising results but sample size was very small. Aramchol, SCD inhibitor, has shown significant reduction in hepatic fat by MR spectroscopy.

**Target-Insulin Resistance**

Peroxisomeproliferator-activator receptors- Peroxisome proliferator-activator receptors (PPARs) are nuclear receptors that bind fatty acids regulate a number of metabolic processes. The three PPARs , /, and  are present in different tissues. PPAR  is expressed in the liver, brown adipose tissue and heart. It increases fatty acid oxidation. PPAR is expressed in the liver and has anti-inflammatory activity. PPAR  is expressed in adipose tissue and regulates glucose metabolism and lipogenesis. **Elafibranor** (dual PPAR / agonist, 120 mg/day), improves hepatic and peripheral insulin sensitivity and reduce ALT (Golden 505 Study). A larger study (RESOLVE-IT) is further evaluating the efficacy of Elafibranor. **Saroglitazar** (dual PPAR / agonist, 4 mg daily) improves ALT in diabetic patients with

dyslipidemia. A phase III study of Saroglitazar on biopsy proven patients with NASH has been concluded recently and the results are awaited. **Pioglitazone** (PPAR  agonist) used

in the management of diabetes and demonstrated to be effective in NASH.

Farnesoid X receptor- **Obeticholic acid** (25 m mg/day), a selective FXR agonist showed promising anti-inflammatory and anti-fibrotic effects in NASH (FLINT trial). Initial worsening of low-density lipoprotein cholesterol and total cholesterol and pruritus were the major concerns. A phase III trial (REGENERATE trial) is evaluating its efficacy in large number of biopsy proven patients with NASH.

Incretin - **Incretins** are gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many physiological roles is to regulate the amount of insulin that is secreted after eating. The two incretinsare glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP).Incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase 4 (DPP4). Exenatide and Liraglutide are two GLP-1 agonist improves NASH histology (LEAN trial). DPP4 inhibitors (Sitagliptin and vildagliptin) reduce liver fat determined by MR-spectroscopy. Sodium–glucose co-transporter 2 inhibitors (SGLT-2 inhibitor, ipragliflozin, inhibits reabsorption of glucose in the kidney) improves liver enzymes and FIB-4 score in diabetic NAFLD patients.

**Target – Inflammation**

Cenicriviroc – An oral antagonist of cysteine-cysteine motif chemokines ligand type 2 and type 5 (CCL2-CCL5) showed anti-inflammatory and anti-fibrotic property in patients with NASH (CENTAUR trial). A larger phase III trial is evaluating its efficacy in AURORA trial.

**Target – Apoptosis**

Emricasan - oral pan-caspase inhibitors, improves hepatic inflammation and fibrosis.

Selonsertib - oral ASK1 inhibitor was shown to be improve hepatic steatosis and fibrosis in an earlier study but has failed to work in larger trials (STELLAR 3 and 4).

**Target – Fibrosis**

Simtuzumab - has direct anti-fibrotic effects but has disappointing results.

Galectin-3 inhibitor - decreases disease activity and fibrosis in a murine model.

**Target – De-novo Lipogenesis**

ACC inhibitor - acyl-CoA carboxylase (ACC) inhibitors reduce de-novo lipogenesis (DNL). But effects are countered

by compensatory increase in triglyceride generation from peripheral free fatty acid.

**Target – Gut Microbiota**

Data is emerging regarding the efficacy of probiotics and other gut manipulations for the treatment of patients with NAFLD/NASH

**Bariatric Surgery**

There are several retrospective and prospective cohort studies that compared liver histology in the severely obese individuals before and after bariatric surgery. Most histological benefits were evident at 1 year with no differences in liver histology between 1 and 5 years following bariatric surgery. Recently one meta-analysis showed that steatosis, steatohepatitis and fibrosis appear to improve or completely resolve after bariatric surgery. But as mentioned earlier, bariatric surgery is still not recommended primarily for the treatment of NAFLD/NASH.

**Liver Transplantation**

Over the years, NASH has become second leading cause among adults waiting for liver transplantation in USA. There is a general perception that liver transplants would happen less commonly in NASH cirrhosis because of accompanying co-morbidities like obesity, diabetes mellitus, etc. Overall outcome and survival after liver transplantation is similar between patients with NASH cirrhosis and cirrhosis due to other aetiologies but recurrence of NAFLD in the graft is the problem. In 20% of liver transplant patients (other than NASH or cryptogenic cirrhosis related), NASH develops de-novo in post-transplant period. In patients who had undergone liver transplantation for cryptogenic cirrhosis, almost 100% have post transplant recurrence of NASH. Risk factors for recurrence or de novo NAFLD in post- liver transplant patient are hyperlipidemia, glucocorticoid therapy, obesity and diabetes.

**Further Reading**

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–57.

2. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388–402.

3. Wong VW, Chan WK, Chitturi S, et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017–Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018;33:70–85.

4. Duseja A, Singh SP, Saraswat VA, et al. Non-alcoholic Fatty Liver Disease and Metabolic Syndrome-Position Paper of the Indian National Association for the Study of the Liver, Endocrine

Society of India, Indian College of Cardiology and Indian Society of Gastroenterology. *J Clin Exp Hepatol* 2015;5:51–68.

5. Duseja A, Sharma B, Kumar A, et al. Nonalcoholic fatty liver in a developing country is responsible for significant liver disease. *Hepatology* 2010;52:2248–9.

6. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.

7. Li J, Zou B, Yeo YH, Feng Y, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis*. Lancet Gastroenterol Hepatol* 2019;4:389–98.

8. Duseja A, Chalasani N. Epidemiology and risk factors of nonalcoholic fatty liver disease (NAFLD). *Hepatol Int* 2013; 7 Suppl 2:755–64.

9. Amarapurkar D, Kamani P, Patel N, et al. Prevalence of non-alcoholic fatty liver disease: population based study. *Ann Hepatol* 2007;6:161–3.

10. Singh SP, Nayak S, Swain M, et al. Prevalence of nonalcoholic fatty liver disease in coastal eastern India: a preliminary ultrasonographic survey. *Trop Gastroenterol* 2004; 25:76–9.

11. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome*. Diabetes Res Clin Pract* 2009;84:84–91.

12. Das K, Das K, Mukherjee PS, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. *Hepatology* 2010; 51:1593–602.

13 Duseja A, Najmy S, Sachdev S, et al. High prevalence of non-alcoholic fatty liver disease among healthy male blood donors of urban India. *JGH Open* 2019;3:133–9.

14. Duseja A, Das A, Das R, et al. The clinicopathological profile of Indian patients with nonalcoholic fatty liver disease (NAFLD) is different from that in the West. *Dig Dis Sci* 2007;52:2368–74.

15. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015;13:643–54e9.

16. Singh SP, Misra B, Kar SK, et al. Nonalcoholic fatty liver disease (NAFLD) without insulin resistance: Is it different? *Clin Res Hepatol Gastroenterol* 2015;39:482–8.

17. Duseja A, Chawla YK. Obesity and NAFLD: the role of bacteria and microbiota. *Clin Liver Dis* 2014;18:59–71.

18. Sookoian S, PirolaCJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology* 2011; 53:1883–94.

19. Kozlitina J, Smagris E, Stender S, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. *Nat* *Genet* 2014; 46: 352–6.

20. Duseja A, Das R, Nanda M, et al. Nonalcoholic steato-hepatitis in Asian Indians is neither associated with iron overload nor with HFE gene mutations. *World J* *Gastroenterol* 2005;11:393–5.

21. Neuschwander-Tetri BA, Loomba R, et al. NASH Clinical Research Network.. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* 2015;385:956–65.

22. Ratziu V, Harrison SA, Francque S, et al; GOLDEN-505 Investigator Study Group. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-á and -ä, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. *Gastroenterology* 2016;150:1147–1159.

23. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–90.

24. Duseja A, Acharya SK, Mehta M, et al. High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study. *BMJ Open Gastroenterol* 2019;6:e000315.

25. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015;148:547–55.

26. Bhagat V, Mindikoglu AL, Nudo CG, et al. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; 15:1814–20.

27. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver* *Transpl* 2001; 7:363–73.

Chapter 46.

**Alcoholic Liver Diseases**

**introduction**

Liver is the primary site of alcohol metabolism. Alcohol consumption can lead to spectrum of the liver diseases ranging from steatosis, to alcoholic hepatitis, to fibrosis and cirrhosis. There is considerable overlap among all these conditions. Alcoholic hepatitis and cirrhosis carries very high morbidity and mortality. Fortunately only 20% of alcoholics develop severe chronic liver disease. Why only a minority of alcoholics develop cirrhosis remains unknown. Male to female ratio of 10%: 1 for alcoholism, but alcohol related liver disease is more likely to develop in female alcoholics. Alcoholic liver disease develops usually after 10 years of heavy alcohol consumption. Exact dose of alcohol producing liver injury remains controversial. Alcohol consumption more than 40–80 g/day in male and 20–30 g/day in female for 10 years have been associated with increased incidence of alcoholic steatohepatitis, fibrosis and cirrhosis. Based on epidemiological evidence of a threshold effect of alcohol, a suggested “safe” limit of alcohol intake had been 21 units per week in men and 14 units per week in women who have no other chronic liver disease (where a unit is defined as the equivalent of 8 g of ethanol).

**Pattern of consumption and type of alcohol**

Pattern and severity of liver injury depends of the pattern and type of alcohol consumption. A standard drink is defined as the amount of alcoholic beverage that contains approximately 0.5 fluid ounces, or about 14 grams of pure alcohol. Bing drinking is consumption of 4–5 drinks in 2 hrs or less. Impact of drinking patter (binge drinking and drinking outside meal) needs to study in large epidemiological study. Various beverages like beer (6% alcohol, 350 mL), table wine (12% alcohol, 150 mL), fortified wine (17% alcohol, 120 mL), brandy or distilled spirit (40% alcohol, 45 mL) considered equivalent to “Standard” drink. There is considerable variability in actual alcohol content within each type of beverage.

**Natural History of ALD**

The spectrum of alcohol-related liver injury varies from simple fatty liver to cirrhosis. These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given person. The spectrum of alcoholic liver disease is grouped into three histological stages of ALD: fatty liver or simple steatosis, alcoholic hepatitis and chronic hepatitis with hepatic fibrosis or cirrhosis. Fatty liver (develops in about 90% of individuals who drink more than 60 g/day of alcohol for 10 yrs) is characterized by the excessive accumulation of fat inside hepatocytes (macrovesicular steatosis). This condition is benign and reversible with abstinence, but in some patients, it may progress to alcoholic hepatitis and cirrhosis (5–15% of patients despite abstinence). Alcoholic hepatitis is characterized by hepatocyte injury and inflammation. Alcoholic fibrosis or cirrhosis (40–60% of patients who ingest more than 40–80 g/daily for an average of 25 yrs) is characterized by excessive accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases. Fibrosis and cirrhosis is sometimes developing without a preceding stage of alcoholic hepatitis.

**Clinical Syndromes of ALD**

**Steatosis**

Fatty liver is the earliest event in the pathogenesis of ALD. Up to 90% of alcoholics feature hepatic steatosis. Alcoholic steatosis is usually asymptomatic except hepatomegaly. Histological findings are characterized by the excessive accumulation of lipids in large droplets inside the hepatocyte (macrovesicular fatty liver). Steatosis can be reversed if alcohol consumption is stopped or significantly reduced, but the condition can lead to inflammation (steatohepatitis or alcoholic hepatitis) and finally to cirrhosis, if alcohol consumption is not reduced or stopped.

**Alcoholic Hepatitis (AH)**

Alcoholic hepatitis is characterized by alcoholic steatosis accompanied by acute or chronic inflammation and a variable amount of fibrosis. Histological features of alcoholic hepatitis include neutrophilic infiltration, various degrees of fibrosis, hepatocyte necrosis and Mallory-Denk bodies/hepatocyte ballooning. The probability of developing cirrhosis in patients with alcoholic hepatitis is approximately 10–20% per year, and approximately 70% of the patients with alcoholic hepatitis will ultimately develop cirrhosis. AH also represents a spectrum of disease, ranging from mild injury

to severe, life-threatening injury, and often presents acutely against a background of chronic liver disease.

A special syndrome of severe alcoholic hepatitis is known as Zieve’s syndrome. It features a triad of jaundice, hyperlipidemia (especially high triglycerides) and haemolytic anemia.

**Cirrhosis**

Fibrosis is considered a model of the wound-healing response to chronic injury. Fibrosis can occur in the absence of alcoholic hepatitis. Patients with alcoholic cirrhosis have clinical features similar to those with cirrhosis of other etiology. Once signs of clinical decompensation develop in patients with alcohol induced cirrhosis, patients who stop drinking can expect a 5-year survival of about 60% vs only 30% if they continue to drink alcohol. Decompensated alcoholic cirrhosis is associated with short survival, and liver transplantation is often indicated as the only effective therapy. Survival rates after liver transplantation are similar among alcoholics and non-alcoholics.

**Hepatic Alcohol Metabolism**

Hepatocytes (about 70% of the liver mass) are the main metabolism site of alcohol. Two enzymes responsible for alcohol metabolism in hepatocytes are: Alcohol Dehydro-

genase (ADH, present in cytosol) and cytochrome P4502E1 (CYP2E1, present in smooth endoplasmic reticulum). Catalase, other enzyme in hepatocytes form minor pathway for alcohol oxidation.

Metabolism of alcohol in the hepatocytes are illustrate below **(Fig. 46.1)**.

**Pathogenesis of Clinical Syndromes of ALD**

**Pathogenesis of Steatosis**

Excess alcohol converts liver into lipid-burning organ to lipid-storing organ. Adipose tissue stores excess calories derived from food consumption as fat. Alcohol ingestion enhances fat breakdown (lipolysis) from adipose tissue stores as triglyceride in the liver. Alcohol ingestions induce secretions of TNF- which is a lipogenic cytokine, reduce adiponectin production. Arrested lipophagy (breakdown of lipid droplets) leads to reduced fatty acid oxidation cause steatosis. Very low-density lipoprotein (VLDL) is the only way to export triglyceride and cholesterol from liver. Alcohol impaired VLDL secretion.

**Pathogenesis of Alcoholic Hepatitis**

Many patients with steatosis never progress to steatohepatitis or fibrosis. This suggests that the occurrence of inflammation, in addition to steatosis, requires the presence

of a ‘second hit.’ The resident macrophages in the liver is called Kupffer cells (KCs, potent innate immune cells), which represents 15% of liver cells. They resided in the liver sinusoids and provide the first line of defense.

Gut-derived endotoxins, including toxic lipopoly-saccharide (LPS), are another important element in the pathogenesis of alcohol-induced liver damage. Endotoxin may trigger both cytokine release and oxidative stress. In the liver, endotoxins activate Kupffer cells, which play a major role in liver inflammation by releasing reactive oxygen species (ROS) and cytokines.

Proinflammatory cytokines produced by activated Kupffer cells are suggested to be involved in ALD. Patients with ALD have increased levels of the proinflammatory cytokines (IL-1, IL-6 and TNF- as well as the chemokines IL-8 and other cytokines among these proinflammatory cytokines, TNF- was postulated to be a key mediator cytokine of ALD.

***Oxidative Stress***

Alcohol induces oxidative stress in the liver by either enhancing the production of ROS and/or decreasing the level of endogenous antioxidants, leading to tissue damage. The sources of ROS include the mitochondria and cytochrome P450 2E1 (CYP2E1) in hepatocytes, and NADPH oxidase in inflammatory cells. Induction of CYP2-E1 by ethanol is also a central pathway by which ethanol generates oxidative stress in hepatocytes. Activated Kupffer cells are the major source of ROS in the liver.

***Acetaldehyde***

Acetaldehyde is the most important metabolite of ethanol leading to liver damage. The toxicity of acetaldehyde is due to its capacity to form adducts with intracellular proteins. Acetaldehyde protein adducts can trigger an abnormal immune response characterized by the production of antibodies directed against acetaldehyde epitopes.

**Pathogenesis of Fibrosis and Cirrhosis**

Hepatic stellate cells (HSCs, reside in the space of Disse) change from a quiescent to an activated phenotype during fibrogenesis and are the major source of ECM proteins in fibrosis, including type-I collagen. During activation HSCs undergo transition into proliferative, fibrogenic, proin-flammatory and contractile myofibroblasts.

Fibrogenesis in hepatic stellate cells is enhanced oxidative stress and lipid peroxidation, production of cytokines, growth factors and acetaldehyde. Inflammation and necrosis in the liver trigger fibrosis as a part of the wound-healing and scarring response. Transforming growth factor is a key profibrotic cytokine.

ROS produced by inflammatory cells, activate HSCs via lipid peroxidation, and lead to increased secretion of collagen. Acetaldehyde stimulates the production of several ECM including type-I collagen and enhance the expression of TGF in HSCs and fibroblasts.

**Cofactors Implicated in Alcoholic Liver Disease**

Numerous cofactors have been implicated in the pathogenesis of alcoholic liver disease, including inherited differences in ethanol metabolism, nutritional abnormalities (e.g., malnutrition, antioxidant depletion, and iron overload), and concomitant infection with hepatitis viruses like HBV and HCV.

**Gender**

Women are more susceptible to alcoholic liver injury than men. Studies suggest that women who consume 80 g/day of ethanol begin to display signs of liver disease after as short a time as 10 years. The relative deficiency of gastric ADH in women may explain why they display higher blood ethanol levels than men after drinking similar quantities of ethanol.

**Nutrition and Obesity**

The role of nutrition in the pathogenesis of alcoholic liver injury is quite controversial. Malnutrition could facilitate alcoholic liver injury by several mechanisms. Depletion of antioxidant vitamins could lead to enhanced oxidative stress in the livers of alcoholics; vitamins A and E in particular are known to be reduced by chronic ethanol ingestion. A diet high in polyunsaturated fat enhances lipid peroxidation which enhances the risk of alcoholic liver injury. Obesity is one of the most important environmental risk factor determining the risk of cirrhosis in heavy drinkers.

**Viral Hepatitis**

Hepatitis C virus infection contributes importantly to liver injury in alcoholics. Roughly 18–25% of alcoholics are infected with this virus. Infection has been reported to correlate strongly with the presence of advanced liver disease; 40% of cirrhotic patients are positive for hepatitis C virus as compared with 25% with non-fibrotic liver injury. Liver cancer risk increases 100-folds in HCV infected patient with heavy alcohol ingestion. Hepatitis B virus infection also increases the severity of liver injury in alcoholics.

**Cigarette Smoking**

Alcoholics who smoke more than one pack of cigarettes per day have three times the risk of cirrhosis as those who do not smoke.

**Coffee Drinking**

Consumption four or more cups of coffee daily leads a 5-fold lower incidence of cirrhosis than in those who do not drink coffee. The reason for the synergistic effect of smoking and the protective effect of coffee is uncertain.

**Clinical Features**

The term alcoholic hepatitis is used to describe the acute clinical manifestations of alcoholic liver injury. To diagnose alcoholic hepatitis, patients should have a significant history of ethanol consumption (approximately 80 g/day of ethanol, preferably for 1 year or more), along with signs or symptoms of active liver injury. Encephalopathy, hyperbilirubinemia and hypoprothrombinemia indicate advanced injury.

The most common clinical manifestation of alcoholic liver disease is hepatomegaly. Hepatomegaly is related in part to the accumulation of fat within liver cells. Hepatocyte swelling rather than steatosis is believed to be the major cause of liver enlargement in moderately or severely ill patients.

The symptoms of mild alcoholic liver disease are vague, with anorexia and weight loss predominating.

Patients with moderate-to-severe alcoholic liver disease exhibit different signs and symptoms, like jaundice, ascites and encephalopathy. Jaundice is a good predictor of disease severity, as it is present in 100% patients with mild to moderate disease, but only 17% of patients with mild disease. Ascites is detectable in over three-fourths of patients, and encephalopathy in over half. Another important feature of alcoholic hepatitis is fever, which is present in roughly 20% patients and does not necessarily predict infection.

**Laboratory Findings**

Leucocytosis is common in alcoholic hepatitis, particularly in patients with moderate-to-severe disease.

The level of the enzyme aspartate aminotransferases (AST) is greater than that of alanine aminotransferases (ALT). When the AST: ALT > 1.5, the most likely diagnosis is ALD. Glutamyl-transferase, mean corpuscular erythrocyte volume and carbohydrate-deficient transferring are frequently used to diagnose ALD. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rarely exceed 400 IU/L. Elevations significantly greater than 400 IU/L should raise concern about other or concurrent causes of liver injury.

**Imaging Studies**

There are no characteristic radiographic features of alcoholic liver disease. The most common finding is hepatic steatosis, detectable by increased echogenicity on sonography or by extremely low attenuation of the liver on unenhanced computed tomography (CT) scan. The major value of imaging studies is to exclude other causes of abnormal liver tests

in a patient who abuses alcohol, such as obstructive biliary pathology, or infiltrative and neoplastic diseases of the liver.MRI has been used as an adjunct to diagnose cirrhosis, and to distinguish end-stage liver disease related to viral hepatitis infection from ALD. Specific features that may be suggestive of alcoholic cirrhosis include a higher volume index of the caudate lobe, more frequent visualization of the right posterior hepatic notch, and smaller size of regenerative nodules of the liver in patients with cirrhosis on the basis of ALD versus chronic viral hepatitis.

**Liver Biopsy**

Ideally, a diagnosis of alcoholic liver disease should be based on histologic findings. If alcoholic liver disease is suspected on the basis of clinical and laboratory information, the diagnosis is correct in approximately 90% of cases. Liver biopsy is helpful in determining the extent of fibrosis in patients with good synthetic function. Cardinal features of alcoholic liver injury that can be recognized with light microscopic studies include steatosis, ballooning of hepatocytes, Mallory bodies and inflammatory infiltrate in which neurtophils are prominent, and fibrosis.

Steatosis, which connotes the presence of fat droplets in hepatocytes, is present in almost 100% of patients with alcoholic liver injury. Alcoholic steatosis is most prominent in pericentral zones, but in severe cases exhibits a panlobular distribution. The classic pattern of alcoholic steatosis is macrovesicular.

Ballooning degeneration of hepatocytes describes marked cell swelling, with a pale, often granular appearance of the cytoplasm. Hepatocyte ballooning can be detected in over 75% of patients with clinical alcoholic liver injury.

Mallory bodies are crescent-shaped, eosinophilic structures than often wrap around the nucleus of hepatocytes. They represent a condensation of intermediate filaments, particularly cytokeratins, within the cytoplasm of hepato-cytes. Mallory bodies are found in 76% of patients.

Fibrosis in alcoholic liver injury begins with deposition of connective tissue around the terminal hepatic venules. As the lesion progresses, connective tissue extends into the hepatic parenchyma, surrounding hepatocytes in a ‘chicken-wire’ fashion.

Specific features on liver biopsy also convey prognostic importance. The severity of inflammation (i.e., degree of polymorphonuclear cell infiltration) and cholestatic changes correlate with increasingly poor prognosis, and may also predict response to corticosteroid treatment in severe AH. Megamitochondria in alcoholic hepatitis may be associated with a milder form of AH, a lower incidence of cirrhosis and fewer complications with a good long-term survival. AH is associated with perivenular and pericellular fibrosis which

may be a harbinger of future cirrhosis, especially in patients who continue to abuse alcohol or those who are coinfected with hepatitis C virus. Mallory bodies, giant mitochondria, neutrophilic infiltration, and fibrosis may be seen in conditions other than ALD.

**Prognostic factors in alcoholic hepatitis**

The Maddrey discriminant function (MDF), a disease-specific prognostic score, has been used to stratify a patient’s severity of illness. The initial formula was derived in the context of clinical trials of alcoholic hepatitis, and later modified to:

**MDF: 4.6 (Patient’s prothrombin time - control prothrombin time) + total bilirubin (mg/dL)**

Patients with a score of greater than or equal to 32 were at the highest risk of dying, with a one month mortality as high as 30–50%.

Other scoring systems have also been proposed to stratify patients, including the combined clinical and laboratory index of the University of Toronto, the Beclere model, the MELD (Model for End-Stage Liver Disease) score, and the Glasgow Alcoholic Hepatitis Score (GAHS). The diagnostic abilities of the latter two models have been tested against the MDF and other scoring systems for cirrhosis (such as the Child-Turcotte-Pugh score, or CTP) in terms of sensitivity and specificity.

**MELD Score: 3.8 x loge (bilirubin in mg/dL) + 11.2 \* loge (INR) + 9.6 x loge (creatinine mg/dL) +6.4**

MELD score >20 suggest severe AH and indicates poor outcome. Lille score (a continuous score with a scale from 0 to 1) at 4–7 days of corticosteroid therapy can be used to assess the response to steroid therapy (Lille score < 0.45). Most of the score cannot predict the mortality beyond 90 days. Combination of baseline MELD score and Lille score at day 7 has the best predictors of mortality at 2-month and 6-month.

**Glasgow Alcoholic Hepatitis Score (GAHS)**

**Score 1 2 3**

Age \_ <50  50 –

WBC <15  15 –

Urea (mmol/L) <5  5 –

PT ratio <1.5 1.5–2.0  2

Bilirubin (mg/dL) <7.3 7.3–14.6  14.6

Poor prognosis if score: >8 (for score calculated on hospital

day 1 or day 7)

**Treatment**

Management of alcoholic liver disease is abstinence as well pharmacotherapy.

**Abstinence**

The mainstay of treatment for alcoholic liver disease is abstinence. Abstinence has been shown to improve the outcome and histological features of hepatic injury, to reduce portal pressure and decrease progression to cirrhosis, and to improve survival at all stages in patients with ALD. Recidivism (relapse to alcohol) is a major risk in all patients at any time following abstinence. There are several medications tried to help sustain abstinence. They are disulfiram, sertraline, gabapentin, baclofen, naltrexone, nalmefene, topiramate and acamprosate. Naltrexone or acamprosate may be considered in combination with counselling to decrease the likelihood of relapse in patients with alcohol abuse/dependence in those who achieve abstinence.

**Non-pharmacological Treatment Including Herbal Treatment**

Cognitive behavioral therapy, motivational therapy and psychoeducation are very importation in the management of alcoholic liver disease to improve abstinence.

Silymarin is an antioxidant compound extracted from milk thistle. The existing data suggests that silymarin can improve survival in select patients with alcoholic cirrhosis, but that the outcome may not exceed that achievable by abstinence alone.

Other herbal remedies are ginseng, green tea, gingko, fenugreek seed polyphnol, betaine and curcumin.

**Nutrition**

The presence of significant protein calorie malnutrition is a common finding in alcoholics, as are deficiencies in a number of vitamins and trace minerals, including vitamin A, vitamin D, thiamine, folate, pyridoxine and zinc. Treatments consists of conventional amino acids, with some protocols substituting branched-chain amino acids and others adding lipids. Alcoholic patients treated with nutritional supplements often display more rapid normalization of biochemical liver tests (AST, bilirubin, albumin) than those receiving standard hospital diets. High protein and high calorie intake (1.2–1.5 g/kg for protein and 35–40 kcal/kg for energy) is the most important in nutrition as patient is severely hypercatabolic.

**Management of Alcohol Withdrawal**

**Syndrome**

Abrupt discontinuation or markedly reduction in alcohol consumption leads to alcohol withdrawal syndrome (AWS).

Mild AWS usually develops within 6–24 hrs of the last drink.

Symptoms of mild AWS are nausea/vomiting, tremors, hypertension, tachycardia, hyperreflexia, irritability, anxiety and headache. These symptoms may progress to more severe forms of AWS, characterized by delirium tremens, generalized seizures, coma, and even cardiac arrest and death. Older patients are at greater risk for delirium tremens.

Benzodiazepines are the most commonly used drugs to treat AWS. Long-acting benzodiazepines (e.g., diazepam and chlordiazepoxide) protect against seizures and delirium; short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function. Precipitation of hepatic encephalopathy is the most important factor once patient is on benzodiazepines.

**Recommendation of treatment of alcoholic hepatitis**

All patients with alcoholic hepatitis should be counselled to completely abstain from alcohol.

All patients with alcoholic hepatitis or advanced ALD should be assessed for nutritional deficiencies (protein-calorie malnutrition), as well as vitamin and mineral deficiencies. Those with severe disease should be treated aggressively with enteral nutritional therapy.

Patients with mild-to-moderate alcoholic hepatitis – defined as a Maddrey score of <32, without hepatic encephalopathy, and with improvement in serum bilirubin or decline in the MDF during the first week of hospitalization – should be monitored closely, but will likely not require nor benefit from specific medical interventions other than nutritional support and abstinence.

Clinical diagnosis of AH is determined in a patient with rapid development or worsening of jaundice and liver-related complications, with serum total bilirubin >3 mg/dL; ALT and AST elevated >1.5 times the upper limit of normal but <400 U/L with the AST/ALT ratio >1.5; documentation of persistent heavy alcohol use until 8 weeks before onset of symptoms; and exclusion of other liver diseases. Severe AH is identify by Maddrey discriminate function score >32 or MELD score >20.

Characteristic histological findings of AH include macro vesicular steatosis, lobular infiltration of neutrophils with hepatocyte damage (Mallory–Denk bodies and/or ballooning), bilirubin stasis and liver fibrosis, which is typically described as pericellular and sinusoidal (“chicken wire” appearance.

**Corticosteroids**

There are more than 13 trials for use of steroid in alcoholic hepatitis had published. Most of these trials were small and therefore had only limited statistical power to detect even

moderate treatment effects; five suggested an improvement in outcome, with decreased short term mortality in steroid-treated patients compared to placebo-treated patients, whereas rest showed no effect. Patients with severe alcoholic hepatitis judged either by a discriminate function of more than 32 or MELD score more than 20 with our without presence of encephalopathy, benefit from Methylprednisolone (32 mg intravenously) or prednisolone (40 mg orally for total duration of 4 weeks) administered daily for 28 days. Corticosteroids are not recommended for patients with active gastrointestinal hemorrhage, infection, or renal insufficiency. The long-term effect of corticosteroids on liver injury and survival rates beyond 1 year is unknown. The STOPAH study - largest randomized placebo controlled multicenter study from the United Kingdom on steroids or pentoxifylline for Alcoholic Hepatitis on 1103 severe AH patients showed only a trend for mortality benefit at 28 days with prednisolone, compared with patients receiving placebo (13.8% vs 18%, *P* =0.056). A meta-analysis of randomized studies (including the STOPAH study) showed that corticosteroids were effective in reducing short-term mortality by 46%.

One widely used model (Lille Model, *www.lillemodel.com*) needs six variables to predict 6-month mortality in patients who were universally treated with steroids (including age, renal insufficiency (serum creatinine >1.3 or creatinine clearance >40), albumin, prothrombin time, bilirubin, and change in bilirubin over 1 week), and showed an improved prognostic ability compared to MDF or GAHS scores.

**Pentoxifylline**

Pentoxifylline is with inhibition of tumor necrosis factor-. It was recently studied as treatment for acute alcoholic hepatitis, in a placebo-controlled trial involving 101 patients. Pentoxifylline (400 mg orally three times a day) increased 4-week survival from 53.9% to 75.5%. Pentoxifylline reduced the incidence of hepatorenal syndrome from 34.6% to 8.2%. The pronounced effect of Pentoxifylline on renal function is unexplained, but may be related to a direct influence of the drug on the renal microcirculation.

**Antioxidants**

No evidence of beneficial effect of cocktails of anti-oxidants including vitamin E and N-acetylcysteine.

**Other Anticytokine Therapy**

Tumour necrosis factor- plays an important role in the pathogenesis of alcoholic hepatitis. Inhibitors of TNF that have been studied include infliximab, a monoclonal chimeric anti-TNF antibody, and etanercept, a fusion protein containing

the ligand-binding portion of the human TNF receptor fused to the Fc portion of human immunoglobulin G1. Clinical trials did not show any survival advantage, thus, the use of these parenteral TNF inhibitors should be confined to clinical trials.

**S-Adenosylmethionine**

This drug has the potential to reduce alcoholic liver injury by replenishing mitochondrial glutathione and diminishing oxidative stress. The drug failed to show a significant survival benefit over placebo.

**Polyunsaturated Lecithin**

This compound, extracted from soybeans, has been shown to prevent hepatic fibrosis in alcohol-fed baboons. It supposedly acts by stimulating collagenase activity in hepatic stellate cells, thus down-regulating the net amount of collagen deposited by these same cells in alcoholic liver injury.

**Propylthiouracil**

This drug is advocated for alcoholic hepatitis based on evidence that liver injury is related to a “hypermetabolic state,” with increased hepatic oxygen consumption.

**Colchicine**

Colchicine (1 mg/d orally for 30 days), which has both anti-inflammatory and antifibrotic properties, has also been tested in alcoholic cirrhosis after several small clinical trials, had suggested improvement in fibrosis on serial liver biopsies in treated patients. However, a systematic metaanalysis by the Cochrane group of 15 randomized trials with 1714 patients showed no benefit of treatment on overall mortality, liver related mortality, liver tests or histology. In addition, there was an increased risk of adverse effects related to colchicine therapy.

**Liver Transplantation**

Transplantation is an option for some patients with end-stage alcoholic liver disease, provided that a defined period of abstinence (preferably 6 months or longer) precedes the surgery. Recent studies show even 3 months of abstinence is enough to prevent recidivism. Despite of concerted efforts at careful patient selection, the rate of recidivism is as high as 20–50%. Recidivism is most likely to be reported after 2 years of LT with the majority of recidivists ]reporting

intermittent use of alcohol. The lack of effective rescue medical therapies for non-responders to prednisolone provides the rationale for considering early LT.

Patient survival rates after LT for alcoholic cirrhosis at 1, 3, 5 and 10 years after LT are reported to be 84–89%, 78–83%, 73–79% and 58–73%, respectively, which are similar to other indications for LT. Recurrent alcoholic cirrhosis is reported in about 5% of all LT performed for alcoholic cirrhosis, with cumulative probability of 33–54% at 10 years after LT among recidivists. Survival of patients with recurrent cirrhosis is about 41 and 21% at 10 and 15 years after LT, respectively, compared to similar survival rates of about 70 and 50% among abstainers.

**Further Reading**

1. Ashwani Singal, Ramon Bataller, Joseph Ahn et al. ACG Clinical Guideline: Alcoholic Liver Disease. *Am J Gastroenterol* 2018;113:175–94.

2. Day CP. Treatment of alcoholic liver disease. *Liver Transpl* 2007;13:S69–75.

3. Levitsky J, Mailliard ME. Diagnosis and therapy of alcoholic liver disease. *Semin Liver Dis* 2004;24:233–47.

4. Wakim-Fleming J, Mullen KD. Long-term management of alcoholic liver disease. *Clin Liver Dis* 2005;9:135–49.

5. Leevy CM, Moroianu SA. Nutritional aspects of alcoholic liver disease. *Clin Liver Dis* 2005;9:67–81.

6. Srikureja W, Kyulo NL, Runyon BA, et al. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. *J Hepatol* 2005;42:700–6.

7. Mathurin P, Mendenhall CL, Carithers RL Jr, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002;36:480–7.

8. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011;141: 1572–85.

9. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. *Cochrane Database Syst Rev* 2011, CD008537.

10. Basra G, Basra S, Parupudi S. Symptoms and signs of acute alcoholic hepatitis. *World J Hepatol* 2011;3:118–20.

11. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009;360:2758–69.

12. Gholam PM. Prognosis and prognostic scoring models for alcoholic liver disease and acute alcoholic hepatitis. *Clin Liver Dis* 2016;20:491–7.

13. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. *Clin Liver Dis* 2012;16:805–26.

14. Singal AK, Kamath PS, Gores GJ, et al. Alcoholic hepatitis: current challenges and future directions. *Clin Gastroenterol Hepatol* 2014;12:555–64.

**Chapter 47.**

**Wilson Disease**

**Introduction**

Wilson disease (WD) results from mutations in the *ATP7B* gene inherited as an autosomal recessive trait on the long arm of chromosome 13.Reduction in ATP7B function results in decreased biliary copper excretion with increased copper accumulation in hepatic and extrahepatic tissues that leads to the clinical features of WD. This disorder has a global incidence of 1:30,000, and is present in all populations.

**Copper Metabolism**

The body contains 110 mg of copper, mainly in the bones (46 mg), muscles (28 mg) and connective tissues. Plasma copper level is around 1 mcg/mL, majority is bound to ceruloplasmin. The average adult diet contains 1.5–5 mg of copper per day, around 50% is unabsorbed and excreted in feces; 25–40% is absorbed from the duodenum and stored by enterocytes. From enterocytes pool, 75% flows via porta system to the liver and rest is bound to albumin in the circulation. From hepatic pool, 20% of copper is re-excreted in the bile, and 80% is transported to the periphery, bound to ceruloplasmin. Foods containing high levels of copper include shellfish, grains, nuts, mushrooms, legumes, chocolate and organ meats. Loss of ATP7B function is the basis for reduced hepatic biliary copper excretion and reduced synthesis of copper-bound ceruloplasmin, which leads to increase cytosolic and mitochondrial copper level. Treatments for Wilson disease block copper absorption by the gut and increase fecal copper excretion (zinc) or increase urinary copper excretion (chelating agents like D-penicillamine and trientine).

**Clinical manifestations**

Liver and brain are two predominant organs involved in WD. Although copper starts accumulating soon after birth, the disease takes at least 3 yrs to manifest. Hepatic presentation is seen in early age group (<10 yrs: 80%), whereas neuropsychiatric presentation increased as age advanced ( >18 yrs: 70%). Family screenings of affected person’s is often asymptomatic (also termed *presymptomatic 3–40%*).

The clinical spectrum of liver diseases associated with Wilson disease is broad ranging from asymptomatic hepatomegaly to cirrhosis including acute liver failure. Acute liver failure (ALF, 8–20%) is seen in childhood and often fatal without liver transplantation. Coombs-negative non immune intravascular haemolysis is usually associated with ALF. The combination of the ratio of serum alkaline phosphates/total bilirubin < 4 and ASL: ALT ratio > 2.2 was described to have very high sensitivity and specificity. But has not been validated in further studies. Chronic haemolytic anemia leads to mixed gallstones in patients with WD. Hepatocellular carcinoma progression is very rare in patients with WD.

Most patients with central nervous system involvement are believed to have significant liver disease at the time of presentation. Deterioration in handwriting, poor school performance, dysarthria and drooling of saliva are the early manifestation of WD. The classical dystonia involving the facial and mandible muscles produce “Wilson’s facies” – Vacuous smile, open mouth, hypersalivation and dull look. Neurologic disease may be manifested as motor abnor-malities with parkinsonian characteristic of dystonia, hypertonia and rigidity, chorea or athetosis, tremors & dysarthria. Disabling muscle spasms can lead to contractures, dysarthria, dyphonia and dysphagia. At this stage of disease magnetic resonance imaging of the brain may be useful in delineating changes in the basal ganglia.

Kayser-Fleischer ring (KF ring) and sunflower cataract (2–17%) are the most common ocular manifestation of WD. Sunflower cataract is due to copper deposition in the anterior capsule of the lens, and usually associated with KF ring. It does not disturb the vision and disappear with chelating therapy.

Copper deposition in the epithelium of proximal and distal convoluted tubules leads to tubular (8%) injury. However, glomerular injury (10%) is contributed by chelating therapy. Urine routine and microscopy should be checked in all patients with WD to evaluate tubular function, while on treatment urine protein should be checked to evaluate drug induce glomerular injury.

Oxidative stress secondary to excess copper leads to haemolysis (Coombs-negative haemolytic anaemia). Haemolytic anaemia usually mild, but it can be severe in ALF. Osteoporosis (20–80%, usually asymptomatic), osteomalacia (14–35%) and spontaneous fracture (9-35%) are the major skeletal manifestation of WD. Asymptomatic cardiac arrhythmias are not uncommon in WD.

**Diagnosis**

Serum ceruloplasmin, KF rings, and 24-hour urine copper is the most commonly used tests to diagnose WD.

**Serum Ceruloplasmin**

Ceruloplasmin, produced by the liver, is a carrier protein for the transport of copper in the blood. The normal range of ceruloplasmin is 20–50 mg/dL. About 95% of homozygotes with Wilson disease have values of less than 20 mg/dL. Up to 5% of all homozygotes and up to 15–50% of persons with liver disease may have normal levels, which is defined as concentrations above 20 mg/dL. In some cases, normal levels are present in patients with active liver injury, probably as a consequence of acute-phase responses in the liver or estrogen supplementation. Low serum concentrations of ceruloplasmin may also be observed in hypoproteinemic states, such as protein–calorie malnutrition, nephrotic syndrome, protein-losing enteropathy, and other forms of severe decompensated liver disease.

**Kayser-Fleischer ring**

Classically, the K-F ring is the hallmark of WD. In fact, evidence of K-F rings in combination with a serum low ceruloplasmin or typical WD neurologic manifestations is diagnostic. Corneal copper deposits within Descemet membrane appear as granular golden-greenish layer that is best seen by slit-lamp observation. Although K-F rings are commonly present in up to 98% of patients with neurologic and psychiatric disease, they are found in only 40–66% of patients with hepatic presentation and are uncommonly seen in young, asymptomatic patients.

**Urinary Copper Assay**

Twenty-four-hour urine copper estimation indirectly reflects the serum free copper level. A level of >100 µg/24-hr is the diagnostic for WD. It may be false negative in asymptomatic patient. When urinary excretion of copper is tested, it is crucial that a metal-free container be used and that the adequacy of the collection is monitored by correlation with volume excreted or with creatinine excretion. D-penicillamine (DP) challenge test was once upon a time very useful, but now out of recommendation in view of lack of validation.

**Serum Copper**

Around 90% of copper is bound to ceruloplasmin. The total concentration of copper in plasma represents ceruloplasmin – bound copper + nonceruloplasmin-bound (“free”) copper. Total serum copper estimation does not reflect tissue levels and so unreliable in the diagnosis.

**Liver Copper Estimation**

Normal concentrations of copper in the liver rarely exceed 50 µg/g dry weight of liver. Most patients homozygous for Wilson disease have levels above 250 µg/g. Its usefulness is limited in view of uneven distribution of copper in the liver as well as low level of copper in regenerating nodules. High hepatic copper also is observed in cholestatic liver disorder.

Liver biopsy specimens for a quantitative copper determination should be obtained with a needle and placed dry in a copper-free vessel. About 1 cm of a 1.6 cm diameter core of liver should be dried overnight at 56oC in a vacuum oven or, alternatively, frozen immediately before being shipped to a laboratory specializing in atomic absorption assay.

**Liver Histology**

Liver histology is non-specific in WD. Early stage of WD, there is hepatic steatosis and subsequently advancing fibrosis. During the phase of steatosis, ultrastructural features in hepatocyte mitochondria include crystalline deposits and dilated cristae. As further copper accumulates, one may see dense lysosomal deposits of copper and copper metallo-thionein. Advanced fibrosis and cirrhosis is common with later recognition of the disease, but can be present even in young patients. Marked hepatocellular disruption with apoptotic as well as necrotic injury on the background of advanced fibrosis is found in ALF due to WD.

**Magnetic Resonance Imaging Brain**

The MRI features of WD are: hyperintesities in basal ganglia, thalamus, and brainstem (55%), tectal plate hyperintensity (75%), central pontine myelinolyis-like abnormalities (62%) and “Face of giant panda” (14.3%).

**Genetic Studies**

Over 600 mutations are reported in ATP7B gene on chromosome 13. Identification of ATP7B genetic mutation in patient with WD, leads to testing for these mutations in his/her presymptomatic siblings. It is useful to identify heterozygote carriers from homozygotes or compound hetrozygotes for WD.

**Modified Leipzig Score**

Modified Leipzig score is the most recent score for WD described. It is described in **Table 47.1**.

**Treatment**

The aim of medical therapy is to abolish symptoms, and prevent the worsening or progression of disease. Serial liver biopsies have no role in the management of Wilson disease.

Liver transplantation should be reserved for patients with severe hepatic insufficiency or liver failure occurring in the context of acute liver failure or end-stage liver disease.

Pharmacologic treatments for Wilson disease include chelating agents and zinc salts. Chelating agents (e.g., penicillamine, trientine) remove copper from potentially toxic sites within cells and detoxify and / or excrete the remaining copper. Zinc salts act mainly by blocking the intestinal absorption of dietary copper, but also stimulate the biosynthesis of endogenous chelators in the liver, such as metallothioneins, that help detoxify the remaining metal.

The treatment of asymptomatic patients and maintenance therapy for previously symptomatic patients is identical. The largest experience for long-term, treatment is still with D-penicillamine, whereas trientine and zinc salts are alternative agents with fewer potential side effects.

DP, binds to copper, is the standard of care in patients with WD. Every gram of DP promotes urinary excretion of 200 mg of copper. The dose of DP is 20 mg/kg/day in children. An adult dose is usually 750–1000 mg/day in 2–3 divided doses on empty stomach. Food reduces its absorption by 50%. Treatment with DP leads to massive copper excretion via urine. Pyridoxine supplements in a dose of 20–40 mg should be given with DP. In patients with neurological WD, paradoxical worsening of symptoms is observed in around 10%. Gradual escalation in the dose with close clinical and biochemical observations is suggested. Around 10–30% of patients reported significant side effects with DP therapy. Skin hypersensitivity, neutropenia and thrombocytopenia are the early side effects (1–3 weeks). Late side (3 weeks – 3 months) effects include lupus-like syndrome, severe thrombocytopenia, proteinuria, total aplasia, and optic neuritis. Higher dose in longer duration leads to progeria-like skin lesions, cutis laxa and elastosis perforans serpiginosa.

Trientine (750–1500 mg daily in 3 doses on empty stomach) is a chelator with similar action like DP but has fewer side effects. It can be used in patients who are intolerant to DP. It is heat sensitive, thus to be stored in 2 and 8ºC. Monitoring for iron deficiency is needed as it chelates iron also.

Zinc induces metallothionein in enterocytes, which binds absorbed copper, thus prevents its entery into the portal circulation. Copper is excreted in the feces. In view of slow action, zinc can act as adjuvant therapy with chelating agent. The dose of zinc is 150 mg/day in three divided dose on empty stomach. Zinc is preferred therapy in presymptomatic patients and patients with neurological WD. Zinc with or without low dose of DP is advocated as long term therapy after adequate initial chelating.

The dietary consumption of foods with a high copper content should be avoided during the initial phases of treatment. These include organ meats such as liver, in addition to nuts, shellfish and chocolate. During the maintenance phase of therapy liberalization of the diet is permitted.

Liver transplantation should be considered for patients with Wilsonian acute liver failure and for those with severe hepatic insufficiency unresponsive to medical therapy. During the acute phase of acute liver failure, when toxic copper complexes are being released into the circulation, plasmapheresis, exchange transfusion and albumin dialysis have utilized in an effort to further reduced copper-induced toxicity.

The goal of treatment in pregnant patients is to maintain adequate disease control in the mother, reduce her risk for bleeding, and prevents interference with wound healing and the possibility of teratogenicity. Pregnancies have been successful in patients taking penicillamine, trientine or zinc. For patients being maintained on chelation therapy, the dosage of penicillamine or trientine should be lowered whenever possible early in the course and the pregnancy. The suggested dosage is 500 mg/day, and monitoring during each trimester is advised. Zinc therapy can be maintained uninterrupted at full dosage during pregnancy and postpartum.

When patients with Wilson disease maintained on chelating agents must undergo surgery, the dose of their medication should be reduced preoperatively and perioperatively to avoid interference with wound healing. The dosage of penicillamine or trientine can be reduced to 250–500 mg daily during this time and rapidly advanced to a maintenance dosage once wound healing has taken place. No adjustment of the dosage is required for patients on zinc therapy, either perioperatively or postoperatively.

The prognosis for patients who comply with pharmacotherapy for Wilson disease is excellent, even if cirrhosis or chronic hepatitis is present at the time of diagnosis. Patient with neurologic or psychaitric symptoms of Wilson disease may continue to recover for months to years after the initiation of treatment.

**Treatment of Presymptomatic Liver Disease**

Presymptomatic patients usually benefit from monotherapy with a chelating agent or with a zinc salt. Treatment goals for these individuals is to prevent any disease progression, and although monitoring may be less frequent it should include both urine copper excretion on therapy as well as liver tests and blood counts. Repeat liver biopsy should be reserved for those with possible treatment failure and is not needed for most patients.

Zinc therapy is the preferred agent to treat WD in this population because it has an excellent safety profile. Asymptomatic children, particularly those who are prepubertal must have adequate copper for proper bone, connective tissue, and mental development balanced with anti-copper therapy to prevent copper toxicity. Close monitoring should include 24-hour urine copper levels maintained in the high-normal range (40–50 g/24 hrs) and complete blood cell count, observing for early signs of overtreatment and copper deficiency such as hypochromic microcytic anaemia and leukopenia.

**Acute Liver Failure**

Wilson disease accounts for about 5% of all cases of ALF. Patients with ALF due to WD should be evaluated for emergent liver transplant as the mortality rate in this subgroup approaches 100%. In this setting, there is typically massive hemolysis and marked elevation of circulating copper in addition to other features of WD. Treatment of the patient to reduce the high level of copper in the circulation may help achieve better outcomes. Renal insufficiency is often present in these patients, and plasmapharesis and molecular adsorbents recirculating system (MARS) has been utilized with success with endpoints being reducing haemolysis, and slowing both hepatic and renal injury serving as a bridge to liver transplantation.

**Pregnancy**

Therapy for WD should be continued during pregnancy with some modifications. Concerns regarding the chelating agents’ effect on teratogenicity and postpartum wound healing have been raised. Hence, dose reduction using these medications has been advised. Recent treatment guidelines recommend that patients reduce the dose to below maintenance dosing

(~10 mg/kg/day) before or early on during their first trimester because this is the highest period of risk for teratogenicity. Patients on zinc monotherapy therapy do not need to change the dose. Alternatively, one can consider switching to a zinc salt at the onset of pregnancy, if tolerated

**Family Counselling**

All first-degree relatives of a patient with WD must be screened for the disease. Statistically, siblings have a 1 in 4 chance and children of a parent with WD have a 1 in 180 chance of inheriting WD. The optimal first-line testing is direct WD mutation analysis; mutation analysis is preferred to screening for polymorphisms around the gene as this is dependent on the diagnosis being firmly established in the proband. When molecular testing is not feasible, standard testing should include the combinations of liver function tests, serum ceruloplasmin, 24-hour urinary copper, and slit lamp eye examination for K-F rings. Testing should be performed at 2 years of age unless any signs or stigmata of liver disease are found earlier. Repeat clinical and biochemical testing is recommended in 2–3 years if the results are normal.

**Prognosis**

The prognosis for patients with Wilson disease is excellent. Prognostic scoring systems for WD are a useful tool to direct therapy, identify which patients can be treated medically and which have a high likelihood for death and will require liver transplant. A prognostic index calculated by Nazer et al (score range 0–12) based on serum bilirubin, serum AST, and prolongation in prothrombin time was able to predict response to chelation therapy in newly diagnosed WD patients who scored 6 or less. An improvement to the Nazer prognostic index score by Dhawan and associates based on serum bilirubin, INR, AST, white blood cell count and albumin (score range: 0–20) was able to predict favorable response to chelation therapy in newly diagnosed pediatric WD patients who scored 11 and less; and those patients who scored >11 died without transplantation. Devarbhavi et al described bilirubin and encephalopathy as best predictors of survival in children and found this more predictive compared to MELD, PELD and modified Nazer index

**Further Reading**

1. Schilsky ML. Non-invasive testing for Wilson disease: revisiting the d-penicillamine challenge test. *J Hepatol* 2007;47:172–3.

2. Scheinberg IH,Sternlieb I. Treatment of the neurologic manifestations of Wilson’s disease. *Arch Neurol* 1995; 23:373–81.

3. Brewer GJ, Johnson VD, Disk RD, et al. Treatment of Wilson’s disease with zinc. XVII: treatment during pregnancy. *Hepatology* 2003;31:364–70.

4. Roberts EA, Schilsky ML. AASLD practice Guideline. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47:2008–111.

5. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson’s disease in children: 37-year experience and revised King’s score for liver transplantation. *Liver Transpl* 2005;11:441–8.

6. Cz³onkowska A, Litwin T. Wilson disease - currently used anticopper therapy. *Handb Clin Neurol* 2017;142:181–91.

7. Litwin T, Dzieyc K, Czonkowska A. Wilson disease-treatment perspectives. *Ann Transl Med* 2019;7:S68.

8. Nagral A, Sarma MS, Matthai J, et al. Wilson’s Disease: Clinical Practice Guidelines of the Indian National Association for Study of the Liver, the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India. *J Clin Exp Hepatol* 2019;9:74–98.

9. Patil M, Sheth KA, Krishnamurthy AC, Devarbhavi H. A review and current perspective on Wilson disease. *J Clin Exp Hepatol* 2013;3:321–36.

**Chapter 48.**

**Autoimmune Hepatitis**

Introduction

Autoimmune hepatitis (AIH) is a chronic disease of unknown cause and is characterized by continuing hepatocellular inflammation and necrosis and has a tendency to progress to cirrhosis. The disease often is associated with other autoimmune diseases. The clinical spectrum is wide, ranging from an asymptomatic presentation to an acute severe disease. It affects all age groups with female gender preponderance. No geographical predilection identify with AIH. Diagnosis is based on elevated levels of serum aminotransferases, gamma globulins, autoantibodies, characteristic findings on histology and exclusion of other causes of chronic hepatitis. It is readily treatable with immunosuppressive therapy in the majority of patients; however, undiagnosed disease is associated with poor outcomes. Many variant, overlapping forms of AIH exist, particularly with coexisting cholestatic features, primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).

Pathophysiology

Inter play of genetic predisposition and environmental triggers lead to necroinflammatory liver damage. Genetic susceptibility to developing autoimmune hepatitis has been associated with the HLA haplotypes B8; B14, DR3, DR4 and Dw3. *C4A* gene deletions are associated with the development of autoimmune hepatitis in younger patients. Non-HLA genetic variants (some rare but functional, e.g., in the genes AIRE, GATA-2, CTLA-4, others common, e.g., in the gene locus for SH2B3 but without a clear-cut coding impact) have also been identified. Rubella, Epstein-Barr, and hepatitis A, B, and C are among the several viruses implicated as triggering agents.

Clinical Features

Clinical features of autoimmune hepatitis widely vary. Autoimmune hepatitis may present as acute hepatitis, chronic hepatitis, or well-established cirrhosis. Autoimmune hepatitis rarely presents as fulminant hepatic failure. Most cases have an insidious onset. Patients may be asymptomatic or have nonspecific symptoms (e.g., fatigue, anorexia, weight loss, behavioural changes and amenorrhea). Systemic or cutaneous abnormalities occur in 25% of patients. Around 20% of patients present initially with signs of decomp-ensated cirrhosis. Pregnancy may lead to spontaneous remission; flare is experienced post partum due immune reconstitution.

Acute presentation mimicked acute viral hepatitis (ie, abdominal discomfort, vomiting, nausea, jaundice) is presenting symptoms in around 50% of children. Fulminant hepatic failure occurred in 11% of the children and was more common in patients with AIH-2. Insidious presentation was characterized by intermittent jaundice or nonspecific symptoms.

Common findings on physical examination are as follows:

1. Hepatomegaly (83%)

2. Jaundice (69%)

3. Splenomegaly (32%)

4. Spider angiomata (58%)

5. Ascites (20%)

6. Encephalopathy (14%)

Biochemical Tests

The laboratory assessment should include determinations of the levels of serum alanine (ALT) or aspartate (AST) aminotransferases, alkaline phosphatase (AP), albumin, total or -globulin, IgG and bilirubin (conjugated and unconjugated). AIH can be asymptomatic in 34–45% of patients. Typically, these patients are men and have significantly lower serum ALT levels at presentation than do symptomatic patients.

An IgG-predominant polyclonal hypergamma-globulinemia is a common finding in patients with untreated autoimmune hepatitis. Gamma globulin values typically range from 3 to 4 g/dL and frequently are as high as 5–6 g/dL. Autoimmune hepatitis is an unlikely diagnosis in patients who have acute hepatitis without hypergammaglobulinemia. The gamma globulin or the IgG level may be followed on a regular basis as a marker of disease responsiveness to therapy.

Autoantibody Analysis

ANA, SMA, anti-LKM1 and anti-LC1 constitute the conventional serological repertoire for the diagnosis of AIH.

Autoimmune hepatitis is characterized by positive findings on autoantibody tests, as follows:

1. AIH-1 - ASMA and ANA

2. AIH-2 - Anti–LKM-1 antibody

3. AIH-3 - Antibodies to soluble liver antigen (anti-SLA) – term AIH -3 is no more in use, present only 15% of patients with AIH.

SMAs are present in 90–100% of patients with autoimmune hepatitis type 1 (AIH-1). ANAs are present in 10% of patients with AIH-1 and in association with SMAs in 40–60% of patients with AIH-1. LKM-1 antibodies are present in 40–45% of patients with AIH-2 and are associated with anti-LC1 antibodies in 50% of patients. Anti-LC1 antibodies occur alone in 30% of patients with AIH-2. In patients negative for conventional autoantibodies in whom AIH is suspected, other serological markers, including at least anti-SLA and atypical pANCA, should be tested. Low autoantibody titers do not exclude the diagnosis of AIH, nor do high titers (in the absence of other supportive findings) establish the diagnosis.

Liver Biopsy

Liver biopsy is the most important diagnostic procedure in patients with autoimmune hepatitis. Autoimmune hepatitis is characterized by a portal mononuclear cell infiltrate that invades the limiting plate surrounding the portal triad and permeates the surrounding lobule (i.e., periportal infiltrate) and beyond. A plasma cell infiltrate sometimes occurs. Biopsies may show evidence for interface hepatitis (i.e., piecemeal necrosis), bridging necrosis, and fibrosis. Interface hepatitis essentially spares the biliary tree but may involve most of the lobule. Lobular collapse, best identified by reticulin staining, is a common finding.

Disease Activity, Severity and Chronicity

Liver biopsy is the most important tool for determining disease activity, severity (inflammatory versus fibrosis) and chronicity of AIH. Interface hepatitis and lymphoplasmacytic inflammation near the portal tract are the cardinal features of AIH. Interface hepatitis is associated with the development of periportal fibrosis, which may progress to bridging fibrosis and ultimately lead to cirrhosis. Hepatocytes ballooning and spotty hepatocytes necrosis are characteristic features of acute AIH. Extensive hepatocyte necrosis, ranging from confluent necrosis through bridging necrosis to panacinar or multiacinar necrosis are characteristic features of fulminant AIH. Untreated moderate-to-severe AIH (aspartate aminotransferase [AST] >5xULN, globulins >2xULN, liver biopsy showing confluent necrosis) had a very poor prognosis, with 5- and 10-year survival of 50% and 10%, respectively. By contrast, 10-year transplant-free survival rates were approximately 90% in treated patients.

Prognosis

The prognosis of autoimmune hepatitis depends primarily on the severity of liver disease at the time of diagnosis. Patients with a severe initial presentation tend to have a worse long-term outcome than patients with mild disease. The inability to enter remission or the development of multiple relapses, either during therapy or after treatment withdrawal, implies a worse long-term prognosis. Without treatment, around 50% of patients with severe autoimmune hepatitis will die in approximately 5 years, and most patients will die within 10 years of disease onset. Treatment with corticosteroids has been shown to improve the chances for survival significantly. The 10-year life expectancies for treated patients with and without cirrhosis at presentation are 89% and 90%, respectively. Immunosuppressive treatment improved the fibrosis scores, with an arrest in progression and no development into cirrhosis.

Hepatocellular carcinoma (HCC) is less common in patients with autoimmune hepatitis-induced cirrhosis than in those with cirrhosis caused by other factors. Nevertheless, HCC is not a rare event in autoimmune hepatitis.

In general, the following factors are associated with a worse prognosis:

1. Young age at presentation

2. AIH-2

3. Coagulopathy

4. Severe initial histologic activity

Diagnostic Criteria

The International Autoimmune Hepatitis Group (IAIHG) published a comprehensive scoring system in 1999, but it was very complex scoring system to be used in clinical practice. A simplified but not validated scoring system was proposed in 2008 **(Table 48.1)**.

**Parameters Discriminators Score**

**ANA or ASMA**  1: 40 +1

 1:80 +2

**Anti-LKM1**  1: 40 +2

**Anti-SLA/LP** Any titre +2

**Total IgG**  > ULN +1

> 1.1 × ULN +2

**Liver Histology** Comparable with AIH +1

Typical of AIH +2

**Absence of viral** No 0

**hepatitis** Yes +2

Definite AIH >7, Possible AIH > 6.

Classification

Two types of AIH (type 1 and type 2) have been recognized based on serological markers but have not been established as valid clinical or pathological entities. A proposed third type (type 3) has been abandoned, as its serologic marker (anti-SLA) is also found in type 1 AIH and in type 2 AIH.

Type 1 AIH is characterized by the presence of ANA, SMA or both, and constitutes 80% of AIH cases. Seventy percent of patients are female, with a peak incidence between ages 16 and 30 years. Fifty percent of patients are older than 30 years, and 23% are at least 60 years old. Associations with other autoimmune diseases are common (15–34%); these include autoimmune thyroid disease, synovitis, celiac disease, and ulcerative colitis. At the time of diagnosis, cirrhosis is present in 25% of patients. Antibodies to SLA have emerged as possible prognostic markers that may identify patients with severe AIH who are prone to relapse after corticosteroid withdrawal.

Type 2 AIH is characterized by the presence of anti-LKM1 and/or anti-LC1 and/or anti-LKM-3. Most patients with type 2 AIH are children, and serum immunoglobulin levels are usually elevated except for the concentration of IgA, which may be reduced. Concurrent immune diseases are common, progression to cirrhosis occurs, and an acute severe presentation is possible.

Management

Treatment benefit in asymptomatic older individuals without cirrhosis or advanced fibrosis and mild disease activity are unclear. Ten-year survival in patients with mild disease without treatment has been reported to range from 67% to 90%. Patients without treatment should be very closely monitored with once in 3 months measurement of ALT and IgG level. Immunosuppressive therapy is the mainstay of the treatment in patients with AIH.

Immunosuppressive treatment should be instituted in patients with classical AIH. Immunosuppressive treatment may be considered in adult patients without symptoms and mild laboratory and histological changes, but the decision must be individualized and balanced against the possible risks of therapy. Immunosuppressive treatment should not be instituted in patients with serious pre-existent comorbid conditions (vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension), or previous known intolerances to prednisone unless the disease is severe and progressive and adequate control measures for the comorbid conditions can be instituted.

Treatment should be instituted with prednisone (starting with 30 mg daily and tapering down to 10 mg daily within 4 weeks) in combination with azathioprine (50 mg daily or 1–2 mg/kg body weight as widely used in Europe) or a

higher dose of prednisone alone (starting with 40–60 mg daily and tapering down to 20 mg daily within 4 weeks) in adults with AIH. The combination regimen is preferred, and prednisolone in equivalent dose can be used instead of prednisone. Treatment should be instituted with prednisone (1–2 mg/kg daily; maximum dose 60 mg daily) in children in combination with azathioprine (1–2 mg/kg daily) or 6-mercaptopurine (1.5 mg/kg daily). Transaminases should be closely monitored during this time to detect reactivation of the disease, which can be controlled by a transient increase in the steroid dose. Azathioprine-related hepatotoxicity is rare. Patients on long-term corticosteroid treatment should be monitored for bone disease at baseline and then annually. Azathioprine monotherapy is as effective at maintaining remission as dual therapy with prednisolone/azathioprine and also associated with fewer side effects.

Azathioprine treatment should not be started in patients with a severe pre-treatment cytopenia or known complete deficiency of thiopurine methyltransferase activity. The possible side effects of therapy with corticosteroids must be reviewed with the patient prior to treatment. Postpartum exacerbation of AIH must be anticipated by resuming standard therapy 2 weeks prior to anticipated delivery and by closely monitoring serum AST or ALT levels at 3-week intervals for at least 3 months after delivery. Blood thiopurine methyltransferase activity should be assessed in patients with cytopenia before or during azathioprine therapy. Counsel patients about steroid and azathioprine-related side effects are integral part of management. Appropriate adjunctive therapies such as vitamin D and calcium supplementation to prevent bone loss should be given. Vaccination against hepatitis A and B should be completed.

Standard treatment regimens lead to sustained remission in majority of patients. 10-year life expectancy for patients with and without cirrhosis and AIH is 89% and 90%, respectively.

Alternative Agents

Budesonide, an oral steroid, with a very high first pass metabolism, may offer an alternative to prednisone. Budesonide was given in a dosage of 3 mg three times daily or twice daily to prednisone. Longer-term follow-up is needed to better assess the efficacy and safety of budesonide, although long term data of budesonide are lacking. Based on moderate-quality evidence, the 2011 BSG guidelines strongly recommend use of budesonide for prednisolone-intolerant patients. Thus, budesonide should not be the first line agent and not used in cirrhotic patients.

Mycophenolate mofetil (MMF) has been established as an effective second line agent for AIH. It is used mostly in azathioprine intolerant patients rather than azathioprine

failure patients. Tacrolimus and rituximab can be used as salvage therapy.

Treatment Endpoints

Patients may achieve 1 of 4 treatment endpoints:

1. Remission

2. Incomplete response

3. Treatment failure

4. Drug toxicity

Remission

Remission is indicated by the absence of symptoms, normalization of aminotransferases and histologic improvement to normal or minimal inflammatory activity on liver biopsy. Histologic remission tends to lag behind clinical and laboratory remission by 3–6 months. Patients achieving remission may be able to taper off prednisone over a 6-week period. Azathioprine can be discontinued after the withdrawal of prednisone. There are no firm guidelines regarding the duration of therapy in either adults or children. However, most patients need relatively long courses of immunosuppressant therapy. It is common for treatment to continue for 2 years or longer before an attempt is made to withdraw medications.

Incomplete Response

Incomplete response (13%) is defined as an improvement that is insufficient to satisfy remission criteria. Many such patients will require indefinite treatment with as low an immunosuppressant dose as is needed to prevent clinical deterioration.

Treatment Failure

Treatment failure (9%) is defined as deterioration in a patient’s clinical condition, laboratory tests, or histologic features during therapy. High-dose prednisone (60 mg/day) alone or prednisone (30 mg/day) plus azathioprine (150 mg/day) are alternative approaches when standard therapy fails. Patients whose condition is resistant to steroids can be treated with cyclosporine, mycophenolate mofetil, tacrolimus or rituximab.

Drug Toxicity

Drug toxicity may occur. Patients must be tapered off from the culprit medication.

Relapse

Relapse occurs in 50% of patients within 6 months of treatment withdrawal and in 80% of patients within 3 years of treatment. Reinstitution of the original treatment regimen usually induces another remission; however, relapse commonly recurs after a second attempt at terminating

therapy. The major consequence of relapse and re-treatment is the development of drug-related complications, which occurs in 70% of patients.

Liver Transplantation

Liver transplantation should be considered in patients with AIH and acute liver failure, decompensated cirrhosis with a MELD score  15, or hepatocellular carcinoma meeting criteria for transplantation. The long-term outlook after liver transplantation is excellent, with 10-year survival rates reported as greater than 75%. Positive autoantibodies and hypergammaglobulinemia tend to disappear within 2 years of transplantation.

Recurrence of autoimmune hepatitis is described after liver transplantation. It has been reported primarily in inadequately immunosuppressed patients. Recurrent AIH should be treated with prednisone and azathioprine in adjusted doses to suppress serum AST or ALT levels or increased doses of corticosteroids and optimization of calcineurin inhibitor levels (preferably, tacrolimus). Continued inability to normalize the serum AST or ALT levels following recurrent disease justifies the addition of mycophenolate (2 g daily) to the regimen of corticosteroids and calcineurin inhibitor. Retransplantation should be considered for patients with refractory de-novo AIH that is progressing to allograft failure.

Overlap Syndrome

The term overlap syndrome has been describe for various forms of autoimmune hepatitis (AIH) that present with characteristics of AIH and primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Patients with overlap syndromes present with both hepatitic and cholestatic biochemical and histological features of AIH, PBC and/or PSC, and usually show a progressive course toward liver cirrhosis and liver failure without adequate treatment. AIH-PBC overlap syndromes have been reported in almost 10% of adults with AIH or PBC, whereas AIH-PSC overlap syndromes were found in 6–8% of children, adolescents, and young adults with AIH or PSC. In addition to AIH-PBC and AIH-PSC overlap syndromes, the outlier syndrome autoimmune cholangitis (AIC), today mainly regarded as antimitochondrial antibody (AMA)-negative PBC.

Treatment of AIH-PBC begins with UDCA (13–15 mg/kg/day). If this therapy does not induce an adequate biochemical response, addition of a glucocorticosteroid at tolerable doses (e.g., prednisone 10–15 mg/kg/day) is advisable. The role of other immunosuppressants (e.g., azathioprine 1–1.5 mg/kg/day) in the long-term management of patients with AIH-PBC overlap syndrome is unclear. Treatment of AIH-PSC begins with UDCA in combination with an immunosuppressive regimen. Liver transplantation should be considered in late-stage disease.

Further Reading

1. Strassburg CP, Manns MP. Treatment of autoimmune hepatitis. *Semin Liver Dis* 2009;29:273–85.

2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015;63:971–1004.

3. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011;60:1611–29.

4. Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol* 2008;14:3360–7.

5. Manns MP, Czaja AJ, Gorham JD, et al. American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51: 2193–213.

6. Dhruv Lowe, Savio John. Autoimmune hepatitis: Appraisal of current treatment guidelines. *World J Hepatol* 2018 27; 10:911–23.

7. Palak Trivedi, Stefan Hubscher, Michael Heneghan, et al. Grand round: Autoimmune hepatitis. *Journal of Hepatology* 2019;70:773–84.

**Chapter 49.**

**Primary Biliary Cholangitis**

Introduction

Primary biliary cirrhosis is now called primary biliary cholangitis (PBC) to better define the spectrum and pathology of the liver disease. PBC is an autoimmune T cell mediated inflammatory chronic disease of liver that leads destruction of intralobular bile ducts within the liver. Granulomatous destruction of these bile ducts leads to ductopenia, cholestasis and liver failure. It is an uncommon disease in India. Epidemiological data regarding prevalence of PBC in India is lacking. PBC is most frequently a disease of women and occurs between the fourth and sixth decades of life. It is commonly associated with other autoimmune liver diseases such as thyroiditis, rheumatoid arthritis, Sjogren syndrome, etc.

Clinical Features

PBC is diagnosed:

1. Incidentally in an asymptomatic individual due to raised alkaline phosphatase or due to presence of anti mitochondrial antibodies.

2. Symptomatic patient, often due to itching as a dominant symptom associated with fatigue.

*Symptoms of PBC include the following:*

1. Fatigue (65% of patients): The first reported symptom. The etiology of fatigue is unclear; although some evidence suggests that abnormalities of the hypothalamic-pituitary-adrenal axis, decreased release of serotonin, and increased production of proinflammatory cytokines may be responsible.

2. Pruritus (55%): Increased opioidergic tone (i.e., increased production of endogenous opioid peptides, up-regulation of endogenous opioid receptors) appears to be the major mechanism.

3. Right upper quadrant discomfort (8–17%).

Physical examination findings depend on the stage of the disease.

In the early stages, examination findings are normal.

1. Skin: hyperpigmentation, xerosis, itching marks, xanthomas, xanthelesmas and jaundice

2. Hepatomegaly.

3. In advanced stages, Features of portal hypertension and end-stage liver disease.

4. Signs of malabsorption and fat-soluble vitamin deficiencies.

Diagnosis

The diagnosis of PBC can be established when two of the following three criteria are met:

1. Biochemical evidence of cholestasis indicated by raised alkaline phosphatase and GGT.

2. Presence of AMA (anti mitochondrial antibodies).

3. Histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts.

***Abnormalities on laboratory studies include the following***

1. Significant elevations of ALP & GGT.

2. Elevated SGPT, SGOT usually less than 4–5 times upper limit of normal. Higher values need evaluation for associated autoimmune hepatitis.

3. Bilirubin rises in the latter part of the disease and it is a poor prognostic marker.

4. Increased lipid and cholesterol levels, with an increased HDL fraction. Despite marked rise in cholesterol levels in PBC, coronary artery disease risk is not markedly disease due to raised HDL levels.

5. Raised immunoglobulin levels (mainly IgM).

6. Antinuclear antibodies (ANAs): Can be identified in up to 70% of patients with PBC. Presence of ANA such as anti-gp210 and Sp100 are specific to PBC. These assays are not commercially available.

7. The hallmark of PBC is the presence AMAs. It can be found in 90–95% of patients with PBC, and they have a specificity of 98% for this disease. Titers of AMA do not predict response to therapy.

8. Some patients have clinical, biochemical, and histologic features of PBC, but their sera are negative for AMA. The diagnosis of autoimmune cholangitis has been used for these patients.

Imaging studies

Abdominal ultrasonography, CT scanning, or MRI is important to exclude biliary obstruction.

Histology

Biopsy is not routinely indicated if clinical picture correlates with AMA positivity. Biopsy is performed if there is disparity in clinical profile in the presence of AMA, or absence of AMA with clinical features suggestive of PBC or there is doubt of associated autoimmune hepatitis (raised transaminases beyond 5 times normal or poor response to UDCA).

PBC is characterized by:

1. Chronic (lymphocytic and plasma cell infiltration, with eosinophilic condensation in the portal tracts).

2. Non-suppurative, destructive cholangitis of the small interlobular bile ducts with a diameter of 40–80 mm.

3. Epithelioid aggregates or granulomas may be found around the bile ducts.

4. Fibrosis and cirrhosis develop later.

Staging

1. Stage 1 (portal stage of Ludwig): Portal inflammation, bile duct abnormalities, or both are present.

2. Stage 2 (periportal stage): Periportal fibrosis is present, with or without periportal inflammation or prominent enlargement of the portal tracts with seemingly intact, newly formed limiting plates.

3. Stage 3 (septal stage): Septal fibrosis with active inflammatory, passive paucicellular septa, or both are present.

4. Stage 4 (cirrhosis): Nodules with various degrees of inflammation.

Natural History

Mean survival for patients with symptomatic PBC is 8 years whereas that for asymptomatic disease is closer to 16 years. Various risks do have been developed to prognosticate outcome in patients with PBC. They either predict long term morality risk or transplant free survival.

Mayo risk score (MRS) which is widely used score is based on initial findings. GLOBE score (bilirubin, alkaline phosphatase, albumin, age and platelet count) or UK PBC score (bilirubin, ALP, aminotransferases, albumin, bilirubin and platelet count) predict outcomes depending on response to UDCA at the end of 1 year of treatment. Inadequate response to UDCA is an indication for addition of new drugs such as Obeticholic acid or fibrates.

Fatigue and pruritus do not correlate with disease severity. In fact pruritus frequently lessens as decompensated disease develops; just as skin xanthoma diminish with disease progression. Variceal haemorrhage is not necessarily a signs of advanced liver disease, as the portal hypertension may initially be due to perisinusoidal cause that is nodular regenerative hyperplasia, cirrhosis being absent.

Follow-up for PBC

1. Liver tests every 3-6 months

2. Thyroid status (TSH) annually

3. Bone mineral densitometry every 2–4 years

4. Vitamins A, D, K annually if bilirubin > 2.0

5. Upper endoscopy every 1–3 years if cirrhotic or Mayo risk score >4.1

6. Ultrasound and alpha fetoprotein in patients with known or suspected cirrhosis

Management

Pharmacologic treatment of PBC is as follows:

1. Ursodeoxycholic acid (UDCA, 13–15 mg/kg/day) is the primary treatment for PBC. It improves symptoms, biochemistry, slows the histological progression of the disease and improves transplant free survival and mortality. 30–40% patients have inadequate response to UDCA, defined as persistent elevation of ALP more than 1.5 times upper normal limit at the end of 1 year.

2. Obeticholic acid (derivative of CDCA, and a ligand for FXR) is a new approved drug for PBC. It is used as an add on drug in case of inadequate response to UDCA at 1 year. It can be used as a primary drug in case UDCA is not tolerated.

Dose recommend is 5 mg daily, which can be increased to 10 my daily. Dose of Obeticholic acid needs to be adjusted in advanced liver disease (Child class B/C). It is 5 mg one a week, to be increased to 10 mg once a week. Obeticholic acid paradoxically can increase pruritus, which meet require discontinuation of the drug.

3. Fibrates (Bezafibrate or fenofibrate) have shown improvement in liver biochemistry in PBC and can be used in case of inadequate response to UDCA. They need care full monitoring for rhabdomyolysis especially when used in combination with statins.

Supportive treatment

Pruritus is often severe and significantly impacts patients’ quality of life. Anti pruritus agents are used in isolation of in combination.

1. Cholestyramine (bile salts sequestrating resins) improves pruritus. It is administered as 4–8 g just before or after breakfast or meals. Palatability is often a problem. It should be spaced at least 2 hrs before or after UDCA intake. It may worsen malabsorption.

2. Other options for management of pruritus are rifampin (150–300 mg twice daily), Oral opiate antagonists such as naltrexone 50 mg daily, antidepressants, sertraline (75–100 mg) and ondansetron.

3. Plasmapheresis may be effective for patients with severe pruritus intractable to medical treatment.

4. Bone disease, vitamin deficiencies and malabsorption are significant issues in PBC and need management as per their merit and standard guidelines.

Liver Transplantation

The increased bilirubin level is an ominous sign of disease progression. Bilirubin beyond 5 mg%, presence of decompensation (ascites, encephalopathy, etc) is an indication for referral to a transplant centre. Severity of liver disease is assessed by MELD score for transplantation. Overall survival at 5 years was 85%. The 1-, 5- and 10-year recurrence-free survivals were 90%, 72% and 54%, respectively. Recurrence of PBC is around 30% at 10 years. Use of UDCA and use of cyclosporine as immuno-suppression instead of tacrolimus has shown to reduce recurrence of PBC after transplantation.

Further Reading

1. Fernanda Q, Gideon M, Aliya F. A Practical Review of Primary Biliary Cholangitis for the Gastroenterologist. *Gastroenterol Hepatol (N Y)* 2019;15:145–54.

2. Kuo A, Kuo A, Bowlus CL. Management of symptom complexes in primary biliary cholangitis. *Curr Opin Gastroenterol* 2016;32:204–9.

3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J* *Hepatol* 2017;67:145–72.

4. Lleo A, Marzorati S, Anaya JM, Gershwin ME. Primary biliary cholangitis: a comprehensive overview. *Hepatol Int* 2017;11:485–99.

**Chapter 50.**

**Acute Liver Failure**

Introduction

Acute liver failure (ALF) is an uncommon condition in which the rapid deterioration of liver function results in coagulopathy (INR>1.5), encephalopathy, and, in many cases, progressive multiorgan failure in a previously healthy individual without liver disease. It is a rare condition, occurs mostly in young adults and is associated with high mortality. Because of its rarity, ALF has been difficult to study; hence standards of therapy are not available. In the pretransplant era the survival rate was around 15% in most studies. Current short-term survival rates with transplantation are about 75%. The development of liver support systems provides some promise for improved survival although it remains a temporary measure and, to date, has no impact on survival. The important components of the management of ALF patient are the severity assessment, prevention or treatment of the complications and the use of transplantation when spontaneous survival is considered unlikely.

Definition

The term fulminant hepatic failure (FHF) and acute liver failure are used interchangeably. The most widely accepted definition describes the development of encephalopathy within 12 weeks of the onset of jaundice. O’Grady further classified the disease into hyperacute (0–1 week), acute (1–4 weeks) and subacute (4–12 weeks) based on the interval between jaundice and onset of encephalopathy. Hyperacute liver failure has the best prognosis despite the high incidence of cerebral edema and marked prolongation of prothombin time. Various classification systems for ALF are shown in Figure 1. Acute liver failure shares the same characteristics but has a much poorer prognosis. The outcome in subacute liver failure is poor despite the lower incidence of cerebral edema and less marked prolongation of prothombin time. Young children with ALF may not develop classical encephalopathy until late in the disease process. Increasingly in this group the diagnosis of ALF is made on the basis of coagulopathy.

aEtiology

There is considerable geographic variation in the aetiology of acute liver failure. Viruses and drugs account for the most of the cases. Worldwide causes of ALF is depicted in **Fig. 50.1**.

Viral Hepatitis

Studies from Spain, India, Hong Kong and Japan have shown that in all these countries viral hepatitis remains the commonest cause of ALF accounting for up to 90% of cases in some of these countries. Any virus that can cause viral hepatitis can potentially lead to ALF. These viruses can be characterized as primary hepatotrophic viruses (A–E) or those in which liver is involved as part of disseminated infection (EBV, CMV, VZV, HSV, and dengue).

Hepatitis A is an uncommon cause of acute liver failure accounts for 1–3% of total cases in a recent US study. Around 1% of acute viral hepatitis A develops acute liver failure. The risk of acute liver failure is significantly increased in adults and there is a positive correlation with age.

The incidence of acute liver failure following acute hepatitis B is around 1–4% of hospitalized patients, but mortality is higher than that with hepatitis A or E infection. It is now well recognized that acute liver failure like syndrome can occur in chronic hepatitis B in association with spontaneous surges in viral replication (HBV DNA levels typically markedly elevated), seroconversion from hepatitis B ‘e’ antigen (HBeAg) to hepatitis B ‘e’ antibody (HBeAb) and with exposure to immunosuppressive or cytotoxic drugs. Viral reactivation is associated with a much higher risk of progression to liver failure and death than in novel actue infection. Both co-infection and super-infection of hepatitis B with hepatitis D virus has been associated with ALF with most patients having superinfection rather than co-infection.

The risk of developing acute liver failure with hepatitis C is extremely low. Co-infection with hepatitis B increases the risk of developing actue liver failure.

Hepatitis E infection is now the most common cause of acute liver failure in India and Southeast Asia. Mortality due to acute hepatitis E is low, around 1%, mainly in elderly individuals and those with underlying chronic liver disease. Previously reported series showed very high mortality rate of acute HEV infection in pregnancy particularly in third trimester. However, recent data suggest that the course of acute HEV in pregnancy might not be any different from the course of any other hepatotropic virus in this cohort of patients.

Seronegative hepatitis is a common cause of acute liver failure in some parts of the world. The diagnosis remains one of exclusion.

Acetaminophen

Acetaminophen (paracetamol) overdose is the commonest cause of acute liver failure in the UK and the USA. In UK, majority of causes are due to suicidal or prasuicidal intent while in USA around 30% were due to unintentional use of acetaminophen. Acetaminophen-induced hepatoxicity is the characteristic hyperacute liver failure leading to progressive multiorgan dysfunction. The median dose of acetaminophen causing acute liver failure is the UK was 40 g, and the mortality was highest at dose exceeding 48 g.

Cases of hepatotoxicity after ingestion of recommended doses of acetaminophen has also been reported especially in those people with long-term exposure to alcohol or enzyme-inducing drugs such as anti-tuberculosis (Rifampicin, INH), anticonvulsants (phenytoin, phenobarbital). The development of ALF in acetaminophen toxicity can be reduced if N-acetylcysteine is given within 15 hrs of exposure.

Others

Other causes of ALF include idiosyncratic drug reactions, autoimmune hepatitis, pregnancy related disorders (HELLP syndrome) mushroom (Amanita) poisoning, veno-occlusive disease, Budd-Chiari syndrome, Wilson’s disease, hepatic ischemia due to cardiogenic or septic shock, heat stroke, other bacterial, rickettsial or parasitic infections and malignant infiltration of the liver. In recent times, acute liver failure due to yellow phosphorus [super warfarin, Rattol] poisoning has been reported from various parts of India. The consumption may be deliberate or accidental, and the syndrome is characterized by a very high INR but late onset encephalopathy. It is important to keep a close follow up on these ‘seemingly normal’ patients, since the early absence of HE can give a false sense of security to the treating physicians. Making an accurate etiologic diagnosis is important, as it affects the outcome as well as dictates specific therapeutic interventions.

Pathogenesis

ALF is not one disease of the liver but rather a consequence of multiple organ dysfunctions at various levels **(Fig. 50.2)**.

Characteristically, hepatocellular injury is central to pathogenesis of ALF.

Haemodynamic Changes

Studies have shown that ALF is characterized by marked splanchnic and systemic arteriolar vasodilatation, hyperdynamic circulation and low arteriovenous oxygen content difference. The early haemodynamic profile reflects a hyperdynamic circulation with increased cardiac output and reduced systemic peripheral vascular resistance. Progressive liver dysfunction leads to circulatory failure either due to a falling cardiac output or an inability to maintain an adequate mean arterial pressure. This leads to impaired ability to extract oxygen at the cellular level. Elevated levels of IL-6 and IL-8 and adrenal insufficiency are believed to contribute to the above.

Hepatic Encephalopathy and Cerebral oEdema

Net increase in the water content of the brain defines cerebral oedema. Significant advances in the understanding of brain oedema have been made the last decade, but the exact pathophysiological mechanisms underlying development of brain oedema and intracranial hypertension in ALF are still not entirely clear and are likely to be multifactorial. With an intact blood-brain barrier (BBB), water moves into brain via three possible routes – via diffusion through the bilipid layer of the plasma membrane, via co-transport with organic and inorganic ions and through specialized water channels called aquaporins. Of special interest is the aquaporin 4, the predominant aquaporin in the brain.

For many years, the accepted etiology has been the presence of cytotoxic oedema with an intact BBB. This concept has been challenged by the so-called ‘leaky’ hypothesis where the tight intercellular junctions are believed to become more permeable by the effect of pro-inflam-matory cytokines or endotoxins. The presumed pathogenesis is that astrocyte swelling is initiated by the presence of accumulating glutamine, the end product of ammonia metabolism. As a result of swelling, ions (K+) and other osmolytes (myoinositol, taurine, glutamate) are released. Ammonia also causes an increase in the expression of aquaporins in the brain causing influx of water. As per diffusion weighted MRI, it is believed that cytotoxic mechanism is the major contributor of cerebral edema.

Normal intracranial pressure (ICP) is 5–10 mmHg and intracranial hypertension becomes clinically relevant when ICP exceeds 20 mmHg. The main complication of severe intracranial hypertension in ALF patients is transtentorial herniation. Severe intracranial hypertension compromises cerebral perfusion pressure (CPP). By definition, CPP is the difference between mean arterial pressure (MAP) and cerebral venous pressure (CVP). As cerebral venous pressure can be approximated by ICP, CPP equals MAP minus ICP. An increase in ICP reduces CPP, and thus a decrease in cerebral blood flow (CBF). This reduction in CBF may cause cerebral ischemia or infarction, resulting in neurological deficits in ALF survivors.

Renal Impairment

Renal impairment occurs in 70% of patients with acetaminophen and 30% of patients with non acetaminophen related ALF. Renal failure after an acetaminophen over-dose is a consequence of direct renal toxicity and develops early in the course of the illness. In the other aetiologies, renal impairment develops relatively late and progress from a sage of prerenal failure to acute tubular necrosis. Hypovolaemia, circulatory disturbances, sepsis and use of nephrotoxic drugs are believed to be the cause of renal dysfunction. Urea synthesis is impaired in acute liver failure and serum creatinine levels are preferred for the purposes of monitoring renal function.

Infectious Complications

Patients with ALF are susceptible to all kinds of infections due to impaired neutrophil and Kupffer cell phagocyte function, impaired hepatic synthesis of complement factors and requirement of invasive procedures (intra-arterial/central venous/indwelling urinary catheter/ICP bolts). Translocation of gut bacteria is also an important cause. About 80% of the infections are due to bacteria, and fungi (predominantly Candida spp.) are isolated in up to 20% cases. Active and uncontrolled sepsis is a major contraindication to liver transplantation. Infection may be difficult to detect with confidence as there is a poor correlation between the presence of infection and body temperature or white cell counts. Surveillance cultures are required on a regular basis. This is important since many of these patients shall have features of systemic inflammatory response syndrome (SIRS), rather than a microbiologically proven infection.

Nutritional Disturbance

Rapid deterioration in nutritional status with depletion of muscle mass and fat stores is often seen. Energy requirements are increased by up to 60% of baseline. Hypoglycemia can occur quite early in the clinical course of ALF. Hypo-phosphatemia, hypomagnesemia and hypokalaemia are also seen. Enteral nutrition has been proven to be better than nutrition given through the parenteral route.

Haemostasis

The liver is responsible for the synthesis of most of the coagulation factors (except factor VIII, which is produced by endothelial cells). The primary mechanism contributing to coagulopathy is the reduced synthesis of clotting or anti-clotting factors together with consumptive coagulopathy. The degree of prolongation of prothrombin time is directly dependent on the severity of liver damage. Factor V being the protein in the clotting cascade with the shortest half-life, is believed to be the most sensitive indicator of hepatic impairment in ALF. Deficiencies in anti-clotting factors may result in thrombosis of dialysis circuits despite the bleeding diathesis. There is a poor correlation between the laboratory and clinical manifestation of the coagulopathy. Anaemia occurs in patient with ALF is due to hemolysis or bone marrow suppression.

Respiratory Complications

Hyperventilation is observed in patient with ALF due to raised intracranial pressure and later in course may be associated with metabolic acidosis. Patients with grade 3–4 encephalopathy are usually intubated and mechanical ventilated to provide airway protection and to hyperventilate for brief periods for acute surges in ICP, to improve cerebral oedema.

Diagnosis and Initial Management

All patients with clinical or laboratory features of acute hepatitis should have immediate measurement of prothrombin time (PT). If the PT is more than 5–6 sec prolonged (INR > 1.5) and there is any evidence of altered sensorium, the diagnosis of ALF is established and hospitalization is mandatory. As the condition may rapidly deteriorate, it is advisable to manage the patient with Grade II HE or higher grades of HE in the ICU.

Clinical evaluation includes detailed history to look for the cause of hepatitis like exposure to virus, toxins and drugs. Physical examination should include careful assessment of mental status, bleeding diathesis, stigmata of chronic liver disease. Jaundice is almost always present. Right upper quadrant tenderness may be elicited with decrease or absent liver dullness on percussion. Enlarged liver span may be seen

in viral hepatitis, malignant infiltration, congestive heart failure or acute Budd-Chiari syndrome. The neurological syndrome (hepatic encephalopathy, HE) is ranging from confusion, disorientation, agitation and altered sleep-wake cycle (Grade I) to a dull but arousable patient with flaps in Grade II HE. In an obtunded patient, pupil size and reaction to light should be assessed. As patients progress from Grade II HE to Grade III (stupor), hypertonia of extremities and brisk deep tendon reflexes are often observed. In Grade IV HE, the patient is comatose and may have abnormal posturing (decerebration).

Initial laboratory evaluation should be extensive to assess the etiology as well as the severity of the liver disease **(Tables 50.1 and 50.2)**. As evaluation continues, decisions need to be taken about shifting the patient to intensive care unit, transfer to transplant facility, as well as listing for urgent liver transplantation.

**For assessing the severity of the disease**

PT, INR or factor V and full coagulation screen including fibrinogen

Liver blood tests including LDH and conjugated and unconjugated bilirubin and creatinine kinase

**Assessment of renal function**

Urine output: hourly.

Low urea is a marker of severe liver dysfunction.

Creatinine may be difficult to assay in the context of

elevated bilirubin.

Arterial blood gas and lactate

Arterial ammonia

**For aetiology**

Toxicology screen in urine and paracetamol serum level

Serological screen for virus infections

HBsAg, anti-HBc IgM (HBV DNA), delta if positive for HBV

anti HAV IgM

anti-HEV IgM

anti-HSV IgM, anti VZV IgM, CMV, HSV, EBV, parvovirus

and VZV PCR

**Autoimmune markers**: ANA, ASMA, anti-soluble liver antigen, globulin profile, ANCA, HLA typing

**For testing for complications**

Lipase or amylase

Cultures (respiratory, blood, urine, ascites)

Chest X-ray/ECG/: axial imaging of the abdomen and chest may also be required

Echocardiography

Medical Management

Management in specialized liver intensive care units is mandatory in all patients with ALF and higher than Grade I hepatic encephalopathy. Supportive medical management is

based on the pathophysiology and aimed at maintaining hemodynamic, cerebral and renal function, treating the metabolic derangements, prevention and treatment of infections and appropriate referral for liver transplantation.

**Routine monitoring**

Oxygen saturation, blood pressure, heart rate respiratory rate, hourly urine output

Clinical neurological status

**Standard care**

Glucose infusions (10–20%): glycemic target ± 140 mg/dl, Na 135–145 mmol/L

Stress ulcer prophylaxis

Restrict clotting factors unless active bleeding

N-acetylcysteine in early stage, even in non-paracetamol cases

**Preventative measures**

Avoid sedatives

Avoid hepatotoxic and nephrotoxic drugs

**In case of hepatic encephalopathy**

Transfer to an appropriate level of care (ideally critical care) at the first symptoms of mental alterations

Quiet surrounding, head of bed >30, head in neutral position and intubate, ventilate and sedate if progresses to >3 coma.

Low threshold for empirical start of antibiotics if haemodynamic deterioration and/or increasing encephalopathy with inflammatory phenotype

In case of evolving HE intubation and sedation prior to the transfer

Ensure volume replete and normalize biochemical variables (Na, Mg, PO4, K)

Haemodynamics and Renal Dysfunction

Haemodynamic derangements are consistent with those seen in multiorgan failure. Management is difficult in face of raised ICP and preservation of renal function is of utmost importance. Intravascular fluid depletion is common due to reduced oral intake, exudation into the extravascular space and possible GI blood loss. A combination of colloids and crystalloids are required to maintain adequate filling pressures (PCWP 8–14 mmHg). Inotropic support may be required if the mean arterial pressure is < 60 mmHg despite good filling pressures. Most experience is with the use of nor adrenaline. N-acetyl cysteine infusion has also been shown to improve haemodynamic stability and increase in global tissue oxygen consumption in patients with acetaminophen and other aetiologies of ALF. Renal dysfunction is a frequent complication of ALF and may be due to dehydration, hepatorenal syndrome or acute tubular necrosis due to hypotension or sepsis. The incidence of renal dysfunction is more in acetaminophen toxicity than with other causes of ALF. N-acetyl cysteine has been found to reduce

the incidence of renal dysfunction. Indications for renal replacement therapy include metabolic acidosis, hyperkalemia, fluid overload, hyperammonemia >150 mcmol/L, oliguria with rising serum creatinine or cerebral oedema not responsive to mannitol/hypertonic saline. Continuous veno-venous hemofiltration (CVVH) is preferable to intermittent dialysis because it has been shown that it results in improved stability in cardiovascular and intracranial parameters.

Cerebral Oedema

The use of ICP monitoring devices is controversial. Clinical signs of raised ICP, CT brain and other non-invasive methods are not very sensitive and hence there has been no worthwhile alternative to the ICP measuring devices. The aim of these is early detection of raised ICP so that interventions can be planned to reduce the same. The ultimate goal is to maintain neurological integrity and stability till the patient receives a liver graft. On the flip side, presence of refractory intracranial hypertension can also be diagnosed, which is considered a contraindication to transplantation. There is a concern over the risks involved in placing ICP measuring devices, mainly of infection and bleeding. Complications like bleeding can be reduced by using recombinant activated factor VII (rFVIIa). Data on 262 patients in the US observed a complication rate of 3.8% with 1.1% fatal haemorrhage. Recent data has not shown improved outcome when ICP monitors were used. The goal of all treatment is to keep the ICP below 20–25 mmHg and CPP above 50–60 mmHg.

A jugular bulb catheter may be utilized to assess cerebrovascular autoregulation. Transcranial Doppler ultrasound is a noninvasive method to measure blood flow velocity in the basal intracranial cerebral arteries, thereby indirectly determining CBF via the linear relationship between flow and velocity. In more recent ICU practice, optic nerve sheath diameter has turned out to be a useful bedside tool to diagnose cerebral oedema (cut off: 6.5 mm).

The current therapy for cerebral edema rests on the use of hypertonic saline, given as continuous infusion (3%) or as boluses to handle ICP surges (23.1%). The target Na+ value should be kept at 140–145 mEq/L. Hypertonic Saline mitigates ICH through both osmotic and nonosmotic effects. It reduces endothelial swelling and inhibits neutrophil activation. Intravenous mannitol is a potent osmotic agent that does not cross the blood-brain barrier.

It reduces ICP by osmotically drawing water from the brain parenchyma into the intravascular space. Mannitol is administered as a 20% solution with the dosage of 0.25–1 g/kg rapidly. Its current status is again to treat ICP surges that occur in spite of regular cerebral oedema measures. One should exercise caution in using it in patients with renal

insufficiency or when the serum osmolality crosses 320 mOsm/L.

Hyperventilation provides a rapid but transient improvement in ICP, with restoration of cerebral autoregulation within several minutes. The goal of hyperventilation is to induce the hypocapnia that causes cerebral vasoconstriction, which in turn reduces CBF leading to decrease in ICP. There is no role for prophylactic hyperventilation in patients with ALF. Hyperventilation is likely best used as short-term rescue therapy.

Hypothermia transiently reduces ICP by restoring CBF autoregulation and reactivity to CO2. Mild hypothermia (core temperature of 34–35oC) is currently preferred, rather than moderate hypothermia (core temperature of 32–33oC). Both have shown to be of equal efficacy. Risk of moderate hypothermia is cardiac arrhythmias, coagulopathy, pancreatitis, predisposition to infections, hypotension and impaired liver regeneration. Rewarming of these patients has to be gentle, as rapid rewarming may precipitate cerebral edema. Hypothermia may be used as a bridge to recovery or to liver transplantation.

Thiopental and barbiturates are centrally acting hypnotics that reduce brain oxygen utilization. They are considered as rescue therapy for severe ICH, not responding to above mentioned measures.

Lactulose may be used in the early encephalopathy but with advancing grade of HE, its role is dubious as it produces gaseous distension of the abdomen and may make ventilation of an intubated patient difficult. Patients should be nursed with head elevated to 20–30 degrees and prophylactic endotracheal intubation may be done for airway protection as grade of HE advances.

N-Acetylcysteine

N-acetylcysteine (NAC) is routinely used in acetaminophen induced hepatotoxicity. It acts by replenishing glutathione and provides substrates for hepatic ATP synthesis. NAC was also used in non-acetaminophen-induced ALF because it was noted to improve systemic haemodynamic and tissue oxygen delivery and consumption.

Antimicrobials

Patients with ALF are at risk of infection due to various factors. Prophylactic intravenous antibiotics and antifungals have been shown to reduce the incidence of infections though survival benefit has not been shown. In case prophylactic antibiotics are not being given, surveillance cultures and keeping a low threshold for starting antibiotics is recommended. Given the relationship between infection and SIRS (systemic inflammatory response syndrome) and progression to deeper encephalopathy and the fact that fever

may worsen ICP, it is possible that antimicrobials may decrease the risk of cerebral oedema.

Nutrition

ALF is a state of high caloric requirement. 35–50 kcal/kg daily are required. Protein intake of at least 1 g/kg/day is required to maintain nitrogen balance. Hypoglycaemia, hypomagnesemia, hypophosphatemia and hypokalaemia need to be corrected aggressively. The enteral route should give nutrition wherever possible.

Coagulopathy

Because prothrombin time is an important prognostic marker in ALF, plasma replacement is only indicated when active bleeding is occurring or any invasive procedure is being planned. Platelet transfusion prior to any procedure is required when the count is <50,000/cu mm. Transfusion triggers should be guided by point of care testing such as thromboelastography (TEG). Sucralfate is the preferred anti-ulcer agent to prevent stress-induced erosions or GI bleed.

Prognostic Factors in ALF

Given that liver transplantation is the only proven treatment for ALF, the timing and selection of candidates for liver transplantation (LT) is very crucial. A false negative selection can result in a preventable death and an unnecessary transplant can lead to wastage of a precious graft as well as a short-term mortality of up to 15–20%, substantial expenditure and lifelong immunosupression.

Selection criteria for LT in ALF have not been standardized owing to the diverse etiologies that cause this syndrome and their inherent shortcomings. The King’s College criteria formulated following retrospective, multivariate analysis of prognostic factors in 588 patients is widely applied **(Table 50.3)**. The positive predictive values for death in acetaminophen and non-acetaminophen groups were 84% and 98%, respectively, whereas negative predictive values were 86 and 82%, respectively. Subse-quently various studies done to validate the King’s College criteria have shown acceptable validity but not as high as in the original study. Furthermore, a clear-cut difference was found between acetaminophen and non-acetaminophen groups with lesser accuracy in the latter.

Alternative prognostic indicators have been proposed. Bernuau et al, in a series of mainly hepatitis B related acute liver failure in 115 patients in Clichy found that criteria based on the presence of coma or confusion along with reduced levels of factor V carried a positive predictive value and negative predictive value of 82% and 98%, respectively. In a head on head comparison between the two criteria on acetaminophen-related ALF, the Clichy’s criteria performed less well with lower positive predictive value. However, negative predictive value of the two criteria was comparable. In another study carried on 28 patients with non-acetaminophen related ALF the overall predictive accuracy increased when both sets of criteria were considered in combination although the ability to identify those patients who recover spontaneously remained low.

The major drawback in the current prognostic indicators is that the time interval from the time of fulfillment of the criteria to becoming unsuitable for transplantation can be very short, hence the need for more sensitive criteria. Both these criteria have also been found to have low negative predictive value, hence additional variables or criteria have been proposed. In a recent study, Model for end stage liver disease (MELD) score was compared to the King’s and the Clichy’s criteria in patients with non-acetaminophen related ALF and was found to be an excellent predictor of survival.

The ALFED (ALF early dynamic model) has been proposed by workers from AIIMS, New Delhi, India **(Table 50.5)**. The model is based on serum bilirubin, INR, arterial ammonia levels, and Gd of HE in patients with ALF, predominantly of viral etiology. The change in these parameters at 72 hrs of ICU care determines the ‘survivors’ from ‘non-survivors.’

Liver transplantation was not considered as a therapeutic option in these patients. However, when these patients are deemed non-responders to LICU care, they may also have become unsuitable for liver transplantation.

A few other easily available lab parameters have shown promise as prognostic agents in these patients **(Table 50.4)**. Most promising of them are blood lactate values and hyperphosphatemia. These markers when used in conjunction with King’s College criteria have been found to have higher sensitivity with reducing the specificity. The USALF Study

group has proposed markers of histological injury along with lab and clinical parameters to predict outcome in these patients (INR, serum bilirubin, serum phosphate, gd of HE and M30 – marker of apoptosis).

Lactate

Phosphate

Factor VIII and V ratio

Serum (Gc), vitamin D binding protein

Serial prothrombin times

Liver volume on CT (<1 L)

Liver histology (necrosis)

Circulating IL-6 and IL-8 levels

Clichy’s Criteria

1. Coma and confusion (encephalopathy grade 3 or 4) and

2. Factor V < 20% if age under 30 years or

3. Factor V < 30% if age over 30 years

Liver Transplantation in ALF

Liver transplant remains the only proven treatment for ALF. With the advent of liver transplantation the survival has improved from 15% in the pre-transplant era to 1 year survival of over 85% after transplantation. It is therefore mandatory to transfer patients to a liver transplant center in a timely manner so that the procedure can be performed in suitable patients before contraindications develop. Euglycemia and cardiorespiratory and neurologic stability should be maintained during transfer of the patients. Contraindications to transplantation include sepsis, severe cardiorespiratory failure, marked and protracted ICH with low CPP, and extrahepatic malignancy.

**Variables over first 3 days Score**

n Hepatic encephalopathy persistent or 2

progressed to > Grade 2

n INR-Persistent or increased to 5 1

n Arterial ammonia Persistent or increased 2

to 123 mmol/L

n Serum bilirubin Persistent or increased to 2

15 mg/dL

ALFED score 4 has high positive predictive value and negative predictive value

ALF is the only condition with priority listing (Status 1) in the UNOS listing criteria. Outcome of cadaveric LT for ALF is not as good as for other indications. However, it remains the best of the available options.

About 25–40% of patients recover from ALF spontaneously with intensive support only. Considering the possibility of patient’s own liver recovering, auxiliary partial liver transplant has been developed to bridge these patients till their native liver recovers. When the native liver regenerates and recovers full function, immunosupression is gradually withdrawn allowing the graft liver to atrophy, thereby preventing the need of lifelong drugs and their side effects. Currently it is difficult to predict, which patients will recover full function but favourable factors include younger age, hyperacute presentation, limited extrahepatic involvement and acetaminophen-related ALF. There are two types of auxiliary liver transplant – heterotopic auxiliary liver transplant (HALT) where graft is placed below unresected native liver and auxiliary partial orthotropic liver transplant (APOLT), in which right or left hemi-liver is resected and replaced by a partial liver graft. The results of HALT are poorer because of primary non-function and portal vein thrombosis.

The availability of cadaver organs is very low in the Far East. Hence, living donor liver transplantation (LDLT), which is already in vogue for paediatric cases, has been extended to adult recipients. The problem with adult recipients is with the inadequate graft size leading to ‘small for size’ syndrome. To overcome this, right lobe LDLT is being performed increasingly to improve the graft recipient weight ratio (GRWR) although at a higher risk to the donor.

Bridge to Transplant

There is considerable interest in developing a device or technique which will provide support to the liver during the period of crisis till a suitable cadaveric or living donor organ

is made available or till such a time the native liver recovers

and resumes normal function. Bridging therapies may be classified as: (a) liver assist devices – biological or non- biological, (b) plasma exchange [conventional or high volume]

Liver Assist Devices

Biological Devices

These may be classified as biological devices which aim to replace all the functions of the liver and artificial devices which mainly carry out detoxification. Bioartificial livers incorporate isolated cultured hepatocytes into the bioreactor. The important issues are the choice of cellular component, stabilization of hepatocyte phenotype, the amount and efficacy of biomass load and the safety of the bioreactor.

Hepatocytes are sourced from either retrieved whole livers, which were found to be not suitable for transplant, from segment IV or caudate lobe of split livers, hepatoblastoma cell lines or porcine liver. The basic design of the bioreactors consists of hollow fibre capillaries through which blood flows while hepatocytes are lodged in the extracapillary space. The hepatocytes extract the nutrients from the blood and detoxify the toxins from the plasma across the fibers. Numerous small trials have been carried out and the only prospective randomized controlled trial has failed to show a statistically significant improvement.

Artificial Devices

The safety concerns and cost factor of biological devices has renewed interest in artificial devices. These devices act mainly as a detoxifying system. The Molecular Adsorbent Recirculating System (MARS) is the most widely used artificial system. It uses a hollow fiber dialysis module in which patient’s blood is dialyzed across albumin impregnated polysulfone membrane primed with 600 mL of 20% albumin. Dialysate carrying toxins is sequentially subjected to haemofiltration where water based toxins are reabsorbed and to charcoal and ion exchange columns where the albumin-bound toxins are reabsorbed and the dialysate is regenerated. So far more than a few thousand sessions of MARS have been carried out in a few thousand patients but the device has failed to conclusively demonstrate any survival benefit. This is despite improvement in different parameters (reduction in bilirubin, improvement in grade of HE, improvement in haemodynamic and renal function). Most studies have failed to show any improvement in synthetic function of the liver. In the authors’ personal experience with the use of this device in patients with ALF, worsening of coagulopathy and increased predisposition to sepsis has been observed.

Prometheus is an artificial device which does not require the dialysate side of the circuit to be primed with albumin

from exogenous source. It works on the principle of fractionated plasma separation and adsorption along with high

flux haemodialysis. More studies are needed on the use of this device in ALF to demonstrate good safety profile and survival benefit. More recently, artificial devices based on cytokine adsorption and albumin replenishment have shown efficacy in ‘proof-of-concept’ studies (UCL liver dialysis device). Human trials are needed before recommending these liver support systems for routine use in ALF.

High-volume Plasma Exchange

High-volume plasma exchange or (HVP), defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma was tested in a randomized controlled multi-centric trial in Europe. ALF patients (n=182), mostly hyperacute ALF and due to acetaminophen over dosage were randomized into standard medical treatment (SMT) group or HVP (for 3 days) plus SMT group. For the entire patient population, overall hospital survival was 58.7% for patients treated with HVP vs 47.8% for the control group [hazard ratio (HR), with stratification for liver transplantation: 0.56; 95% confidence interval (CI), 0.36–0.86; *p* = 0.0083]. HVP prior to transplantation did not improve survival compared with patients who received SMT alone (CI 0.37–3.98; *p* = 0.75). The incidence of severe adverse events was similar in the two groups. Systemic inflammatory response syndrome (SIRS) and sequential organ failure assessment (SOFA) scores fell in the treated group compared to control group, over the study period (*p* < 0.001). Since this publication, there has been a renewed interest in this modality of treatment, though most centers use much lower exchange volumes (1.5–2.5 L). This modality of treatment has shown remarkable efficacy in Rattol poisoning patients presenting as ALF.

Conclusion

ALF is a medical catastrophe with extraordinarily high mortality. Although our understanding of the pathophysiology of failing liver has improved substantially, standards of therapy still remain less than satisfactory. Better markers of prognostication are needed to decide, which patient will recover spontaneously and who will need transplantation.

Transplantation remains the only proven therapy for ALF till date. Liver assist devices and cell transplantation are far from satisfactory though plasma exchange has shown promise in a cohort of patients.

Further Reading

1. Rovegno M, Vera M, Ruiz A, Benítez C. Current concepts in acute liver failure. *Ann Hepatol* 2019;18:543–52.

2. Kandiah PA, Subramanian RM. Extracorporeal devices. *Crit Care Clin* 2019;35:135–50.

3. Sheikh MF, Unni N, Agarwal B. Neurological monitoring in acute liver failure. *J Clin Exp* *Hepatol* 2018;8:441–47.

4. Rajaram P, Subramanian R. Acute liver failure *Semin Respir Crit Care Med* 2018;39:513–22.

5. Montrief T, Koyfman A, Long B. Acute liver failure—a review for emergency physicians. *Am J Emerg Med* 2019; 37:329–37.

6. Escorsell À, Castellote J, Sánchez-Delgado J, et al. Management of acute liver failure. Clinical guideline from the Catalan Society of Digestology. *Gastroenterol Hepatol* 2019; 42:51–64.

7. Squires JE, McKiernan P, Squires RH. Acute liver failure—an update. *Clin Liver Dis* 2018;22:773–805.

8. Brown SA, Axenfeld E, Stonesifer EG, et al. Current and prospective therapies for acute liver failure. *Dis Mon*. 2018;64:493–522.

9. Khan R, Koppe S. Modern management of acute liver failure. *Gastroenterol Clin North Am* 2018;47:313–26.

10. Olivo R, Guarrera JV, Pyrsopoulos NT. Liver transplantation for acute liver failure. *Clin Liver* *Dis* 2018;22:409–17.

11. Rajaram P, Subramanian R. Management of acute liver failure in the intensive care unit. *Clin* *Liver Dis* 2018; 22:403–08.

12. Mishra A, Rustgi V. Prognostic models in acute liver failure. *Clin Liver Dis* 2018;22:375–88.

13. Wendon, J; Panel members, Cordoba J, et al. EASL clinical practice guidelines on the management of acute liver failure. *J Hepatol* 2017;66:1047–81.

14. Flamm SL, Yang YX, Singh S, et al; AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guidelines for the diagnosis and management of acute liver failure. *Gastroenterology* 2017;152:644–47.

15. Bernal W, Murphy N, Brown S, et al. A multicenter randomized controlled trial of moderate hypothermia in acute liver failure. *J Hepatol* 2016;65:273–9.

16. Larsen FS, Schmidt LE, Bernsmeier C, et al. High volume plasma exchange in patients with acute liver failure: an open randomized controlled trial. *J Hepatol* 2016;64:69–78.

17. Bernal W, Hyyrylainen A, Gera A, et al. Lessons from look back in acute liver failure—a single centre experience of 3300 cases. *J Hepatol* 2013; 59:74–80.

**Chapter 51.**

**Hepatic Encephalopathy**

Introduction

Hepatic encephalopathy (HE) is as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction ranging from personality changes to intellectual impairment, to a depressed level of consciousness. Overt hepatic encephalopathy occurs in about 30–45% of patients with cirrhosis. It is observed in 24–53% of patients who undergo portosystemic shunt surgery. Subtle signs of hepatic encephalopathy are observed in nearly 70% of patients of cirrhosis. Diversion of portal blood into the systemic circulation through portosystemic collateral vessels is important for the development of HE, although in advanced liver failure (ALF, ACLF & CTP C cirrhosis) encephalopathy can be seen even without significant shunting. Cirrhosis leading to portosystemic shunting is the leading cause of HE, but spontaneous or surgically created portosystemic shunts are also lead to HE without cirrhosis liver. Patients of cirrhosis who undergo TIPS have a 30–50% chance of overt HE.

Pathogenesis

Many theories have been proposed to explain the pathogenesis of HE. Astrocyte dysfunction and accumulation of neurotoxins are the main pathophysiologic mechanism for development of HE.

Astrocyte Dysfunction

Astrocytes account for about one third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxi-fication of a number of chemicals, including ammonia. In case of liver cell failure, there is disruption of blood brain barrier, which leads entry of neurotoxin substances like ammonia and manganese. These neurotoxins lead to morphologic changes in astrocytes. In ALF, astrocytes swollen due to cerebral edema, but there is no morphological changes. In cirrhosis, there are morphological changes in the astrocytes called Alzheimer type II astrocytosis. Brain astrocytes also possess glutamine synthetase. However, the brain is not able to increase glutamine synthetase activity in the setting of hyperammonemia.

Thus, the brain remains vulnerable to the effects of hyperammonemia.

Ammonia Hypothesis

Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines and urea.

Normally, ammonia is detoxified in the liver by conversion to urea by the Krebs cycle. Ammonia is also consumed in the conversion of glutamate to glutamine, a reaction that depends on the activity of glutamine synthetase. Two factors contribute to the hyperammonemia that is seen in cirrhosis. First, there is a decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified. Secondly, portosystemic shunting may divert ammonia-containing blood away from the liver to the systemic circulation. Glutamine synthetase presents in the skeletal muscles metabolizes ammonia to glutamine.

However, the muscle wasting that is observed in patients with advanced cirrhosis may potentiate hyperammonemia. Ammonia has multiple neurotoxic effects. It can alter the transit of amino acids, water, and electrolytes across astrocytes and neurons. It can impair amino acid metabolism and energy utilization in the brain. Ammonia can also inhibit the generation of excitatory and inhibitory postsynaptic potentials. Additionally, glutamine produced in the astrocytes from ammonia leads to increased osmolarity of the cell leading to cell swelling because of influx of water. Increases in brain glutamine concentration have been seen in acute liver failure.

GABA Hypothesis

GABA is a neuroinhibitory substance produced in the gastrointestinal tract. Of all brain nerve endings, 24–45% may be GABAergic. Chemicals capable of acting on GABA-ergic neurons have been identified in brain, serum and CSF as benzodiazepines. Some may be exogenous but there are also endogenous ones. Neurosteroids are the endogenous benzodiazepine with potent, selective action on GABA receptor complex. Allopregnenolone and pregnenolone are examples of neurosteroids.

Classification

Type A hepatic encephalopathy describes encephalopathy associated with **a**cute liver failure.

Type B hepatic encephalopathy describes encephalopathy associated with portal-systemic **b**ypass and no intrinsic hepatocellular disease.

Type C hepatic encephalopathy describes encephalopathy associated with **cirr**hosis and portal hypertension or portal-systemic shunts. Type C hepatic encephalopathy is, in turn, subcategorized as episodic, persistent or minimal.

Clinical Features and Subclassification of HE

Clinical features and subclassification of HE is given below **(Table 51.1)**:

Grading of the symptoms of hepatic encephalopathy is performed according to the West Haven classification system.

1. Grade 0 - Minimal hepatic encephalopathy (also known as covert hepatic encephalopathy and previously as subclinical hepatic encephalopathy); lack of detectable changes in personality or behaviour; minimal changes in memory, concentration, intellectual function, and coordination; asterixis is absent.

2. **Grade 1** - Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks.

3. **Grade 2** - Lethargy or apathy; disorientation; inappropriate behaviour; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behaviour, and intermittent disorientation, usually regarding time.

4. **Grade 3** - Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech.

5. **Grade 4** - Coma with or without response to painful stimuli. Some patients with hepatic encephalopathy show evidence of fetor hepaticus, a sweet musty aroma of the breath believed to be secondary to the exhalation of mercaptans.

Extrapyramidal symptoms due to altered dopaminergic function – including tremor, bradykinesia, cog-wheel rigidity, and shuffling gait – have been described in

patients with portosystemic shunting and are seen to be associated with high manganese concentrations of the basal ganglia. Manganese acts to bring dopamine levels to normal and hence high manganese levels may reflect action of brain to correct dopamine deficiency.

Precipitants of Hepatic Encephalopathy

Common precipitating factors of HE are as follows:

1. Infection: Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels.

2. Constipation: Constipation increases intestinal production and absorption of ammonia.

3. Gastrointestinal bleeding: The presence of blood in the upper gastrointestinal tract results in increased ammonia and nitrogen absorption from the gut. Bleeding may predispose to kidney hypoperfusion and impaired renal function. Blood transfusions may result in mild hemolysis, with resulting elevated blood ammonia levels.

4. Renal failure: Renal failure leads to decreased clearance of urea, ammonia, and other nitrogenous compounds.

5. Diuretic therapy: Decreased serum potassium levels and alkalosis may facilitate the conversion of NH4+ to NH3. Diuretic-induced hypovolemia is the most common reason for patients with previously well-controlled hepatic encephalopathy to present to the emergency room with worsening mental function.

6. Renal failure: Renal failure leads to decreased clearance of urea, ammonia, and other nitrogenous compounds.

7. Medications: Drugs that act upon the central nervous system, such as opiates, benzodiazepines, antidepressants and antipsychotic agents, may worsen HE.

Investigations

1. Blood ammonia level: An elevated blood ammonia level is the classic laboratory abnormality reported in patients with HE. As high ammonia level may be seen in cirrhotic patients without HE also, it does not contribute to diagnosis, staging or prognosis of HE. Both arterial and venous levels checked against the reporting laboratory’s values are acceptable but the sample must be collected without a tourniquet, transported in ice and analysed within 20 min for accurate results. Normal ammonia levels in a patient of overt HE should prompt search for other causes of altered sensorium. Serial levels can give us an idea regarding efficacy of the treatment.

2. EEG: Classic EEG changes associated with hepatic encephalopathy are high-amplitude low-frequency waves and triphasic waves.

3. Imaging: Computed tomography (CT) and magnetic resonance imaging (MRI) studies of the brain may be

important in ruling out intracranial lesions. MRI has the additional advantage of being able to demonstrate hyperintensity of the globus pallidus on T1-weighted images, a finding that is commonly described in HE. This finding may correlate with increased manganese deposition within this portion of the brain.

Testing for minimal and covert HE

Covert HE includes minimal & grade 1 HE . MHE is defined as the brain dysfunction which is detected on testing and is not apparent clinically. The prevalence of MHE in cirrhotics without HE is more than 50%. Diagnosis of minimal HE is becoming more and more important as it has been shown to impair Health related quality of life (HRQoL), impairs driving skills predisposing to accidents as well as affects fitness for technical jobs. Presence of MHE also predicts future development of overt HE.

The tests to diagnose MHE are psychometric and neurophysiological. The established tests are as follows:

1. Portosystemic encephalopathy syndrome (PSE) test: Five paper and pen tests make up this test.

2. Critical flicker frequency test: It is a psycho physiological tool wherein frequency at which a fused light appears flickering to the patient. This is the simplest test with good validation but the equipment used for testing is expensive.

3. Continuous reaction time test measures the reaction time of muscular action to auditory stimuli. It can differentiate between organic and metabolic brain dysfunction.

4. Inhibitory control test: Computerized test to judge inhibition of response and working memory.

5. Stroop test: It evaluates psychomotor speed and cognitive flexibility. It has also been developed into a mobile app.

It is not practicable to administer these tests to all patients of cirrhosis so norms have to be developed locally as regards indications, expertise, convenience and cost.

Management

Clinical Rationale

The development of HE heralds a worsening of the clinical condition and is a harbinger of mortality.

The impairment of mental status worsens the quality of life further in such patients. The key goals of treatment are to maintain normal neurocongnitive function, to reverse alterations in sensorium, improve quality of life and reduce the burden of the disease on the patients and their family.

Pathophysiologic rationale

There are two key pathophysiologic substrates for HE: (1) Hepatocellular dysfunction and (2) Portosystemic shunting. The latter is usually seen as a consequence of portal

hypertension and spontaneous splenorenal shunts are a common location of such shunts. These shunts can also be iatrogenic and be produces surgically or by a Transjugular intrahepatic portosystemic shunt (TIPS). Traditionally, it has been held that circulating mediators in cirrhosis alter neurologic function and cause HE. Of the various markers that have been implicated, ammonia remains a leading candidate as a cause of HE. Hence most of the treatment options target lowering of ammonia as a treatment of HE.

Pharmacologic agents available for the

treatment of HE

Various pharmacological agents are available for the treatment of hepatic encephalopathy **(Table 51.2)**.

Nonabsorbable Disaccharides

Nonabsorbable disaccharides were introduced for the treatment of HE over fifty years ago. Lactulose is composed of a lactose and galactose molecule. It is available as syrup. Lactitol is also derived from lactose but is available in powder form and is not as sweet as lactulose. Both drugs are metabolized in the colon to acetic and lactic acid. This acidifies the colonic environment, trapping soluble ammonia as NH4 anion and excreting in stools. The impact of these compounds on other key pathophysiologic pathways has not been well characterized. Lactulose is dosed (usually 20 g (30 mL) 2–4 time/day) to achieve 2–4 semi-solid bowel movements a day. Increasing the dose to get severe diarrhea does not improve HE but may cause worsening due to volume depletion, and azotemia. In those who are unable to take lactulose by mouth, it may be administered as a retention enema (200 g in 700 mL of water or saline). Lactitol is dosed 10 g every 6 hrs (or 67 g/100 mL) titrated to two bowel movements a day. The principal side effects of these drugs are their taste, bloating, cramping, flatulence and occasional fecal incontinence.

1. Non-absorbable disaccharides:

Lactulose

Lactitol

2. Antibiotics:

Neomycin

Rifaximin

Metronidazole

3. Drugs that improve ammonia clearance:

Ornithine aspartate (LOLA)

Sodium benzoate

Zinc supplements

4. A-glycosidase inhibitors:

Acarbose

5. Pre- and probiotics

Antimicrobials

Rifaximin is a poorly absorbed synthetic compound with both aerobic-anaerobic and gram positive–negative coverage. It is a rifampin derivative and binds the  subunit of a DNA-dependent RNA polymerase of bacteria. Majority of an orally administered dose can be recovered from stool and usually <1% of a dose is absorbed. At usual doses (1100 mg/day) it does not have major effects on normal bowel flora such as *E. coli*. It is approved for the treatment of HE at a dose of 550 mg twice a day. Headaches, constipation, vomiting are the most common adverse effects reported in clinical trials.

Neomycin and other antibiotics, such as metronidazole, oral vancomycin, paromomycin and oral quinolones, are administered in an effort to decrease the colonic concen-tration of ammoniagenic bacteria. Initial neomycin dosing is 250 mg orally 2–4 times a day. Doses as high as 4000 mg/day may be administered. Neomycin is usually reserved as a second-line agent, after initiation of treatment with lactulose. Long-term treatment with this oral amino-glycoside runs the risks of inducing ototoxicity and nephrotoxicity because of some systemic absorption.

Branched chain amino acids (BCAA)

In subjects with cirrhosis, the ratio of aromatic amino acids to branched amino acids is increased and this is believed to contribute to encephalopathy. It has been proposed that restoring balance by branched chain amino acid supplementation can improve HE. A recent meta-analysis on the use of oral BCAA for HE concluded that it is beneficial for HE but does nothing for nutrition, quality of life and mortality. It may be considered for addition over and above lactulose and rifaximin if need be. Oral BCAA are not used as primary therapy because of cost and unpalatability.

L-Ornithine-L-aspartate (LOLA)

This is a substrate for ureagenesis and allows conversion of ammonia to urea and glutamine. It has been shown to improve mental status and serum ammonia in clinical trials. The doses of LOLA range from 18 to 30 g/day and when given intravenously have shown to be of benefit in HE. It can be recommended after lactulose and rifaximin. Oral therapy is not effective. It does not improve encephalopathy in acute liver failure. It is not currently FDA-approved for the treatment of HE.

Glyceryl Phenyl Butyrate (GPB)

In a recent trial, patients who were on a combination therapy of lactulose and rifaximin and had episodes of overt HE showed response to GPB in the form of reduced hospitalizations and fewer episodes. Further trials are awaited.

Zinc Supplements

Zinc is a co-factor for several enzymes of the urea cycle and enhances urea formation. Currently, in cases of refractory encephalopathy, if zinc deficiency is present it should be corrected.

Benzodiazepine Antagonists

Flumazenil has been used in several studies for the treatment

of HE, especially acute HE. A systemic review identified a beneficial effect of flumazenil on symptoms of HE. The benefits of flumazenil is however short-lived due to its short half life. It is not recommended for use for encephalopathy associated with cirrhosis.

Pre- and Probiotics

There is currently great interest in prebiotics and probiotics in the management of HE. The disaccharides may function as prebiotics. Probiotics reduce circulating ammonia levels.

Fecal Microbiota Transplant

It is documented that there is overgrowth of potentially pathogenic bacterial taxa and reduction of autochthonous species in the stool and the colonic mucosa of the patients with HE. The altered bacterial profile has been linked with congentive dysfunction in patients with HE. Fecal microbiota transplant (FMT), infusion of faeces from a healthy donor to the gastrointestinal tract of a recipient patient, seems promising approach to treat HE by restoring altered gut dysbiosis. The concept of modulating human gut microbiota (through FMT) and thereby improvement in subjective and objective outcomes has been well documented in animal studies and human studies. Further trials are awaited before FMT can be recommended as a treatment option for HE.

Approach to pharmacologic treatment of HE

General Principles

Altered mental status in a patient with cirrhosis should be considered to be HE until proven otherwise. The initial approach includes a full assessment of the cause of mental status particularly the presence of infection. Potential precipitating factors that are identified should be treated aggressively. Empiric treatment with broad-spectrum antibiotics is often initiated after cultures are drawn although the value of this in subjects with acute worsening of mental status remains to be experimentally demonstrated.

Episodic HE

This may be due to a precipitating factor or spontaneous. In cases of acute worsening of mental status in a patient with cirrhosis, the initial evaluation should proceed. The first-line

treatment in such cases is usually lactulose (or lactitol) or rifaximin. The goals of treatment are return the mental status to baseline prevent future hospitalizations, improve the functional status of the patient and their quality of life. The overall efficacy endpoints were similar in the two treatments but those on lactulose appeared to report more adverse events. Rifaximin appears to be of at least similar efficacy compared to lactulose in this setting but with fewer side effects. The role of combination treatment of acute HE unresponsive to either lactulose or rifaximin has not been verified.

Chronic HE

This usually manifests as waxing and waning of mental status on a chronic ongoing basis in subjects with cirrhosis. Patients with this either have an underlying shunt or have advanced liver disease frequently with substantial muscle wasting. Rifaximin and lactulose are commonly used to prevent further worsening of mental status in such cases. When the liver function is poor, liver transplantation is the optimal way to manage such cases.

Prevention of Recurrent HE

Rifaximin on top of lactulose therapy is the preferred approach for the prevention of recurrent breakthrough HE.

Refractory HE

In such cases, it is prudent to reassess the clinical status with particular reference to the presence of precipitating factors, presence of underlying dementia or a primary neurologic disease (stroke, syphilis, etc). If HE persists, second line agents such as LOLA may be considered. If zinc deficiency is present, it should be corrected. The use of metronidazole in short courses may lead to improvement in mental status. In refractory HE, despite maximum pharmacological treatment, liver transplant remains the best approach irrespective of MELD score.

Minimal Encephalopathy

It is now appreciated that the spectrum of HE includes even those who have apparently normal mental status but who have impaired neurocongnitive function when asked to take on complex activities like psychometric testing. This is often referred to somewhat inappropriately by the term minimal hepatic encephalopathy (MHE). Subjects with so called MHE have an increased risk of developing overt HE, a greater risk of motor vehicle accident. MHE has also been associated with a greater impairment of driving skills and fatigue induced driving errors. Rifaximin and lactulose have both been shown to improve psychometric test scores in subjects with MHE.

Rifaximin has been also shown to improve scores on a driving simulator.

HE after TIPS

One third of subjects receiving TIPS develop HE. The risk factors for HE following a TIPS include increasing age, worsening liver function, the size of the shunt and a history of HE prior to TIPS. Prophylactic treatments of HE with these

drugs do not work in majority. If encephalopathy occurs, it usually responds to lactulose and rifaximin. In those with encephalopathy refractory to both drugs, the size of the shunt may be reduced.

Further Reading

1. Bajaj JS, Riggio O. Drug therapy: rifaximin. *Hepatology* 2010; 52:1484–8.

2. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaimin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–81.

3. Poordad FF. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* Feb 2007;25 Suppl 1:3–9.

4. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002;35:716–21.

5. Mullen KD, Dasarathy S. Hepatic encephalopathy. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff’s Diseases of the Liver*, 8th ed. Philadelphia, Pa: *Lippincott-Raven*; 1999:545–81.

6. Butterworth RF. Editorial: rifaximin and minimal hepatic encephalopathy. *Am J Gastroenterol* Feb 2011;106:317–8.

7. Ferenci P. Hepatic encephalopathy. *Gastroenterology Report* 2017;5:138–47.

8. Vilstrup H, Amodio P, Bajaj J et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014;60:715–35.

9. Dbouk N, McGuire BM. Hepatic encephalopathy: a review of its pathophysiology and treatment. *Curr Op Gastroenterology* 2006;9:464–74.

10. Bajaj JS, Kassam Z, Fagan A, Gavis EA, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017;66:1727–38.

Chapter 52.**Renal Dysfunction in Chronic Liver Disease**

**Anil Mannavar**, MD, DNB, Consultant Gastroenterologist, Gleneagles Global Hospitals, Hyderabad, India

**Dharmesh Kapoor**, MD, DM, Consultant Hepatologist, Gleneagles Global Hospitals, Hyderabad, India

Introduction

Renal impairment in patients with cirrhosis was defined more than 30 years ago by serum creatinine value  1.5 mg/dL, because this value was considered an index of estimated GFR (eGFR)  40 mL/min. The use of serum creatinine in the evaluation of renal function in patients with cirrhosis, has several well-known limitations. Acute kidney injury (AKI), defined by a significant reduction in glomerular filtration rate (GFR) over a short time period, is a common and severe complication in patients with cirrhosis and is often triggered by a precipitating event (i.e., overdose of diuretics, large-volume paracentesis without albumin replacement, gastrointestinal bleeding, bacterial infections, etc). AKI has an estimated prevalence of approximately 20–50% among hospitalized patients with cirrhosis and patients with cirrhosis are more likely to develop renal failure compared to individuals without liver disease. AKI is associated with poor prognosis and represents an important predictor for short-term mortality in patients with cirrhosis.

Assessment of renal dysfunction in chronic liver disease

The issues with the use of serum creatinine in cirrhotic patients to define renal function or dysfunction are known to scientific community since a long time – it is a poor marker in malnourished, sarcopenic patients, is not always ‘filtered’ but may be excreted through tubules or it may be falsely assayed in the presence of elevated serum bilirubin levels. Therefore, the actual serum creatinine value or the estimated glomerular filtration rate (eGFR) derived from the same may falsely classify the renal dysfunction in a given patient. The actual measurement of GFR is more cumbersome and seldom practiced. Cystatin C (CysC) has found the fancy of some workers to define renal dysfunction in cirrhotic, but the cost and non-availability for most, are the deterrents. That being said, the MDRD-6 (modified diet in renal disease-6) is supposedly the closest estimate of eGFR to actually measured GFR.

Renal dysfunction in acute on chronic liver failure

Before one proceeds to describe the syndrome of renal dysfunction in cirrhotic patients with liver dysfunction, it is relevant to discuss renal dysfunction in the context of patients with acute-on-chronic liver failure (ACLF). Renal dysfunction forms an important component of non-hepatic organ failure in patients with ACLF as defined by the EASL-AASLD definition (CLIF-SOFA score) or the APASL definition (AARC score). In this syndrome, liver dysfunction precipitates hepatic (jaundice, ascites, coagulopathy) and extra-hepatic (renal, cerebral, respiratory and cardio-haemodynamic) failure. Depending on the numbers of organ which fail, short term (28 days and 90 days) mortality is predicted in this cohort of patients. The pathophysiology of renal dysfunction in these patients is different from the patients with decompensated cirrhosis who develop renal dysfunction – in that DAMPS (disease associated molecular patterns resulting from early hepatic injury) and PAMPS (pathogen associated molecular pathogens arising from increased gut permeability) initiate the cascade of systemic inflammation. This in turn leads to SIRS (systemic inflammatory response syndrome) initially, and later CARS (compensatory anti-inflammatory response syndrome) and resultant organ damage and predilection to sepsis. The hepatic injury does leave a trail of portal hypertension, but that is very different from what is observed in patients with decompensated cirrhosis. Also, some of these patients are very cholestatic, and renal injury is contributed by ‘*cholemic nephropathy’* in them. The 28 d and 90 d mortality of this condition is very high, 30–50% and cannot be captured by conventional scores of liver disease severity like the MELD score. The manage-ment of this condition entails the treatment of the precipitating factor as well as the underlying cause of liver disease. However, a significant number of these patients require organ support, including renal replacement therapy and liver transplantation. Therefore, the recognition of this syndrome is of paramount importance.

AKI in cirrhosis

The spectrum of causes for AKI in cirrhosis includes: (i) prerenal AKI (i.e., hypovolemia due to gastrointestinal bleeding, aggressive diuretic treatment, lactulose-induced diarrhea or infections), (ii) the hepatorenal syndrome-type AKI (HRS-AKI), which is defined as a potentially reversible

deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence

of alternative identifiable causes, (iii) intrinsic causes such as acute tubular necrosis or primary glomerular diseases, or systemic disorders producing nephropathy like hypertension, diabetes and, although very rarely (iv) post-renal causes.

The most common cause of AKI in hospitalised patients with decompensated cirrhosis is pre-renal, accounting for approximately 68% of the cases. Intrarenal-AKI is mainly represented by acute tubular necrosis (ATN). Finally, post-renal AKI is uncommon in decompensated cirrhosis. Considering that most cases of pre-renal AKI are resolved by volume expansion and that post-renal AKI is uncommon, the key point is to differentiate HRS-AKI from ATN. The outcome of AKI is dependent on the aetiology, with the pre-renal AKI having the best prognosis, and the ATN having the worst.

AKI in cirrhosis is defined as an acute increase in serum creatinine of 0.3 mg/dL within 48 hours or by 50% from a stable baseline serum creatinine (sCr) within 3 months (or presumed to have developed within the past 7 days when no prior readings are available). The main modifications over the former, rather stringent criteria that were based on absolute serum creatinine level, was abandoning the arbitrary threshold of sCr  1.5 mg/dL to diagnose AKI.

In addition, the use of urine output as part of the diagnostic criteria was eliminated, as many patients with

cirrhosis and ascites maintain a preserved renal function

despite being oliguric due to sodium and water retention. The International club of ascites definition for AKI in cirrhosis is shown in **Table 52.1**.

Hepatorenal Syndrome (HRS)

The prototype of renal dysfunction in advanced liver disease is hepatorenal syndrome. Also known as ‘functional renal failure’ secondary to end-stage liver disease (ESLD), the condition is characterized by no significant histological changes in the kidneys at autopsy. Using clearance techniques, the hallmark of the HRS was found to be severe renal vasoconstriction. Historically, HRS was classified into Type 1 and type 2 based on time frame in which the serum creatinine increases. In the recent revised classification, type 1 HRS now corresponds to HRS-AKI. Consequently, type 2 HRS should now include renal impairment which fulfills the criteria of HRS but not of AKI, namely non-AKI-HRS (NAKI). In case the eGFR in the context of HRS 2 is less than 60 mL/min/m2 and lasts for more than three months, this would be classified as HRS-CKD.

With a yearly incidence of 8–12%, HRS-AKI is quite common in decompensated cirrhosis with ascites. The correct classification of AKI is essential since HRS-AKI, representing one of the most lethal complications of portal hypertension, requires a specific treatment approach.

However, despite adequate treatment mortality is still about 60% and higher. HRS-AKI is a diagnosis by exclusion and thus, often difficult to establish. The diagnostic criteria for HRS is shown in **Table 52.2**.

Presence of cirrhosis and ascites

No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day)

Absence of shock

Exclusion of recurrent or recent use of nephrotoxic agents (e.g. NSAIDs, aminoglycosides, contrast media)

Exclusion of parenchymal kidney disease:

n absence of proteinuria (>500 mg/day)

n absence of microhematuria (>50 RBCs per high-power

field)

n Normal renal ultrasonography

Pathophysiology

The pathophysiology of AKI in cirrhosis is complex and not completely understood. The hallmark of HRS is profound renal vasoconstriction. In contrast, there is severe arterial underfilling in the systemic circulation due to pronounced arterial vasodilatation in the splanchanic circulation, which is the result of portal hypertension **(Fig. 52.1**). Not all patients with seemingly equally severe hepatic dysfunction develop HRS. Therefore, the role of liver dysfunction in the pathogenesis of HRS appears to be an important background factor, or “first hit,” that requires an additional factor, or “second hit,” to initiate HRS.

Clinical Features

HRS occurs in about 8% of patients admitted with decompensated cirrhosis, with a cumulative probability of 18% at 1 year and 39% at 5 years. Patients with spontaneous bacterial peritonitis have a 33% chance of developing HRS. Most patients with HRS- AKI have a MELD score of more than 20. Patients with HRS- CKD who have a MELD (Model of End Stage Liver Disease) score of more than 20 have a survival intermediate between 2 weeks and 6 months.

Patients with HRS- AKI have low arterial blood pressure, wide pulse pressure and bounding pulses. The urine output is drastically reduced. Patients with refractory ascites, defined as a lack of response to high doses of diuretics (400 mg of spironolactone per day plus 160 mg of furosemide per day) have an increased risk of developing HRS-AKI, generally in the setting of supervening sepsis or large volume paracentesis without adequate intravascular replacement.

Biomarkers for AKI

Currently, numerous biomarkers have been assessed in the setting of AKI and liver cirrhosis including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, liver-type fatty acid binding protein (L-FABP), kidney injury

molecule-1, toll-like receptor 4, ð-glutathione S-transferase and á-glutathione S-transferase. Among all of them, current data show that NGAL is the most useful marker. NGAL detects patients with acute tubular necrosis (ATN). On the contrary, NGAL is not helpful to differentiate between pre-renal azotemia and HRS. NGAL urinary levels are much higher in patients with ATN compared to patients with other causes of AKI. Urinary levels of NGAL in ATN were 417 g/L, compared with levels at 30 g/L in pre-renal azotemia, 82 g/L in chronic kidney disease and 76 g/L in HRS, *P* < 0.001. Thus, incorporating NGAL into the clinical decision algorithm would be of benefit to rule out structural kidney injury and detecting a group of patients in whom treatment with vasoconstrictors wouldn’t be effective and only would produce potentially serious side effects.

Management

Until recently, HRS has been considered a rapid and fatal complication of end-stage liver disease unless liver transplantation can be immediately performed. Fortunately, with better knowledge of the pathogenesis of this condition, new pharmacological treatments have been devised to improve short-term outcome and enhance the feasibility of performing liver transplantation for patients with HRS.

Patients with cirrhosis and ascites with initial ICA-AKI stage 1 should be managed as soon as possible with the following measures:

1. Review drug chart: review of all medications (including over-the-counter (OTC) drugs), reduction or withdrawal of diuretic therapy, withdrawal of all potentially nephrotoxic drugs, vasodilators or non-steroidal anti-inflammatory drugs (NSAIDs).

2. Plasma volume expansion in patients with clinically suspected hypovolemia (with crystalloids or albumin or blood (in patients who had AKI as a result of gastrointestinal bleeding) or according to clinical judgment.

3. Prompt recognition and early treatment of bacterial infections when diagnosed microbiologically or strongly suspected **(Fig. 52.2)**.

Patients who respond with a return of sCr to a value within 0.3 mg/dL of the baseline value should be followed closely (assessment of sCr every 2–4 days during the hospitalization and checked as outpatients at least every 2–4 weeks during the first 6 months after the discharge) for early identification of potential new episodes of AKI. In those cases where there is progression of the AKI stage, the patients should be treated as patients who present with ICA-AKI stage 2 and 3. This treatment should include the withdrawal of diuretics, if this had not been previously implemented, as well as the expansion of plasma volume with intravenous albumin at the dose of 1 g per kg bodyweight per day for two consecutive days, in order to treat pre-renal AKI and to allow differential diagnosis of AKI. The maximal dose per day of albumin should not exceed 100 g.

Further management of patients who do not respond to diuretic withdrawal and plasma volume expansion will obviously depend on the final diagnosis of the AKI type and, pragmatically, on the differential diagnosis between an HRS-AKI, an intrinsic AKI, and post-renal-AKI.

Vasoconstrictor Therapy

Many pharmacological interventions have been tried for treating HRS. Use of renal vasodilators (dopamine and prostaglandin analogues) was abandoned due to side effects and lack of adequate data confirming the benefits. Systemic vasoconstrictors with plasma expansion are now the best therapy since several uncontrolled studies have confirmed a beneficial role in HRS. They have been in use for more than 10 years and their actions are to suppress the arterial splanchanic vasodilatation and endogenous vasoconstrictor system activation (by replenishment of effective arterial blood volume) with improvement of renal function.

In most studies, vasoconstrictors were given in combination with albumin, with improved efficacy. Vasopressin analogues (ornipressin and terlipressin) have been used in the management of acute variceal bleeding in cirrhotic patients since they have a marked vasoconstrictor effect in the splanchanic circulation. Use of ornipressin was abandoned since it caused significant ischemic side effects. Terlipressin has been shown to have the most successful outcomes of the vasoconstrictors studied. Administration of terlipressin (0.5–2 mg/4–6 hrs intravenously) is associated with an improvement in renal function in about 60–75% of the patients and the incidence of ischaemic side effects is about 5–10%. The recurrence of HRS after treatment withdrawal is about 15–50%, and retreatment of recurrence is generally effective [half the patients in whom it recurs]. The drug may be given as a bolus or as an infusion. Recent studies have shown the side effect profile to be favourable with continuous infusion. Nevertheless, the patients should be continuously monitored for any side effects like cold extremities, features of peripheral vascular disease, skin discolouration, cardiac rhythm disturbances, EKG changes of cardiac ischaemia, and features of volume overload.

Diarrhoea is almost always seen when terlipressin administration is initiated. However, it settles with continued usage among responders. Somatostatin analogues (octreotide) and alpha-adrenergic agonists (midodrine) have also been used. A recent meta-analysis has favored the use of terlipressin along with albumin infusion, in patients with HRS-AKI. When cost becomes a constraint, noradrenalin can be used with intravenous albumin in this group of patients although large patient series treated with this regimen are not reported in literature. Also, noradrenalin requires a central venous catheter for administration and has to be given under haemodynamic monitoring.

Predictors of response to terlipressin

Patients in whom terlipressin did not increase the mean arterial pressure (MAP) by at least 5 mmHg at day 3 of treatment had a lower rate of response. Effectiveness of treatment is also related to the degree of liver dysfunction. Those patients who did not have an increase in MAP at day 3 and who also had high baseline bilirubin levels  10 mg/dL had a poor response rate, of only 9%. Another study showed that baseline creatinine levels predicted HRS reversal, suggesting that early intervention would be more effective. A recent study (REVERSE Trial) showed that those patients with systemic inflammatory response syndrome (SIRS) had a much higher response rate to terlipressin, while terlipressin did not show more efficacy than placebo when employed in patients without SIRS.

Transjugular Intrahepatic Portosystemic Shunt Stent (TIPSS)

This is a non-surgical method of portal decompression previously used as an alternative therapy for cirrhotic patients bleeding from oesophageal or gastric varices who do not respond to endoscopic and medical treatment. An interventional radiologist fashions a side-to-side porto-caval

shunt that connects the portal and hepatic veins within the hepatic parenchyma. TIPSS stent reduces portal pressure and returns some of the volume of blood pooled in the splanchanic circulation to the systemic circulation. This suppresses the renin-angiotensin-aldosterone and sympathetic nervous systems activities and decreases their vasoconstrictor effect on the renal circulation. However, there are also many complications associated with TIPSS including bleeding (transcapsular haematoma), shunt dysfunction and most importantly, hepatic encephalopathy (cumulative incidence of 33% at the end of 1 year). TIPSS shunt is contraindicated in patients with advanced Child C cirrhosis and most patients with type 1 HRS (HRS-AKI) fall in this category. However, when patient selection is careful, the procedure prolongs the survival in this group of patients (1 month - 60%, 3 months - 50%, 6 months -30%). For type 2 HRS (HRS-CKD) patients, TIPS remains a useful procedure while these patients await transplantation.

Renal replacement therapy

Small uncontrolled studies using haemodialysis and peritoneal dialysis suggest that both are ineffective mainly due to a high incidence of severe side effects, including arterial hypotension, coagulopathy and gastrointestinal bleeding. However, haemodialysis may be useful in suitable liver transplant candidates as a bridge to transplantation when there is no response to vasoconstrictor therapy or in patients with severe volume overload, metabolic acidosis or refractory hyperkalaemia, along with oligoanuria. Depending on the availability of resources, one may use SLED (slow low efficiency dialysis) or CVVHF/CVVHDF (continuous veno-venous haemofiltration or haemo-diafiltration). Liver assist devices like the MARS (molecular adsorbent recirculating system) or Prometheus (frac-tionated plasma separation, adsorption) have been used to manage patients with HRS AKI and AKI ATN. There is no added advantage over the standard renal replacement therapies (interested reader may refer to the HELIOS and MARS RELIEF trials).

Liver Transplantation

This is the definitive treatment for HRS. However, transplantation for type 1 HRS is limited by the fact that many patients die before the operation because they have a short survival against a prolonged waiting time in most centers. If

liver transplantation can be performed, the 1, 3 and 5-year survival probability after transplantation for HRS patients is similar to that of cirrhotic patients without HRS. In the first month following transplantation, the morbidity and mortality of this group (type 1 HRS) is somewhat higher due to need for renal replacement therapy in the postoperative period. Those who have received RRT for more than 6–8 weeks prior to liver transplantation are considered for simultaneous liver kidney transplantation. This is because the renal function is less likely to improve in them regardless of the cause of AKI—HRS or ATN. These patients also need judicious modification of the immunosuppression regimens in the post-transplant period, especially with calcineurin inhibitors.

Conclusion

Renal dysfunction is very common in patients with cirrhosis, especially those with advanced liver disease and decompensation. The recently described syndrome of acute on chronic liver failure also has renal dysfunction as its key component. Recognition of early renal dysfunction is the key and paves way for optimal management and prognosis. However, some patients do not respond to medical therapy, and need renal replacement therapy as bridge to liver transplantation. Such patients should also be identified early, as prolonged use of RRT pre-transplantation may be a precursor to simultaneous liver kidney transplantation, a luxury which the transplant community cannot afford in this era of organ shortage.

Further Reading

1. Adebayo D, Neong SF, Wong F. Ascites and hepatorenal syndrome. *Clin Liver Dis* 2019;23:659–82.

2. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites Consensus Statement. *J Hepatol* 2019;71:811–22.

3. Francoz C, Durand F, Kahn JA, et al. Hepatorenal syndrome*. Clin J Am Soc Nephrol* 2019;14:774–81.

4. Wong F, Reddy KR, O’Leary JG, et al. Impact of chronic kidney disease on outcomes in cirrhosis. *Liver Transpl*. 2019;25:870–80.

5. Cullaro G, Verna EC, Lai JC. Association between renal function pattern and mortality in patients with cirrhosis*. Clin Gastroenterol Hepatol* 2019; 17:2364–70.

6. MacDonald AJ, Nadim MK, Durand F, Karvellas CJ. Acute kidney injury in cirrhosis: impact on liver transplantation. *Curr Opin Crit Care* 2019;25:171–78.

7. Amin AA, Alabsawy EI, Jalan R, Davenport A. Epidemiology, pathophysiology and management of hepatorenal syndrome. *Semin Nephrol* 2019;39:17–30.

8. Singal AK, Ong S, Satapathy SK, et al. Simultaneous liver kidney transplantation. *Transpl Int* 2019;32:343–52.

9. Appenrodt B, Lammert F. Renal failure in patients with cirrhosis: novel classifications, pathophysiology and management. *Visc Med* 2018;34:246–52.

10. Ginès P, Solà E, Angeli P, Wong F, et al. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018;4:23.

11. Solé C, Pose E, Solà E, Ginès P. Hepatorenal syndrome in the era of acute kidney injury. *Liver Int* 2018;38:1891–901.

12. Durand F, Francoz C, Asrani SK, Khemichian et al. Acute kidney injury after liver transplantation. *Transplantation* 2018;102:1636–49.

13. Wong F, Pappas SC, Boyer TD, et al. Terlipressin improves renal function and reverses hepatorenal syndrome in patients with systemic inflammatory response syndrome. *Clin Gastroenterol Hepatol* 2017;15:266–72.

14. Boyer TD, Sanyal AJ, Garcia-Tsao G, et al. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics*. J Hepatol* 2011;55:315–21.

**Chapter 53.**

**Irritable Bowel Syndrome**

**Rajesh Sainani**, MD, DNB, Consultant Gastroenterologist, Smt. Motiben Dalvi Hospital & Jaslok Hospital, Mumbai, India

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, and with features of disordered defecation.

Diagnostic Criteria\* for Irritable Bowel

Syndrome [Rome IV]

Recurrent abdominal pain, on average at least 1 day per week in the last 3 months associated with *2 or more* of the following:

1. Related to defecation

2. Associated with a change in frequency of stool

3. Associated with a change in form (appearance) of stool

*\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*

Subtyping IBS by Predominant Stool Form

1. IBS with constipation (IBS-C) – Bristol stool scale 1 or 2 >25% and Bristol stool scale 6 or 7 <25% of bowel movements.

2. IBS with diarrhoea (IBS-D) – Bristol stool scale 6 or 7 >25% and Bristol stool scale 1 or 2 <25% of bowel movements.

3. Mixed IBS (IBS-M) – Bristol stool scale 1 or 2 >25% and Bristol stool scale 6 or 7 >25% of bowel movements.

4. Unsubtyped IBS – Insufficient abnormality of stool consistency to meet criteria for IBS-C, D or M.

The Bristol Stool Form Scale

The Bristol stool scale **(Fig. 53.1)** is used to classify stool types objectively. The different types depend upon the intestinal transit time. Type 1 is at one end of the scale, which signifies slow transit and type 7 is at the other end of the scale which signifies rapid transit of stool.

Pathophysiology

1. **Motility Abnormalities in the Gut**

There is an increase in transit in diarrhoea patients and a slow transit in constipation patients. Stress and meals shows an increased response in the ileum, colon and rectum. High amplitude propagating contractions are more commonly seen in IBS patients who have diarrhea and seem to be pain predominant. It has been seen that pharmacological stimulation of gut motility has led to reduced gas retention and improvement in symptoms.

2. **Visceral Hypersensitivity**

IBS patients have increased sensitivity to the normal passage of gas, fluids and regular contractions in the gastrointestinal tract. Balloon inflation in the colon or rectum shows pain thresholds at lower values of balloon inflation in patients with IBS. Patients also complain of bloating although they do not have increased volumes of gas compared to controls but impaired transit of gas loads.

3. **Brain Gut Axis**

Signals from the brain modulate the gut to maintain the digestive functions of the body. The signals from the gut to the brain have a role in reflex regulation and mood modulation. Visceral afferent signals from the gut reach only to the brainstem and thalamus and very few are perceived by the cortex. Stress and anxiety can enhance the perception of painful events.

4. **Inflammation**

There seems to be an alteration in the immune gut function. Elevated levels of plasma proinflammatory interleukins and tumor necrosis factor are reported. Microscopic inflammation is seen in the colon and small bowel. Lymphocyte infiltration of myenteric plexus, neuronal degeneration, colonic mucosal lymphocytes and increased nitric oxide synthetase expression in the gut has been reported.

5. **Postinfectious IBS**

Studies showed that patients who developed symptoms of IBS did so after they recovered from bacterial gastroenteritis. The odds of developing IBS are 6 fold after an acute gastrointestinal infection. *E. coli* and *Campylobacter jejuni* are the common pathogens responsible. Risk factors seem to be female sex, prolonged episodes of infectious diarrhoea and use of antibiotics. The ability of probiotics to modify intestinal flora and their role in gut immune modulation has brought about focus to their role in postinfectious IBS. Probiotics were found to decrease symptoms in patients suffering from IBS.

6. **Bacterial Overgrowth**

The data on small intestinal bacterial overgrowth and IBS is conflicting. There are data to suggest that there are abnormal breath hydrogen levels in IBS patients after receiving a test dose of carbohydrate, which suggests bacterial overgrowth and there is a response to antibiotics in patients with diarrhoea predominant IBS.

7. **Food Sensitivity**

Some patients perceive intolerance to certain foods. IBS patients have more positive food skin prick tests than controls. All foods with which patients had an elevated IgG response do not exacerbate patient’s symptoms.

FODMAPs (fermentable, oligo, di, monosaccharides and polyols) get fermented in the distal bowel and colon and are known to cause symptoms. Increased incidence of flatus, pain, bloating, belching and altered bowel habits maybe related to fructose intolerance. Dietary restriction of fructose, fructans or low carbohydrate diet may benefit diarrhea predominant IBS patients.

There may be an overlap between celiac and IBS patients. Patients in whom gluten antibodies are positive but have absence of villous atrophy may benefit from gluten exclusion but need steps to ensure celiac disease is excluded.

8. **Genetic**

Conclusive evidence for genetic basis is not identified. There has been an increased incidence in monozygotic twins than dizygotic twins. There may be some familial aggregation of IBS cases.

9. **Psychosocial**

Gastrointestinal symptoms get exacerbated by stress. Psychiatric and psychological factors coexist in IBS.

Clinical outcome of IBS is affected by psychosocial factors.

Evaluation

Initial Evaluation and Workup

The diagnosis of IBS is symptom based as defined by the Rome IV criteria.

A detailed physical and rectal examination will be helpful to exclude any pre existing condition. Patients with alarm symptoms like fever, gastrointestinal bleeding, anaemia, unintended weight loss, family history of inflammatory bowel disease or colonic malignancy should undergo further investigations.

Complete blood counts, blood chemistries, stool examination for occult blood and parasites, thyroid functions tests, antibodies for celiac sprue and colonoscopy should be done where indicated. Therapeutic trial of treatment can be given based on the symptom severity even before inves-tigations are performed in a given case without alarm symptoms.

Diagnostic Workup Symptom Based

If patients do not respond to a therapeutic trial of treatment then further workup should be done.

If they are constipation predominant, and have infrequent bowel movements then a colon transit study is suggested. If patients give a history of digital evacuation during defecation or symptoms suggestive of obstructive defecation or rectal examination suggests poor pelvic floor relaxation, then anorectal manometry with balloon expulsion studies can be performed.

In diarrhoea predominant patients, 24-hr stool for fat, a trial of cholestyramine, and small and large bowel biopsies can be done to rule out other medical disorders if clinically indicated. Hydrogen breath tests for small bowel overgrowth, fructose and sorbitol intolerance can be performed. Rectal sensory function tests may be beneficial in a subgroup of patients.

Patients in whom pain is their predominant symptom, abdominal X-rays, small bowel enema, ultrasonography and CT/MRI scans of the abdomen can be done.

Biopsychosocial model of IBS

There is an interaction of psychological factors and physiological factors, which can be approached using a biopsychosocial model. In this model psychological and environmental stressors seen in early life, genetic history, abuse history interact with psychological stress, coping skills, symptom presentation, visceral sensitivity, altered gut motility and brain gut axis interaction to present with functional gastrointestinal symptoms. Based on these factors pharmacotherapy and psychotherapy is directed to achieve better clinical outcomes.

Treatment

The initial approach to the management of IBS is the early and correct diagnosis of the condition. An important aspect is to establish a therapeutic physician–patient relationship. The physician should be non-judgmental, have realistic expectations and involve the patient in treatment decisions.

The patient should receive an appropriate explanation of his symptoms and reassurance of his condition. They should be told that their symptoms are not due to any cancer or pathological disease. They should be advised symptom based drug treatment. Proper dietary advice should also be given.

Diet

An empiric trial of lactose free diet should be given because patients may have undiagnosed lactose intolerance and may

have significant improvement with stopping lactose containing products. Patients who do not have lactose

intolerance on breath test but have symptoms on taking milk, may have intolerance to other milk components such as cow milk protein. These individuals may tolerate soy or almond milk.

If excessive gas is a predominant symptom then gas producing foods like broccoli, cabbage, Brussel sprouts, onions, asparagus, celery, carrots, raisins, bananas, apricots, prunes and whole wheat and bran should be avoided.

A diet low in FODMAP’s (fermentable oligo-, di-, and monosaccharides and polyols) has been shown to reduce symptoms. Examples are fructans (wheat, onions and artichokes), galactans (legumes, cabbage, Brussel’s sprouts), lactose, fructose, sorbitol, xylitol, and mannitol.

In patients gluten sensitivity without overt celiac disease (normal duodenal biopsies but positive antibodies) a trial of gluten-free diet gives a better control of symptoms. Patients with non-celiac gluten sensitivity may also respond to gluten avoidance but this usually due to avoidance of fructans rather than gluten.

Fibre

Dietary fibre supplementation is a simple, inexpensive and safe therapy to try but it is not well proven in clinical trials. It has been not been found to be better than placebo. There is no difference between soluble and non soluble fiber. If synthetic fibres such as polycarbophil and methylcellulose cause less bloating that natural fibres [psyllium] has not yet been proven.

Bulking agents like psyllium help in constipation predominant patients. It may actually worsen diarrhea and bloating in some patients with diarrhea predominant symptoms. Due to its safety and frequently observed placebo effect, a trial of fibre is a reasonable therapeutic strategy.

Others

Physical activity trials have shown improvement in clinical symptoms in patients compared to controls.

The patient should eat regular and unhurried meals. Keeping a diary and observing which food worsens their symptoms may be useful in identifying intolerant foods.

The physician should watch for changing social and psychological conditions and alter therapy accordingly. Cognitive therapy, psychotherapy and hypnotherapy reduces anxiety promotes healthy behaviour and involves the patients in his treatment and improves pain tolerance and may benefit a select group of IBS patients.

Diarrhea Predominant Symptoms

Loperamide 2–4 mg at one time

(maximum - 16 mg/day)

Diphenoxylate 1 tablet 3–4 times

(combined with atropine

sulphate)

Alosetron 1 mg twice daily (now

withdrawn by US FDA)

Cholestyramine 4 g with each meal

Colesevelam 1.875 g twice daily

Eluxadoline 100 mg twice daily

Abdominal Pain Predominant Symptoms

Smooth muscle relaxants 1–3 times daily

(Mebeverine, Dicyclomine,

Hyoscine, Otillonium bromide)

Tricyclic Antidepressant 10–50 mg at night (e.g.,

Amitriptyline, chlorimipramine)

start with a small dose and

increase as per the requirement

Serotonin reuptake 10–15 mg once daily

inhibitors (Fluoxetine, Sertaline,

Paroxetine, Citalopram,

Escitalopram)

Antibiotics for bloating, abdominal pain,

altered bowel habits

Rifaximin 550 mg three times daily for 14 days

(TARGET trial)

**Fecal Microbiota Transplantation (FMT)** has shown benefit at 3 months in reducing IBS symptoms but did not show sustained benefit at 12 months.

Others

(Drugs on which trials have shown some benefit)

Peppermint oil

Probiotics (Bifidobacterium infantis, Lactobacillus plantarum, VSL#3)

Conclusion

IBS is a chronic relapsing disorder with recurrent symptoms of variable severity. There is no increased risk of developing any organic disease in the long term. Treatment is directed towards symptoms, which should be an adjunct to dietary modifications and psychological support.

Further Reading

1. AGA Technical Review on Irritable Bowel Syndrome *Gastroenterology* 2002;123:2108–31.

2. American Gastroenterological Association Medical Position Statement: Irritable Bowel Syndrome. *Gastroenterology* 2002;123:2105–7.

3. Longstreth GF, Thompson WG, Chey WD, et al. Functional Bowel Disorders. *Gastroenterology* 2006;130:1480–91.

4. Camilleri M, Spiller RC. Irritable Bowel Syndrome: Diagnosis and Treatment; 2007.

5. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104:S1–35.

6. Ghoshal UC, Abraham P, Bhatt C, et al. Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol* 2008;27:22–8.

7. Lacy BE. Bowel disorders. *Gastroenterology* 2016;150:1393–1407.

**Chapter 54.**

**Manometry in Gastrointestinal Disorders**

**Rajesh Sainani**, MD, DNB, Consultant Gastroenterologist, Smt. Motiben Dalvi Hospital & Jaslok Hospital, Mumbai, India

Manometry is the study of the pressures in the gastrointes-tinal tract from the mouth to the anal canal.

Equipment

Manometry system consists of manometry catheters, transducers and the amplifiers. The transducers measure the pressures in the esophagus. The amplifier transfers the data to the computer where it can be stored and reported by a physician.

The catheter can be a solid state catheter (transducers are in built into the catheter) or water perfused catheter (external transducers). The water perfusion systems have an external reservoir and a low compliance pump through which water is perfused. The water perfused catheters have multiple side holes through which water flows. The flow of water through the side holes is impeded by contraction of the wall of the oesophagus, which causes the recorded pressure to rise.

Pressures are recorded from different sites across the length of the catheter. Multiple side holes make placement easy and does not require repeated pull through of the catheter.

In high-resolution (water perfusion) manometry (HRM), pressures are recorded at multiple sites (16–32) throughout the lower esophageal sphincter (LES) and oesophageal body (16 sites as standard, 8 across the LES with 1 cm spacing, 8 in the body of the oesophagus with 3 cm spacing). This placement of sites ensures that ‘complete’ data are obtained for each swallow.

The different colours in the graph represent different pressure values **(Fig. 54.1a)**.

Clinical Indications for Oesophageal

manometry

1. Evaluation of patients with:

n Dysphagia (oesophageal/pharyngeal)

n Chest pain – non-cardiac

n Recurrent food impaction

2. Primary oesophageal motility disorders

n Achalasia

3. Spastic disorders

n Distal oesophageal spasm

n Jackhammer oesophagus

4. Secondary oesophageal motor disorders

n Scleroderma

n Chronic intestinal pseudo-obstruction (visceral myopathies/neuropathies)

5. Evaluate peristalsis prior to fundoplication

6. Assist in placement of pH probe

7. Boutique

n Unusual symptoms (Belching, Rumination)

n Intraoperative (achalasia myotomy)

Manometric Features of oEsophageal Motility Disorders

The Chicago classification v3.0 introduced the following topographic metrics to define oesophageal motility characteristics.

1. CDP (contractile deceleration point): Inflection point along the 30 mmHg isobaric contour at which propagation velocity slows, demarcating peristalsis from ampullary emptying. The CDP must be localized within 3 cm of the proximal margin of the LES.

2. DCI (distal contractile integral): Amplitude x duration x length (mmHg-s-cm) of the distal oesophageal contraction (Clouse 2nd and 3rd contractile segments) exceeding 20 mmHg from the transition zone to the proximal margin of the LES.

3. DL (distal latency, sec): Interval between upper oesophageal sphincter relaxation and the CDP.

4. IRP (integrated relaxation pressures, mmHg): Mean of the 4 sec of maximal deglutitive relaxation (contiguous or non-contiguous) in the 10-s window beginning at UES relaxation and referenced to gastric pressure.

EGJ Morphology: Pressure Topographics

1. Type I: Complete overlap of CD (crural diaphragm) and LES components with single peak on the spatial pressure variation plot.

2. Type II: Double-peaked pressure zone with the interpeak nadir pressure greater than gastric pressure and a separation of 1–2 cm between peaks.

3. Type IIIa: Double-peaked pressure zone with the interpeak nadir pressure less than or equal to gastric pressure, but the pressure inversion point remains at the CD level.

4. Type IIIb: Double-peaked pressure zone with the interpeak nadir pressure equal to gastric pressure and the pressure inversion point at the LES level.

oEsophageal Contractility Criteria

As per the Chicago v3.0 criteria, characterization of the esophageal contractility is based on 3 criteria viz contraction vigor, contraction pattern and intrabolus pressure pattern.

Contraction vigor

1. Normal peristalsis: DCI (distal contractile integral) >450 mmHg-s-cm but <8000 mmHg-s-cm

2. Failed peristalsis: DCI <100 mmHg-s-cm

3. Weak peristalsis: DCI >100 mmHg-s-cm, but <450 mmHg-s-cm

4. Ineffective peristalsis: Failed or Weak Peristalsis

5. Hypercontractile peristalsis: DCI ³ 8000 mmHg-s-cm

Contraction pattern

1. Premature contraction: DL (distal latency) <4.5 sec.

2. Fragmented peristalsis: Large break (>5 cm length) in the 20 mmHg isobaric contour with DCI >450 mmHg-s-cm.

3. Intact peristalsis: Not achieving the above diagnostic criteria.

Intrabolus pressure pattern

1. Panesophageal pressurization: Uniform pressurization of >30 mmHg extending from the UES to the EGJ.

2. Compartmentalized oesophageal pressurization: Pressurization of >30 mmHg extending from the contractile front to the EGJ.

3. EGJ pressurization: Pressurization restricted to zone between the LES and CD in conjunction with LES-CD separation.

4. Normal: No bolus pressurization >30 mmHg.

Clinical Indications for pharyngeal manometry

1. Incoordinated UES

2. Hypopharyngeal diverticulum (Zenker’s diverticulum)

3. Cricopharyngeal (UES) achalasia

Clinical Indications for anorectal manometry

1. Fecal incontinence

n Diabetes mellitus

n Multiple sclerosis

n Traumatic – Postpartum, Accidents, Iatrogenic

2. Constipation

3. Dyssynergic defecation

4. Hirschsprung’s disease

5. Post rectal surgery: Prior to colostomy closure to assess anal sphincter

6. Idiopathic megarectum

7. Anal fissures

pH Monitoring

Oesophageal pH monitoring is a test that measures the frequency and duration of gastric acid entering the oesophagus.

Equipment

It consists of an electrode, recording device and a computer on which the data are transferred and then reported by the physician.

The electrodes are of 2 types, glass and antimony.

Glass electrodes can be reused multiple times. They are fragile but harden on repeated use and thus can be uncomfortable to patients. The antimony electrodes can be single use or multiple uses (5 times). Antimony catheters are thinner in diameter and are more comfortable to the patient. Also the antimony electrodes can have 1–3 sensors unlike the glass electrodes which have only a single sensor. Electrodes are subject to drift during the recording and need to be always calibrated before the study.

The pH electrodes are placed transnasally into the oesophagus 5 cm above the upper border of the LES (which is determined by manometry) and secured to the nose. In infants Strobel’s formula (length of child in cm x 0.25 + 5 x 0.875) can be used to determine the exact position of the pH electrode. LES in children can also be determined by manometry. In infants (0–2 yrs of age, <75cm body height) place pH 2 cm above LES. In paediatric age group (2–10 yrs) place electrode 3 cm above LES in 2–6 years and 4 cm above LES in 6–10 years children. The proximal end of the pH electrode is connected to the recording device, which records the pH level in the esophagus every 4 seconds.

There is an electrode (Bravo Capsule), which can be attached to the esophagus and it wirelessly transmits data to the recorder. The main advantage of this device being that it can record for 48 hrs vs conventional 24-hr recording and cosmetic reasons, since no wire needs to be secured to the nose. The disadvantage of the Bravo Capsule being its high cost per patient and need for endoscopy.

Clinical Indications of 24hrs ambulatory pH monitoring

1. Atypical symptoms of GERD

n Pulmonary symptoms – cough, asthma, recurrent aspiration pneumonia

n Otolaryngologic symptoms – hoarseness, laryngitis, recurrent stridor

n Unexplained chest pain of noncardiac etiology

n GERD not responding to drug therapy

2. Fundoplication

n Pre- and postoperative assessment

n If symptoms recur after surgery

3. To determine whether dosage of PPI is adequate in patients with Barrett’s esophagus

**pH is not useful in**

1. Simple regurgitation in children

2. Reflux oesophagitis diagnosed by endoscopy or biopsy

Normal Values for 24 Ph Monitoring

**Normal Values**

% total time pH < 4 <4.2%

Upright <6.3%

Recumbent <1.2%

No of episodes of pH < 4 <50

No of episodes  5 min (pH < 4) <3

Longest episode (min) <9.2min

DeMeester Score <14.7min

Although the DeMeester score is the more popular score, most gastroenterologists now prefer the % of the total time in 24 hrs that the pH < 4. Symptom correlation associated with low pH is an important association that needs to be reported by the physician. If the symptom correlation with low pH is low then it is unlikely to be the cause of the symptom and if the symptom correlation with low pH is high then it maybe the only cause of the symptom.

Combined Multichannel Intraluminal

Impedance- pH [MII- pH] Monitoring

The gold standard for reflux measurement is 24-hr ambulatory pH recording. The biggest disadvantage of the pH recorder is that it labels reflux episodes only with a pH <4.

Impedance monitoring is used to measure non-acid (pH >4) reflux in the oesophagus. It also helps to determine bolus transit.

Intraesophageal impedance is inversely proportional to electrical conductivity between a pair of electrodes. The impedance catheter consists of pairs of metal rings throughout the length of the catheter. The distal tip of the catheter also has pH recording electrodes in between the impedance metal rings. The movement of intraluminal liquid or air changes impedance in different ways. Gases raise impedance (>3000 ohms) due to poor conductivity and liquids decrease

impedance (50% drop from baseline) due to better conductivity between the electrodes.

The clinical importance of non acid or weakly acidic episodes needs to be determined and the use of impedance is mainly for patients on proton pump inhibitors. Impedance helps detect more reflux events than pH alone. It can differentiate if the refluxate is acid, non acid or weakly acid. It can also differentiate between liquid, air or mixed reflux. Acid reflux episodes detected by impedance are shorter than those measured by pH because volume clearance is faster than acid neutralization.

Combined MII-pH can assess symptom correlation with all types of reflux events (acid and non-acid). Thus a negative MII-pH is a better tool to exclude reflux as compared to pH monitoring.

Further Reading

1. Castell D, Diederich L, Castell J. Esophageal Motility and pH Testing: Technique and Interpretation, 3rd edition.

2. Schuster M, Crowell M, Koch K. Schuster Atlas of Gastrointestinal Motility, 2nd edition.

3. Rao SC, Conklin JL, Johlin FC, et al. Gastrointestinal Motility - Tests and Problem Oriented Approach; 1999.

4. Spechler S, Castell D. Classification of esophageal motility abnormalities. *Gut* 2001;49;145–51.

5. Fayyad A, Gaumnitz E. Esophageal Motility Disorders. *eMedicine* 2005.

6. AGA Technical Review on the clinical use of esophageal manometry. *Gastroenterology* 2005;128:209–24.

7. Fox MR, Bredenoord AJ. Oesophageal high resolution manometry – moving from research to clinical practice. *Gut* 2007 Sep 25.

8. Pandolfino JE, Kwiatek MA, Nealis T, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135:1526–33.

9. Bredenoord AJ, Fox M, Kahrilas PJ, et al. International High Resolution Manometry Working Group. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol Motil* 2012;24:57–65.

10. Kahrilas PJ, Bredenoord AJ, Fox M, et al. International High Resolution Manometry Working Group.The Chicago Classification of esophageal motility disorders. *Neurogastroenterol Motil* 2015;27:160–74.

11. Ghoshal Uday. Evaluation of gastrointestinal motility and its disorders, *Springer*; 2016.

***Chapter 55.Clostridium Difficile* Infections**

Introduction

*Clostridium difficile* is a Gram-positive spore-forming anaerobic bacteria associated with the development of a spectrum of clinical illnesses ranging from diarrhoea to severe pseudomembranous colitis, sepsis and death. Mode of transmission is by the fecal-oral route and antibiotic therapy, old age, and hospital or nursing home stay are the important risk factors for *C.difficile* infection (CDI).

Pathophysiology

Approximately 5% of adults and 15–70% of infants are colonized by *C. difficile*, and the colonization prevalence is much higher in hospitalized patients or nursing home residents. Spores of *C. difficile* survive in the environment for several months. The spores can be transferred to patients via the hands of healthcare personnel; therefore, good hand hygiene with soap and water and regular Vinyl glove use is crucial to reduce the transmission.

Intestinal microflora is the main protective barrier against CDI. Bile acids are crucial for the induction of *C. difficile* spore germination. Primary bile acid (cholic acid and chenodeoxycholic acid) helps in the spore germination, while secondary bile acid (deoxycholic acid and lithocholic acid) inhibits it. The pathogen is not invasive, and virulence is mostly due to enzymes, such as collagenase, hyaluronidase, chondroitin-sulfatase, as well as toxins, which damage the epithelial cell cytoskeleton, leading to disruption of tight junctions, neutrophil adhesion, and local inflammation. The result is a breakdown of gut barrier integrity and loss of functionality.

*Clostridium difficile* associated diarrhea (CDAD) is characterized by a progression from an uncolonized state to *C*. *difficile* colonization, followed by toxin production. This process, in part, depends on the specific strain of *C.* *difficile*, as well as the immune status of the host. Strains of *C*. *difficile* have a number of virulence factors that assist in adherence and colonization, including flagellar proteins, surface-layer proteins and surface-exposed adhesion proteins.

Toxin Production

CDAD is associated with active toxin productions, which underlines tissue injury associated with infection. When a large *C. difficile* population is in the vegetative form, toxin production is at its greater level. Pathogenic strains of *C. difficile* typically express either 1 or 2 endotoxins classified as toxins A and B. Toxin A is a potent enterotoxin while toxin B is a potent cytotoxin in vitro, but has little activity in vivo unless there is prior damage to mucosal epithelium. Purified toxin A loosen epithelial tight junctions in the colonic surface and facilitates the entry of toxin B into epithelial cells. Both of these toxins are known to glycosylate Rho proteins and disrupt cell signaling leading to cytoskeleton actin disintegration and epithelial apoptosis. Most strains of *C difficile* that cause disease in humans contain both toxins A and B; however strains that only produce toxin B can also cause CDAD, in about 2% of cases.

Recent reports have identified a third toxin (binary toxin, the epidemic PCR ribotypes 027) that has been implicated in the present *C. difficile* epidemic. It causes fluid secretion, but no evident epithelial damage in animal studies.

RISK FACTORS AND CLINICAL PRESENTATION

Environmental Risk Factors, Infection Control and CDAD

Environmental factors play a key role in the transmission of *C. difficile*, especially in healthcare facilities and long-term care institution. With increasing environmental contamination, the prevalence of *C. difficile* found on the hands of healthcare workers will also increase, which is believed to be a key mechanism of cross-contamination in the healthcare setting. Commonly used alcohol based hand-gels are ineffective against spore-forming organisms. The most effective and the simple measure for *C. difficile* decontamination of healthcare workers remains hand washing with soap and water. Environmental decontamination for *C. difficile* will require 10% sodium hypochlorite solutions.

Host Risk Factors and CDAD

Host immunity appears to play an important role in susceptibility and the development of CDAD. Previous studies have also identified immunosupression in oncology and transplant patients to be a significant risk factor for the development of CDAD.

Antibiotic use remains the most widely recognized risk factor associated with development of CDAD. Broad spectrum penicillins and cephalosporins, clindamycin, and fluoroquinolones possess a higher risk for CDI. Gastric acid

suppression has also been implicated as a risk factor for the acquisition of *C. difficile* although this associated between proton pump inhibitor (PPI) use and risk of CDAD remains controversial. Antibiotics that are associated with lower risk of CDI, such as macrolides, aminoglycosides, sulfonamides, vancomycin or tetracyclines.

Clinical Symptoms and Complications

The clinical expression of *C. difficile* ranges from asymptomatic carriage to its most serious and characteristic form, pseudomembranous colitis (PMC). The typical clinical symptoms of CDAD include diarrhoea, lower abdominal pain and tenderness, fever, anorexia, nausea, malaise and leukocytosis. Stools are usually watery, voluminous and lacking gross blood or mucous. In addition to pseudomembranous colitis, *C. difficile* can cause a variety of complications including toxic megacolon, colonic perforation, sepsis and death.

DIAGNOSIS

According *European Society of Clinical Microbiology and Infectious Diseases* (ESCMID) guidance, there is no single test is suitable as a stand-alone test confirming CDI.

*C. difficile* toxins assay using an enzyme immunoassay (EIA) has sensitivity of 75–85% and specificity of 95–100%. Nucleic acid amplification test (NAAT Test) has higher sensitivity (80–100%) and specificity (87–99%) compared to an EIA test. Tests detecting *C. difficile* antigens are based on the detection of glutamate dehydrogenase (GDH) has specificity of almost 100%; but they do not distinguish whether the strain is toxigenic. Two tests algorithm is the best way to detect CDI. First test should be GDH-EIA assay, if it is negative - exclude CDI. If GDH-EIA is positive, toxin assay should be done. If toxin assay is positive – confirm CDI. If toxin assay is negative, there are three situations – CDI with very low toxin levels, false-negative toxin A/B EIA result, or *C. difficile* carriage. A negative GDH result but positive for toxin need to be retested, as this is an invalid result.

Anaerobic stool culture is a very sensitive modality for the detection of *C. difficile*, but this will requires additional testing to discriminate toxigenic from nontoxigenic strains.

Laboratory findings associated with CDAD are nonspecific include leukocytosis, hypoalbuminemia and fecal leukocytosis. Therefore, a high index of suspicion and prompt stool testing (i.e., ELISA for the presence of toxins) remain essential for confirming the diagnosis of *C. difficile*.

The classic endoscopic finding in CDI is the presence of pseudomembranes on the colonic mucosa, which is estimated to occur in more than 50% of the patients. In severe cases, histology may show focal ulceration of the colonic mucosa associated with the eruption of purulent material containing

inflammatory cells and necrotic debris that covers the area of ulceration, the classic “summit” or “volcano” lesion.

Treatment of CDAD

*Presence of C. difficile* without symptoms of CDI is not the indication of treatment. According to ESCMID guidelines published in 2014, metronidazole and vancomycin is the cornerstone of the treatment of CDI. Metronidazole is used for non-severe disease, whereas vancomycin is used for severe CDI. One meta-analysis published in 2017 showed metronidazole is inferior to vancomycin in the treatment of CDI. If there is high suspicion of CDI with a negative toxin assay, it is reasonable to start empiric antibiotic therapy for CDI. Other antibiotics that show activity against *C. difficile* include teicoplanin, tigecycline, bacitracin and nitazoxanide. Two out of three criteria define severe-CDI (hypoalbuminemia, leukocytosis and high fever). Fulminant CDI is defined as severe CDI with organ dysfunction or toxic megacolon.

Metronidazole

Metronidazole was considered the first-line therapy for mild CDI. It is typically orally dosed as 500 mg 3 times a day or 250 mg 4 times a day with duration of therapy of 10 days. The advantages of metronidazole include the low cost and the potential advantage of not contributing to the emergence of strains of vancomycin-resistant *Enterococcur faecium*. Adverse effects include nausea and vomiting, a metallic taste, peripheral neuropathy, and a disulfiram-like reaction when used in conjunction with alcohol.

Vancomycin and Fidaxomicin

Oral vancomycin (125 mg orally four times a day for 10 days) was the first drug to be widely used to treat CDI. Its efficacy against *C. difficile* has been confirmed by numerous controlled trials. Vancomycin may be administered by month (which will result in very high concentrations in the feces), nasogastric tube or enema. It should not be given intravenously for the purpose of treating *C. difficile* because effective colonic luminal concentration of the agent cannot be obtained by this route. If ileus is present, vancomycin should use per rectally (vancomycin 500 mg in 100 ml saline as enema) four times a day (10–14 days).

Fidaxomicin (200 mg orally twice a day for 10 days) is a macrocyclic, bactericidal antibiotic of narrow spectrum, directed primarily against gram-positive pathogens. It has high efficacy against *C. difficile*, with no significant influence on the physiological flora of the colon. Fidaxomicin is effectiveness in reducing CDI recurrence than vancomycin. Vancomycin and fidaxomicin are the cornerstone of CDI treatment according to Infectious Diseases Society of America

(IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines published in 2017.

Anion-Binding Resins and Antimotility Agents

Anion-binding resin such as colestipol and cholestyramine may bind to the *C. difficile* toxins and can be used in combinations with vancomycin for patients with recurrent CDAD. However, these agents can also bind the concomitantly administered oral antibiotics used for treatment of *C. difficile* and need to be given at least 2–3 hrs apart from antibiotic. Concurrent use of antiperistaltic agents and narcotic analgesics (loperamide, diphenoxylate) for symptom relief in patients with severe CDAD should be discouraged because of the theoretical risk of precipitating toxic megacolon by slowing the clearance of the toxin from the gut.

Probiotics

The role of probiotics in the treatment of active CDAD is still unclear. A recent meta-analysis combined 6 randomized controlled trials comprising 354 patients that examined the role of probiotics in treatment of CDAD. Only 2 studies (33%) identified significant reduction of CDAD recurrences among the probiotic treated group, and among the different agents, only *S. boulardii* shows a significant effect.

Rifaximin and Nitazoxanide

Rifaximin is a nonabsorbed rifamycin derivative approved for use in traveler’s diarrhoea that as good in-vitro activity against *C. difficile*. Nitazoxanide is an antibiotic that is approved for the treatment of parasitic diarrhoeal diseases but also has demonstrated in-vitro activity against *C. difficile.*

Monoclonal antibody

Bezlotoxumab (a monoclonal antibody that binds to *C. difficile* toxin B) and actoxumab (a monoclonal antibody that binds to *C. difficile* toxin A) used in prevention of recurrent CDI in patients with high risk of CDI recurrence. Larger data are required for these molecules.

Fecal microbiota transplantation

Abnormal gut microflora is a key factor for the development of *C. difficile* infection. Despite thousands of species in gut microflora, Bacteroides and Firmicutes play predominant role in immunological responses against C. difficile. Fecal microbiota transplantation (FMT) has changed the management of CDI. FMT restores the microflora and improves CDI.

FMT procedure has not yet been standardized. Fecal transplant can be administrated via oral capsules, lower gastrointestinal (GI) tract procedure (colonoscopy, retention

enema), or upper GI tract procedure (nasojejunal tube). Two main concerns of FMT are the risk of transferring infectious

pathogens from the donor to the recipient, and development of autoimmunological disorders. Potential donors should be healthy, have normal bowel movement, and screened for bacterial, viral and parasites infection in the stool.

Prophylaxis of CDAD

Minimizing exposure to antibiotics is the key measure to prevent CDAD. Using metronidazole or vancomycin to prevent CDAD in patients who are receiving other antimicrobials appears unwarranted at this time. In recent meta-analysis, probiotics (Saccharomyces *boulardii, lactobacillus rhamnosus GG*, and probiotic mixtures) is effective for the prevention of CDAD.

The most important initial step in managing CDAD is discontinuation of the offending antibiotics whenever possible. Between 15–23% of patients with CDAD had spontaneous resolution of symptoms once the offending antibiotic was discontinued.

RECURRENT CDAD

The rate of relapse/recurrence after the first episode of *C. difficile* infection will vary between 12 and 20%. In patients who have had a first recurrence, relapse rates will be even higher (33–60%). In the non-IBD patient population the risk factors for recurrent disease included age greater than 65 yrs, increased severity of underlying disease, and exposure to additional antibiotics after treatment. Persistent *C. difficile* spores present in the colon may lead to recurrent episodes of infection and CDAD.

Surgical Therapy for CDAD

Patients with refractory fulminant colitis, toxic megacolon, and frank sepsis will require urgent surgical management with abdominal colectomy and end-ileostomy. The indication and timing of colectomy for a patient with severe CDAD remains unclear.

Studies have shown that patients have better survival if they undergo colectomy before they patients have: (a) sepsis, (b) need of vasopressors and 3) patient age >70 yrs.

Further Reading

1. Debast SB, Bauer MP, Kuijper EJ, et al. ESCMID European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014;20:1–26.

2. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America

(IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018;66:e1–e48.

3. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014;59:345–54.

4. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile associated diarrhea in adults. *Cochrane Database Syst Rev* 3;2017:CD004610.

5. Goldberg EJ, Bhalodia S, Jacob S, et al. *Clostridium difficile* infection: A brief update on emerging therapies. *Am J Health-Syst Pharm* 2015;72:1007–12.

**Chapter 56.**

**Cystic Neoplasms of the Pancreas**

Introduction

Pancreatic cystic neoplasms (PCN) are estimated to be present in 2–45% of the general population. Majority of them are accidently detected on imaging. PCN includes spectrum of benign to malignant lesions. The benign lesions include: serous cystadenoma (SCN), pseudocysts and squamous epithelium lined lesions (lymphoepithelial cysts, epidermoid cysts). Pancreatic cystic lesions with malignant potential include: mucinous cystic neoplasm (intraductal papillary mucinous neoplasms and mucinous cystic neoplasm), solid pseudopapillary tumours and cystic neuroendocrine tumours. Accurate diagnosis of PCN is a big challenge. Surgery is the only curative option PCNs with malignant potential.

Epidemiology

The rising clinical recognition of cystic neoplasms of the pancreas today is a direct consequence of improvements in imaging technology. Cystic neoplasms were once thought rare conditions of the pancreas, with pseudocysts representing the vast majority of pancreatic cysts. The widespread use of imaging like CT and MRI has fundamentally changes this perspective. These lesions are quite common and they represent as opportunity for the early detection and treatment or prevention of pancreatic cancer.

Diagnosis and Biomarker

Dedicated pancreatic protocol CT and pancreatic MRI/MRCP are reported to have a similar accuracy for the characterisation of PCN. But, MRI /MRCP is the preferred method for the investigation of patients with PCN. MRI/MRCP is more sensitive than CT in identifying ductal communication, single or multiple lesions, internal septations and the presence of a mural nodule. Role of CT scan is important to detect parenchymal and ductal calcification in patient with chronic pancreatitis with cystic lesion to differentiate from pseudocyst.

The diagnosis of a PCN has been greatly facilitated by the development of EUS. EUS is recommended as an adjunct to other imaging modalities. EUS imaging alone, however, does not provide adequate diagnostic accuracy (51%) for differentiating mucinous from non-mucinous cystic lesions. Contrast harmonic-enhanced EUS (CH-EUS) is important for the evaluation of mural nodules, septations and internal vascularity in the PCN. CH-EUS seems superior to standard EUS and CT for the identification of mural nodules with minimal inter-observe variations.

EUS-FNA improves diagnostic accuracy in PCN for differentiating mucinous versus non-mucinous PCN. Cyst fluid CEA, cyst fluid lipase and cytology provide the highest accuracy for differentiating mucinous from non-mucinous PCN. The role of EUS-FNA in the diagnosis of PCN is still a matter of debate. EUS-FNA should be performed only when it changes the management of PCN. Use of dual anti-platelet agent and distance of >10 mm from cyst wall and transducer are the relative contraindications of EUS-FNA. Solid component of PCN or thickened cyst wall are the target for EUS-FNA. Evaluation of cyst fluid CEA, combined with cytology, or KRAS/GNAS mutation analyses, may be more useful for differentiating from mucinous to non-mucinous PCN. A cyst fluid CEA level of  192 ng/mL can distinguish mucinous, from non-mucinous cysts, with a sensitivity of 52–78% and specificity of 63–91%. EUS-FNA is highly specific but has very poor sensitivity. ERCP has no role to play in the diagnosis of PCN. Pancreatoscopy has little role in the diagnosing various types of intraductal papillary mucinous neoplasm.

Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMN) are mucin-secreting lesions with malignant potential that originate from the pancreatic ductal epithelium. IPMNs commonly present in patients in the sixth and seventh decade with a similar distribution among females and males. These lesions are classified by their growth within the main duct (MD-IPMN), the branch duct (BD-IPMN) or both (mixed type, MT-IPMN). Lesions that originate from the main duct are associated with a higher prevalence and risk of cancer. Lesions that originate from the branch ducts have much lower risks of cancer. Mixed-type lesions with gross dilatation of main pancreatic duct are more closely associated in risk of cancer to main duct lesions.

By imaging, main-duct lesions present with dilated main pancreatic duct (>6 mm in diameter) often filled with globules of mucin and intrapapillary growths of ductal tissue. Side-branch IPMNs represent dilation of a side branch. Solitary side-branch lesions located in the body/tail of the pancreas in women can be difficult to differentiate between branch-duct IPMNs and MCNs.

Histologically, both main-duct and side-branch IPMNs reveal columnar epithelial cells with varying atypia without any ovarian-type stroma. The intrapapillary growths can be classified into 4 histological subtypes the correlate with malignant potential. The gastric subtype infrequently leads to cancer. The intestinal and pancreaticobiliary subtypes are associated with a high risk of cancer development. The oncocytic type is a rare subtype but when found is often described harbouring features consistent with high-grade dysplasia. Once progression from these premalignant subtypes progress to cancer, IPMNs can present as 2 histopathological variants – tubular type and colloid type. Tubular type behaves similarly to ductal adenocarcinoma, while the colloid type is less aggressive with a better prognosis.

Jaundice, the presence of an enhancing mural nodule (5 mm) or a solid component, positive cytology, or a MPD measuring 10 mm are highly predictive of malignancy, requires urgent surgical resection. Chance of high-grade dysplasia is around 30–90% once MPD diameter is 5–9.9 mm. Patients with an IPMN measuring  30 mm have a 5% risk of developing malignancy. Even for BD-IPMN <30 mm, the 5-year risk for developing malignancy is reported to be 45% if a cyst increases in size by >2 mm/year. Low-risk IPMN should be follow up once in 6 months and then yearly with MRI/MRCP. Following surgical resection, IPMN needs life-long follow-up. Factors need to evaluate during surveillance is diffuse MPD dilatation, serum CA 19–9, serum alkaline phosphatase, and absence of extrapancreatic cysts. MD-IPMN diameter  10 mm is an absolute indication of surgery, while diameter between 5–9.9 mm is relative indication of surgery. In view of high potential of malignancy, patients with MD-IPMN who are fit for surgery should undergo resection **(Fig. 56.1)**.

Resected IPMN with low-grade dysplasia have a low risk of recurrence (5.4–10%) with disease-free survival (DFS) of approximately 52 months, whereas IPMN with high-grade dysplasia or an IPMN-associated invasive carcinoma have a higher risk of recurrent (>50%), with DFS 29 months.

Mucinous Cystic Neoplasm

Mucinous cystic neoplasms (MCN, 10% of pancreatic cystic neoplasm) are mucin- secreting lesions with malignant potential. They occur almost exclusively in young women (fourth decade of life), and almost invariably found in the body or tail region of the pancreas, and has no pancreatic ductal communication. By imaging, these lesions are well capsulated, sometimes seen with a few septae. Peripheral calcifications can be observed along the wall of the cyst.

MCNs can be found incidentally or on investigation for abdominal symptoms. The histological hallmark of MCNs involves the presence of columnar epithelial cells with

variable degrees of atypia and overlying ovarian type stroma. MCN size greater than 3 cm and presence of intracystic papillary nodules are associated with invasion and should undergone surgical resection. Overall 5-year survival for MCN is 75–93%.

Serous Cystic Neoplasm

Serous cystic neoplasms (SCNs) are non-mucin secreting lesions with little to no malignant potential. They commonly present in elderly patients in their seventh decade of life and affect females more than males. Body and tail of the pancreas is the most common site. They can be found incidentally when imaging the abdomen for other reasons and also when investigating a cause of abdominal pain. On imaging a well -defined lesions is appreciated with multiple small fluid- filled cavities called microcysts in a honeycomb –like pattern. In approximately 20% of cases, a central scar, which represents either calcifications or fibrosis, can be observed in a sunburst- like pattern. Histologically, the thin septae encasing the microcysts are cuboidal epithelial cells that stain positively for glycogen. Surgery in SCN is recommended only when it compress the adjacent organ.

Solid Pseudopapillary Tumours

Solid pseudopapillary tumour (SPT, 5% of pancreatic cystic neoplasm) has very low malignant potential with excellent survival rate following resection. It affects to young women and pancreatic head and tail is the most common site. CT scans shows encapsulated lesions with peripheral solid and central cystic components. Cellular origin of SPT is not clear, some authorities suggests it arises from totipotent cells, while others are not agree. SPTs do not have mucus producing cells or extra-cellular mucus.

Cystic Neuroendocrine Tumours

Cystic neuroendocrine tumours (cystic-NET, <10% of pancreatic cystic neoplasm) is a non-functional tumour with negative prediction for malignancy. Solid lesion has more malignant behaviour than cystic lesion. Excellent 5-year survival is observed in both solid and cystic-NET. Imaging is unable to differentiate with other benign cystic lesions like pseudocyst and SCNs. EUS-FNA with immunohistochemistry (positive for synaptophysin and chromogranin) has been suggested in the diagnosis of cystic-NET.

Management

An early diagnosis of malignancy is important because there is a significant difference in survival for surgical resection of non-invasive malignant cysts (5-year survival, 90–100%) compared with invasive malignant cysts (5-year survival, 36–60%). When pancreatic cystic lesion identified, the clinician must determine first whether it is a mucinous cyst with malignant potential. The next critical question is that if it is mucinous cyst, whether cancer is present. If cancer is not present, then the next decision is whether to recommend surgery based on a pretest probability that the cyst harbors advanced dysplasia of a high risk of malignant transformations such that surveillance is considered too risky. If surveillance is recommended, how to perform surveillance?

**Sendai Criteria**: Guidelines apply pre-operative clinical symptoms, cross-sectional imaging and cytology data **(Fig. 56.2)**.

Further Reading

1. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of pancreas. *Pancreatology* 2006;6:17–32.

2. Verbesey JE, Munson JL. Pancreatic cystic neoplasms. *Surg clin North Am* 2010;90:411–25.

3. European evidence-based guidelines on pancreatic cystic neoplasms. The European Study Group on Cystic Tumours of the Pancreas. *Gut* 2018;67:789–804.

4. Antoinette Pusateri, Somashekar Krishna. Pancreatic cystic lesions: pathogenesis and malignant potential. *Diseases* 2018;6:50–62.

5. Del Chiaro M, Segersvärd R, Lohr M, et al. Early detection and prevention of pancreatic cancer: is it really possible today? *World J Gastroenterol* 2014;20:12118–31.

6. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015;148:819–22.

SECTION 6

MISCELLANEOUS

Chapter 57.

**Radiology**

**Introduction**

Present chapter includes discussion of plain X-ray abdomen and barium examination. Discussion of ultrasonography, CT scan and MRI is out of scope of the present chapter. Percutaneous biliary decompression has been discussed in Chapter 44. Recent advances in radiology like MRCP (magnetic resonance cholangiopancreatography), PET (positron emission tomography) and virtual colonoscopy are described in Chapter 45.

**X-Ray abdomen**

**Introduction**

Despite its limitations, plain radiograph of abdomen is the initial imaging study in patients with suspected bowel obstruction or perforation. X-ray abdomen is usually taken as supine or erect film using anterioposterior view (AP, X-ray film behind the patient and the X-ray beam passes from front to back).

Relative positions of bowel lumen, solid organs, fluids and gas make for differentiation of supine versus erect film.

Standard X-ray cassette size for adult is 35 x 43 cm (14"x 17"). Before interpretation of plain X-ray abdomen, it is very important to note the age, sex of the patient (if it is written) as well as left and right side of the film. Fluid levels usually do not appear on supine film. To demonstrate fluid levels, either erect film or a decubitus film is required.

The small bowel is central and contains fluid and gas, while colon is peripheral, containing feces and gas.

X-ray abdomen should involve the dome of diaphragm and pelvic brim, whereas X-ray KUB (kidney, ureter and bladder) should involve pelvis up to pubic symphysis and gonads.

*There are five types of basic densities present on X-ray*:

1. Intense white: Metal (with streaky artifacts)

2. Bright white: Bone/calcification

3. Light white: Fluid

4. Dark grey: Fat

5. Black: Gas

**Pneumoperitoneum**

Pneumoperitoneum is the most important sign in radiology. It means extraluminal free gas in abdomen.

A plain X-ray can make diagnosis of hollow viscous perforation by demonstrating pneumoperitoneum. It is very important to have a clinical history before interpreting pneumoperitoneum because, pneumoperitoneum can occur following laparotomy, laparoscopy and peritoneal dialysis without viscous perforation.

Gas acts as a natural contrast medium and appears dark on X-ray film. Normally, gas is confined to the lumen of gut. In a radiograph of abdomen gas is generally seen in fundus or body of the stomach, splenic flexure, descending colon and in cecum. There is rarely sufficient gas present in the small bowel to outline more than a few segments. Amount of gas present in the colon is extremely variable.

Pneumoperitoneum (extraluminal gas in the peritoneal cavity) is diagnosed by dark crescents of gas under both hemidiaphragms. As little as 1 mL of air is enough to demonstrate gas under hemidiaphragm, if X-ray is taken properly.

X-ray abdomen erect film or chest X-ray PA view demonstrates pneumoperitoneum. X-ray chest PA view erect is best for demonstrating free gas under diaphragms (diaphragms better seen on chest X-ray PA view rather than on X-ray abdomen erect view). In case of sealed off perforation, gas may not be visible on plain X-ray.

In critically ill patients where erect film may not be possible, lateral shoot through or horizontal beam radiograph with grid cassette films should be taken.

An absence of gas under hemidiaphragm on erect film does not exclude bowel perforation. A perforating ulcer situated posteriorly demonstrates only air in the retroperito-neum. Patient should ideally be in erect position for 10 min before X-ray is taken. Plain CT is the best modality to conclusively detect both extraluminal free gas or gas in loculated gas.

***Radiological Signs of Pneumoperitoneum***

Gas (darkness) under both hemidiaphragms.

1. ***Double-wall sign***: Isolation of bowel loops due to air outside and inside the loops (both the outer and inner wall of the bowel is outlined by gas).

2. ***Dome sign***: Large pneumoperitoneum underneath the diaphragm appears as a dome.

3. ***Silver’s sign***: Tracking of gas makes visualization of falciform ligament.

***Causes of Pneumoperitoneum***

*Associated Peritonitis*

1. Perforated gastric or duodenal ulcer

2. Ruptured diverticular disease

3. Penetrating injury

4. Colon ruptured secondary to inflammatory bowel disease

5. Bowel gangrene

*Without Peritonitis*

1. Post laparotomy or laparoscopy

2. Peritoneal dialysis

3. Jejunal diverticulosis

*Causes of Small Bowel Perforation*

1. Strangulating obstruction

2. Non-steroidal anti-inflammatory agents

3. Trauma

4. Chemotherapeutic agents

5. Jejuno-ileal diverticulitits

6. Carcinoma

7. Lymphoma

8. Mesenteric ischaemia

*Causes of Large Bowel Perforation*

1. Carcinoma

2. Diverticulitits

3. Ulcerative colitis

4. Amebic colitis

5. Post procedure like colonoscopy, polypectomy

***Chilaiditi’s Syndrome***

Pockets of air beneath the right hemidiaphragm secondary to colonic interposition. Chilaiditi’s syndrome occurs following surgery, or in patients with COPD and liver cirrhosis.

***Retroperitoneal Air***

1. It is diagnosed by outlining adrenal and spleen. Black density near psoas muscle margins, the spleen and kidneys.

2. Air does not change position on decubitus films.

3. It looks more linear, streak like, scattered (non confluent).

***Gas in the Wall of Intestine-better Appreciated on CT Scan of Abdomen***

1. Pneumatosis coli

2. Necrotizing enterocolitis

3. Bowel infarction

4. Bowel gangrene

5. Emphysematous enterocolitis

**Gastric Outlet Obstruction**

1. Abnormally large stomach outline

2. Excess undigested food in the stomach

3. Paucity of air in the small intestine

4. “Double-bubble sign” – classical sign of duodenal atresia where gastric fundus and first part of duodenum are distended with air.

5. Gastric atony leads to gastric dilatation without obstruc-tion. Radiologically it is difficult to distinguish from mechanical obstruction.

**Multiple Air-fluid Level**

Small or large bowel obstruction leads to multiple air-fluid levels, best demonstrated in erect film. Most important to differentiate small bowel from large bowel obstruction. It may be very difficult to differentiate mechanical obstruction from adynamic ileus.

The normal small bowel gas pattern refers to either absence of small bowel gas or small amounts of gas within up to four variably shaped non-distended (<2.5 cm in diameter) loops of small bowel. Air-filled level less than 3 is considered normal in erect or decubitus film. The normal colonic diameter should be less than 5 cm. Visualization of more bowel loops in case of distal obstruction. Air-fluid levels are directly proportionate to duration of obstruction.

**Radiological Feature of Small Bowel Obstruction**

Multiple centrally placed loops of distended bowel with multiple air-fluid level. Small number of loops indicates proximal small bowel obstruction. Presence of colonic gas indicates incomplete small bowel obstruction, while gasless colon suggests definite complete small bowel obstruction. Causes of intestinal obstruction are given in the **Table 57.1**.

**Radiological Features of Large Bowel Obstruction**

1. Dilated (>6 cm) peripherally placed bowel loops

2. Gasless colon distal to the obstruction

3. Lack of distension of small bowel indicates competent ileocecal valve. Marked distension of the cecum.

**Barium examination**

**Introduction**

Barium examination of gastrointestinal tract helps to detect various pathological conditions of gastrointestinal tract. Detailed discussion of barium studies and various disorders is out of scope of this book. Various barium examinations and their interpretation in different pathological conditions

are mentioned briefly in present chapter. However, readers are advised to read standard radiological textbook for detailed study. In the era of CT scan, MRI and endoscopy, role of barium examination is very much limited.

**Different Barium Examinations Used in Gastroenterology**

1. Barium swallow

2. Barium meal

3. Barium meal follow through

4. Small bowel enema (enteroclysis)

5. Barium enema

**Contrast Media**

There are two types of contrast media used for evaluation of gastrointestinal tract:

1. Water soluble (gastrograffin)

n Sodium diatrizoate

n Meglumine diatrizoate

2. Barium sulfate

Water-soluble contrast medium is used during suspected intestinal perforation or meconium ileus. The most common complications of water-soluble contrast are allergic reactions and pulmonary edema if aspirated.

Barium suspension is made up of small barium sulfate particles (0.1–3µ). Excellent coating to the mucosa and low cost are the main advantages of barium over water-soluble contrast agent. Aspiration of barium is relatively harmless, unlike aspiration of water-soluble contrast agent. Barium study is contraindicated in suspected perforation in view of high morbidity associated with barium study.

**Barium swallow**

**Indications**

1. Evaluation of dysphagia

2. Evaluation of esophageal motility disorders

**Cautions during Barium Swallow Examination**

1. Suspected oesophageal perforation – water soluble contrast can be used.

2. Tracheoesophageal fistula – better to use barium exami-nation rather than water-soluble contrast due to high chance of pulmonary oedema.

**Methods**

Single-contrast barium (low viscosity and low density) study is used to demonstrate oesophageal contours. While, double-contrast barium (high viscosity and high density) study demonstrates the oesophageal mucosa.

Patients should be examined in both the erect and supine positions. One mouthful of barium is swallowed, and spot films of upper and lower oesophagus including gastro-esophageal junction are taken.

Videofluoroscopy or cineradiography help to study swallowing dynamics. Five swallows should be performed (20 sec) in suspected esophageal motility disorders.

**Features of Various Pathology on Barium Swallow**

1. ***Achalasia cardia***

n Oesophageal dilation, mainly distal oesophagus.

n Smooth tapered barium column at tight non-relaxing sphincter with dilated distal oesophagus gives “bird’s-beak” appearance.

n Upright film shows oesophageal air-fluid level.

n Lower and mid-oesophageal pulsion diverticula.

n Tortuous dilated oesophagus >7 cm is called advanced megaesophagus.

n Fundal gas may be absent.

n May contain food particles.

2. ***Benign oesophageal stricture***

n *Corrosive stricture* – Strictures can appear as soon as 2 weeks after the ingestion of a caustic substance. Strictures tend to be long involving large portion of the thoracic oesophagus, occasionally extending the entire distance between the aortic knob and the diaphragm. Lye stricture is longer than acid stricture.

n *Peptic stricture* – Stricture secondary to reflux oesophagitis tends to be, typically smooth, tapered, and concentric narrowing located in the distal oesophagus with no demonstrable mucosal pattern.

n  *Radiation stricture* – Benign strictures situated mostly in the mid oesophagus, with tapered margins and relatively smooth mucosal surfaces.

n *Postsclerotherapy stricture* – Fixed, noncollapsible, rather rigid-appearing filling defects in the barium column lead to complete fixation and lack of disten-sibility of the oesophagus. The stenotic zone may be asymmetric and even have overhanging edges mimicking carcinoma. If overlying mucosa becomes denuded, ulceration may develop.

3. ***Esophageal malignancy***

n Irregular filling defect with rat-tail appearance

n Detect level of obstruction

n Demonstration of tracheoesophageal fistula.

4. ***Diffuse oesophageal spasm***: Segmental, non-propulsive tertiary contractions of an abnormal high amplitude, which leads to irregularly narrowed lumen of the oesophagus (corkscrew oesophagus).

5. ***Hiatus hernia***

n Herniation of the stomach through the diaphragmatic hiatus into the thorax is called hiatus hernia.

n Best demonstrated by single contrast technique.

n A sliding hiatus hernia is present when both the gastroesophageal junction and the stomach herniate into the thorax.

n A para-esophageal (rolling) hernia is present when the stomach herniates into the thorax and GE junction remains in its position below the diaphragmatic hiatus.

n Active maneuvers to increase abdominal pressure may be necessary to demonstrate hernia.

6. ***Oesophageal candidiasis***: Double-contrast esopha-gogram shows linear, elevated 2–3 mm plaque-like lesions, giving granular appearance of the oesophagus.

7. ***Schatzki ring (B ring)***: Thin, smooth symmetrical mucosal narrowing near gastroesophageal junction above sliding hiatus hernia.

8. ***Oesophageal varices***: Supine film shows thickened longitudinal oesophageal folds with fusiform separation (worm eaten appearance). After a swallow, direction of filling of the varices denotes direction of shunt.

9. ***Oesophageal web-Plummer Vinson syndrome***: Shelf like filling defect seen in posterior pharyngeal wall.

**Barium meal examination**

**Introduction**

Role of barium meal is narrowed in the era of endoscopy and other imaging modalities. But in certain situations it has definite role in diagnosis. These situations are:

1. Linitis plastica (reduced distensibility)

2. Demonstration of fistula and reflux

3. Used when endoscopy is difficult

4. Suspected malposition or volvulus

**Indications**

***Single-contrast Study***

n It requires less patient preparations and operator expertise.

n It is used to demonstrate stomach contour.

***Double-contrast Study***

n It requires good patient preparations and operator expertise.

n Used to demonstrate mucosal abnormality.

***Contraindications***

n Large bowel obstruction

n Impending gastric/abdominal surgery

***Methods***

n Nil by mouth for 6 hrs before the examination.

n The patient is asked to take the gas-producing agent.

n The patient is then positioned lying supported on the left side and drinks the barium mixture.

n A smooth muscle relaxant is administered.

n To demonstrate reflux the patient is positioned in supine left side with tilted Trendelenburg position.

n Series of fluoroscopically guided films is taken in a variety of positions to demonstrate the stomach, duodenal cap and first part of duodenum.

***Complications***

1. Aspiration of barium mixture

2. Leakage of barium into the peritoneum with an unsuspected perforation

3. Barium impaction and large bowel obstruction

**Barium Meal Features of Benign Gastric Ulcer**

n Clear projection of ulcer crater outside of the normal barium-filled gastric lumen due to the ulcer representing an excavation in the stomach wall.

n Hampton line: A thin, sharply demarcated, lucent line situated at the base of the ulcer crater.

n Ulcer collar: Large lucent ulcer collar separating the ulcer from the gastric lumen.

n Symmetrical radiation of mucosal folds to the edge of the crater.

n Size, shape, number and location of the ulcer have no practical value to differentiate from the malignant ulcer.

**Malignant Gastric Ulcer**

n Carmen’s meniscus sign: Large ulcer crater with a semicircular configuration and an inner margin convex toward the lumen.

n Abrupt transition between normal mucosa and abnormal mucosa.

n Asymmetrical mucosal folds. Differential diagnosis for ulcer on barium examination is stated in **Table 57.2**.

**Benign ulcer Malignant ulcer**

Peptic ulcer Carcinoma

Granulomatous ulcer Lymphoma

Radiation induced Leiomyosarcoma

Leiomyomas Carcinoids

MALT lymphoma Metastasis (melanoma)

**Benign Polyp**

1. Filling defect less than 1 cm in diameter

2. Normal gastric peristaltic activity

3. Normal gastric folds near the polyp

4. Visibility of stalk

**Polypoid Carcinoma**

1. Large, sessile, irregular filling defect

2. Mucosal irregularity and ulceration

**Differential Diagnosis of Thickened Gastric Folds**

1. Granulomatous gastritis

2. Lymphoma

3. Carcinoma

4. Menetrier’s disease

5. Gastric hypersecretory states like Zollinger-Ellison syndrome

6. Eosinophilic enteritis

**Causes of Simultaneous Involvement of Gastric Antrum and First Part of Duodenum**

1. Lymphoma

2. Adenocarcinoma of the antrum

3. Crohn’s disease

4. Peptic ulcer disease involving stomach and duodenum

5. Eosinophilic gastroenteritis

6. Tuberculosis

**Causes of Widening of Duodenal C-loop**

1. Acute pancreatitis

2. Pancreatic cancer

3. Cystic lesion of the pancreas

4. Lymph node enlargement

5. Retroperitoneal mass

**Barium follow-through examination**

**Introduction**

Barium follow-through examination is used to demonstrate the small intestine, from the duodenum to the ileocecal region.

**Indications**

1. Unexplained recurrent abdominal pain.

2. Evaluation of small bowel in patients with suspected Crohn’s disease.

3. Evaluation of chronic diarrhoea or malabsorption syndrome.

4. Evaluation of obscure gastrointestinal bleeding to identify small intestinal stromal tumour and adenocarcinoma.

5. Evaluation of patients with sub acute intestinal obstruction.

**Contraindications**

1. Intestinal obstruction

2. Imminent surgery and/or suspected perforation

**Methods**

n Patient requires nil by mouth for 12 hrs. Laxative preparation should start 12 hrs before examination and metoclopramide 20 mg orally 30 min before the examination. It is ideal to give low fibre diet for 24 hrs.

n The patient should rapidly drink about 300–500 mL of contrast media and then lie on his right side.

n The films are taken at 20-min intervals until the contrast media passes into the colon; ensure that the early films include the stomach; a pad under the abdomen may help to separate out the loops of bowel.

**Complications**

1.Aspiration of barium mixture

2. Leakage of barium into the peritoneum with an unsuspected perforation.

**Malabsorption Syndrome**

1. Diffuse small bowel dilatation.

2. Flaccid and poorly contractile small bowel loop.

3. Segmentation and flocculation of the barium due to dilution.

4. The barium in the dilated loops of small bowel has a coarse, granular appearance due to hypersecretion.

5. Moulage sign: Featureless duodenum and jejunum.

6. Reversal of the jejunoileal fold pattern.

**Ischaemic Bowel Disease**

Picket-fence pattern of regular thickening of small bowel folds is classical of ischaemic bowel disease.

**Crohn’s Disease**

1. Small bowel follow-through and barium enema both are needed to define the extent of the disease.

2. Isolated small bowel is seen in 30–40%, whereas isolated colonic disease is seen in 20–27% of patients with CD.

3. Earliest sign is the aphthous ulcer (punctuated, slit-like collection of barium surrounded by radiolucent halo).

4. As disease advances aphthous ulceration coalesce together to form stellate, serpiginous or linear areas of ulceration.

5. Deep transverse and longitudinal ulcer separated by edematous mucosa gives cobble-stone appearance

6. Polyps, stricture and fistula can be identified.

7. String sign: Markedly narrowed terminal ileum secondary to edema, inflammation and spasm.

8. Pseudosacculation: Shrinkage of mesenteric border due to fibrosis.

9. Separation of bowel loops

10.Fistula

**Tuberculosis**

1. Early sign – Hypersegmentation and flocculation.

2. Irregularly thickened folds, mucosal ulceration, which may be linear and situated along the circumference of the wall.

3. Inverted umbrella/Fleischner’s sign – Thickened ileo-caecal valve gives triangular appearance, base of which lies near cecum.

4. Sterling sign – Rapid transit and lack of barium retention in terminal ileum.

5. String sign – Narrow segment before ileocecal valve.

**Differential Diagnosis of Thickened Small Bowel Folds**

1. Giardiasis

2. Lymphoma

3. Amyloidosis

4. Whipple’s disease

5. Paraproteinemia

6. Intestinal lymphangietasia

7. Zollinger-Ellison syndrome

**Differential Diagnosis of Separation of Small Bowel Loops**

1. Crohn’s disease

2. Tuberculosis

3. Amyloidosis

4. Lymphoma

5. Radiation enteritis

6. Primary tumours of the small bowel

**Enteroclysis (Small bowel enema)**

**Introduction**

Enteroclysis is a more detailed technique for imaging the small bowel, in which the patient is intubated and medium-density barium and methylcellulose are injected into the proximal small bowel in a controlled manner for double-contrast views of the jejunum and ileum. Enteroclysis could be single-contrast or double-contrast study.

**Indications**

1. Partial or intermittent small bowel obstruction

2. Malabsorption states

3. Obscure GI tract bleeding

4. Evaluation of the extent and severity of known Crohn’s disease

**Contraindications**

1. Intestinal obstruction

2. Imminent surgery and/or suspected perforation

**Methods**

1. Patients should be on low-residue diet, ample fluids, laxative at least 24 hrs before the examination, and nothing to eat by mouth on the day of the examination. Vigorous bowel preparation is not recommended.

2. Administration of prokinetic agent like metoclopramide (10 mg intravenous) immediately prior to beginning the study facilitates nasointestinal intubation and allows for faster contrast infusion rates.

3. The upper administration route is topically anaesthetized 15 min before insertion of the nasogastric tube. The duodenum is intubated, either nasally or orally, using 13

Fr catheter with a balloon attachment at the tip (Maglinte Enteroclysis Catheter; Cook, Inc., Bloomington, IN).

4. The tube is passed into the stomach and maneuvered under fluoroscopic control into the duodenum using a guide wire inserted into the tube; it is passed sufficiently far to reduce the risk of the contrast agent refluxing back into the stomach.

5. The balloon is typically anchored in the descending duodenum.

6. The barium mixture is then introduced down the tube either using gravity feed or using electronic pump.

7. Small bowel enema is either single contrast or double contrast barium study.

8. Low-density barium is used for single-contrast study, while methylcellulose is used for double-contrast study.

9. The double-contrast enteroclysis should be the technique of choice when there is a need to see subtle surface details, such as for the diagnosis of early Crohn’s disease or for the evaluation of subtle ulcerations in an unexplained gastrointestinal bleeder.

10. In the patient suspected of partial mechanical small bowel obstruction, CT enteroclysis is better than barium enteroclysis.

**Advantages of Enteroclysis**

1. It gives comprehensive inspection of the entire mesenteric small bowel.

2. It demonstrates lumen distensibility, bowel wall thickness, circular fold morphology and mucosal surface of entire small bowel.

3. It is one of the best diagnostic modalities to identify subtle lesions like erosions, ulceration, small neoplasm, etc.

**Disadvantages**

1. Nasal or oral intubation of the duodenum is the most disadvantage of this procedure.

2. Longer radiation exposure.

3. Enteroclysis is incapable of identifying submucosal vascular abnormalities such as varices, angiodysplasia or arteriovenous malformations.

**Advances in Enteroclysis Technique**

1. CT enteroclysis is a combination of enteroclysis and CT scan. It is excellent for detection of small lesions in the bowel wall and improves the detection of low-grade partial small bowel obstruction. The disadvantages of CT enteroclysis are increased exposure of ionizing radiation,

poor soft tissue contrast and lack of functional information.

2. MR enteroclysis is better than barium enteroclysis by detecting extraluminal pathologic conditions and providing

detailed information about the wall of the small bowel and the entire abdomen. MR enteroclysis is better than CT enteroclysis due to its excellent soft tissue contrast and multiplanar imaging capabilities.

**Barium enema**

**Introduction**

Barium enema is the examination of entire colon including terminal ileum. Barium enema is of two types – single-contrast or double-contrast barium enema. With the increased use of colonoscopy and CT abdomen, the volume of barium enemas has gradually declined over the past couple of decades. Most patients undergo a double-contrast study in which a high-density barium suspension is introduced into the colon, followed by insufflations of air. This is the best radiological technique for demonstrating subtle lesions such as small polyps or cancers and early changes of inflammatory bowel disease. However, a single-contrast examination should be performed on patients with suspected obstruction, active colitis and in patients who are too old or debilitated to tolerate a double-contrast study.

**Contraindications**

1. Toxic megacolon

2. Pseudomembranous colitis

3. Rectal biopsy within 7 days

4. Imminent abdominal bowel surgery

**Methods**

1. Patient is put on low residue diet 12 hrs before the procedure. Colon should be prepared by using laxatives or enema.

2. A scout film is taken to assess preparation, exposure and anatomy.

3. The patient lies on his left side and the rectum is catheterized, the catheter taped in position and connected to the barium/air introduction equipment.

4. The patient lies prone; and the barium is infused slowly till the splenic flexure, under fluoroscopic control.

5. The patient may be turned to the left anterior oblique or Trendelenburg’s position to aid barium passage. Once the barium column reaches the mid transverse, the enema bag is lowered to remove barium from the rectum. The goal is not to clear the rectosigmoid colon of barium, but to remove barium from the rectum so that when air is insufflated, bubbles are not formed.

6. Air is insufflated into the colon with gentle, intermittent squeezes on the air-bulb. Rapid insufflations may be painful. During air insufflations, the patient is turned into

various positions, so the air and barium are distributed throughout the colon.

7. The patient position is adjusted under fluorscopic control as the complete colon is visualized as the barium travels round to the cecum and there is demonstration of terminal ileum.

**Complications**

1. Rectal perforation

2. Leakage of barium into the peritoneum with an unsuspected perforation

3. Barium impaction

**Ulcerative Colitis**

1. For mild-to-moderately active disease double-contrast enema is safe.

2. In patients with severe attack with dilated colonic segments, barium examination is contraindicated.

3. Following are the characteristic features of barium enema in ulcerative colitis:

n Fine granular mucosa

n Irregularly thickened mucosa

n Superficial and deep ulceration

n Edematous and thickened haustral folds

n Shortening of colon

n Presence of pseudopolyps

n Widening of pre-sacral space (>1 cm)

**Ischemic Colitis**

1. Superficial ulceration is the earliest sign due to inflammatory oedema.

2. Longitudinal, deep penetrating ulceration with pseudopolyp and “thumbprinting.”

**Colorectal Cancer**

1. Diffusely ulcerated mucosa with overhanging margin.

2. Large, polypoidal filling defect with abnormal mucosa.

3. Apple-core appearance: Bilateral contour defect with ulcerated mucosa, eccentric and irregular lumen, and overhanging margins.

**Diverticular Disease**

1. Round or oval outpouchings of barium projecting beyond the confines of the lumen.

2. They are usually multiple and tend to occur in clusters.

3. Air-contrast examinations demonstrate more diverticula than single-contrast studies.

4. It is important to detect the complications of diverticular disease, like perforation – detected as a tiny projection of contrast from the tip of the diverticulum or as obvious filling of a pericolic abscess.

**Colonic Polyp**

1. The double-contrast study is better to detect the polyps than single-contrast study especially for small polyps.

2. Artifacts like fecal matter, air bubbles and oil droplets, can be confused with polyps.

3. On *en face* views, the sessile polyp appears rounded.

4. Demonstration of a thin pedicle of 2 cm or more in length is pathognomonic of a benign polyp.

5. Retraction of indentation of the colon seen on profile view at the site of origin of a large sessile polyp is considered malignant polyp.

**Hirschsprung’s Disease**

Funnel-shaped zone of transition with a narrowed rectum and a markedly dilated, feces-filled colon proximally.

**Differential Diagnosis of Thumbprinting of Colon**

n Ischaemic colitis

n Ulcerative colitis

n Crohn’s colitis

n Pseudomembranous colitis

n Lymphoma

n Amebiasis

**Chapter 58.**

**Pathology**

oEsophagus

Normal Histology

The wall of the oesophagus consists of mucosa, submucosa, muscularis propria and a coat of periesophageal adventitia. The mucosa is composed of a non-keratinizing stratified squamous epithelial layer. A small number of specialized cell types such as melanocytes, endocrine cells and Langerhans cells are present in the basal layers of the epithelium. The submucosa consists of loose connective tissue containing blood vessels, a rich network of lymphatics, a sprinkling of chronic inflammatory cells and scattered mucus producing glands that open onto the mucosa. The muscularis propria consists of an inner circular and an outer longitudinal coat of smooth muscle with an intervening well-developed myenteric plexus **(Fig. 58.1)**.

Barrett’s Oesophagus

In Barrett’s oesophagus, the distal oesophagus becomes lined with columnar secretory epithelium of intestinal type rather than the usual stratified squamous epithelium **(Fig. 58.2)**. There may be associated acute and chronic inflammation with or without ulceration.

Squamous Cell Carcinoma Oesophagus

Like in other locations, squamous cell carcinoma of oesophagus begins as an area of in-situ cytological atypia that over an unknown interval of time, progresses to overt carcinoma. Three morphological patterns may evolve. The most common one is that of a polypoid fungating lesion that protrudes into the lumen. The second pattern is a necrotic ulcer that excavates deeply into surrounding structures. The third variant is a diffuse infiltrative form that tends to spread within the wall of the esophagus causing thickening, rigidity and narrowing of the lumen. Microscopically, there will be recognizable squamous cells with production of keratin and intercellular bridges (in the well-differentiated forms) and are seen as irregular buds penetrating stromal connective tissue. These cells show malignant features characterized by variation in size and shape, nuclear enlargement and hyperchromasia. Mitotic figures will be found **(Fig. 58.3)**.

Stomach

Normal Histology

The mucosa is covered by tall, columnar mucin secreting surface cells with basal nuclei and small mucigen-containing granules in the supranuclear region (stained with PAS or mucicarmine stains). Glands vary in the three major anatomic regions. Those of the cardia are mucin secreting. The ones in the body and fundus contain both acid secreting *parietal* cells and pepsinogen secreting *chief* cells. The former are recognized by their bright eosinophilia (due to presence of numerous mitochondria) while chief cells are rendered distinctive by their large, pale zymogen granules. Pyloric (antral) glands are made up of mucin secreting cells and numerous gastrin secreting G cells. In addition, heterogeneous populations of endocrine cells (Kulchitsky or entero-chromaffin cells) characterized by granular pink cytoplasm are widely distributed in the mucosa throughout the GIT **(Fig. 58.4)**.

Adenocarcinoma Stomach

Early gastric carcinoma appears as flat areas of mucosal thickening and induration or may be protuberant, ulcerated or excavated. Advanced cancers are classified as expanding or infiltrative carcinoma. Expanding carcinoma is characterized by an apparently cohesive mass of tumour cells that grow along broad fronts creating a pushing invasive margin. In the infiltrative pattern, on the other hand, the tumour cells penetrate individually and in small clusters resulting in diffuse involvement of the stomach.

Histologically, all gastric carcinoma is composed of two cell types: metaplastic intestinal cells with large apical vacuoles of mucus and gastric mucous cells. Either cell type may form well-developed neoplastic glands, occasionally with papillary ingrowths. In less well-differentiated neoplasms, the cells tend to be disposed in disorderly masses, islands,

small clusters or sometimes singly **(Fig. 58.5)**. Mucus may lie within neoplastic glands or in other instances it distends

the cells and compresses the nucleus against the plasma membrane to create *signet ring cells*. Sometimes, large lakes of mucin in which isolated tumour cells or glands appear to float dissect through cleavage planes. In diffuse infiltrative cancers, the tumour cells are often accompanied by an abundant fibrous stroma *(desmoplasia*), which accounts for much of the thickening of the gastric wall (linitis plastica or leather bottle stomach).

Small intestine

Normal Histology

Histological identification of small bowel rests on the recognition of villi between which are pit like crypts that extend into deeper levels of the mucosa. Height of the villi is three times greater than depth of the crypts in the small bowel **(Fig. 58.6)**. Distinctive of the duodenum are the elaborately branched *Brunner’s glands*, which penetrate the muscularis mucosae into the submucosa. The lamina propria contains phagocytic cells, lymphocytes (in great abundance in the ileal Payer’s patches) as well as plasma cells. The surface covering of the villi is made up of three types of cells, principally absorptive cells interspersed with *goblet cells* and a few endocrine cells. The absorptive cells are highly specialized on their luminal surface by microvilli (appreciable only under electron microscope) forming a brush border and expanding their luminal surface by perhaps thirty fold. Goblet cells are packed with mucigen granules creating large apical vacuoles. Four types of crypt epithelial cells have been identified – Paneth cells, undifferentiated cells, goblet cells and endocrine cells. Paneth cells contain large secretory

granules. They appear to play a role in mucosal immune system.

Malabsorption Syndrome–Celiac Disease

In a typical untreated case of celiac disease, histological examination reveals marked atrophy of villi. The surface epithelium shows degeneration and flattening of the normally tall columnar cells and an increased number of lymphocytes in the epithelial layer. The crypts, on the other hand, are hyperplastic. The lamina propria has an overall increase in plasma cells, lymphocytes, macrophages, eosinophils and mast cells **(Fig. 58.7)**.

Colon

In contrast to small intestine, the colon has no villi but has numerous straight tubular crypts that extend from the surface into the underlying lamina propria. The crypts are lined mainly by goblet mucous cells with occasional endocrine cells. The mucosal surface is covered mainly by absorptive cells that bear microvilli that are less abundant than those found in the small intestine. Paneth cells found mostly in the lower crypts are dispersed throughout the right colon. Scattered within the mucosa are lymphoid aggregates covered by somewhat flattened cells that are thought to engulf and transfer antigens to the underlying immunocytes **(Fig. 58.8)**.

Ulcerative Colitis

In the acute stage, there is development of small mucosal hemorrhages, many of which develop suppurative centres (crypt abscesses) that may give rise to small ulcerations. With progression, these small ulcers coalesce to become irregular in shape. Swollen, inflammatory tags of mucosa may bulge to create inflammatory pseudopolyps. Over the long chronicity of recurring attacks, fibrosis and thickening of the bowel wall develop but rarely sufficiently to cause obstruction.

Histologically, the active phase of disease is charac-terized by crypt abscesses and ulcerations surrounded by prominent mucosal infiltrate of inflammatory cells **(Fig. 58.9)**. The ulcerations rarely extend significantly into the muscularis and hence there rarely is fistula formation. There is no granuloma formation and there are no skip lesions as in Crohn’s disease.

Crohn’s Disease

One of the most distinctive macroscopic features of Crohn’s disease is the sharp demarcation of segmental bowel involvement producing ‘skip’ lesions. Rubbery, edematous, hyperemic thickening of the bowel wall with minute aphthous ulcerations marks early Crohn’s disease. As the disease evolves, the affected segment becomes thickened and inflexible likened to a lead pipe or rubber hose with narrowing of the lumen producing the ‘string sign‘on barium studies. Varying degrees of mucosal edema, ulceration and sloughing are found. The ulcers are long and serpentine and often form narrow fissures.

In chronic cases, the ulcers/fissures may penetrate deeply to form fistulous tracts. The most characteristic histological features of Crohn’s disease:

1. Transmural inflammation affecting all layers to the serosa.

2. Discrete noncaseating granulomas **(Fig. 58.10)**.

3. Dilatation or sclerosis of lymphatic channels.

4. Lymphoid aggregates in all levels of the bowel wall.

The granulomas, however, are absent or not well developed in approximately 40% of cases. There is variable ulceration and destruction of the mucosa with deeply penetrating fissures, marked submucosal fibrosis with chronic inflammation, relative preservation of the muscularis and again marked subserosal fibrosis with chronic inflam-matory changes.

Colonic Polyp

1. The common types of colonic polyps encountered in our daily practice are non-neoplastic hyperplastic polyps and neoplastic adenomatous polyps.

2. The former are composed of well-formed glands and crypts lined by epithelial cells showing a saw tooth appearance owing to in folding of the crowded cells.

3. Adenomatous polyps include tubular adenoma, villous adenoma and tubulovillous adenoma depending upon the growth pattern.

4. Tubular adenoma **(Fig. 58.11)** has a central core of fibrovascular tissue that arises in the submucosa and extends in continuity through the centre of the stalk. The stalk is usually covered by normal colonic mucosa but in the head of the lesion, the epithelium is clearly neoplastic and composed of closely aggregated elongated tubules and glands. The cells are tall and crowded and have pseudo-stratified nuclei giving the appearance of a picket fence. Mitotic figures may be found depending on the degree of dysplasia.

5. Villous adenoma is composed of finger-like branching papillae, each composed of a fibrovascular core cov-

ered by epithelium ranging from a single layer of regularly aligned tall columnar cells to cells having a disorderly multilayered arrangement with variable mitoses **(Fig. 58.12)**.

6. Tubulovillous adenoma, as the name implies, combines features of both tubular and villous adenomas.

Colorectal Cancer

95% of all colorectal cancers are adenocarcinomas, many of which produce mucin, which is secreted extracellularly either within gland lumina or within the interstitium of the gut wall. Rare types of cancers include adenosquamous carcinoma arising in the distal colon close to the anus and small cell carcinoma arising from neuroendocrine cells.

Liver

Normal Histology

1. Liver can be subdivided into roughly hexagonal lobules oriented about a central vein, which in microscopic sections seen as cords of cells radially disposed about the central vein **(Fig. 58.13)**.

2. The cells show considerable variation in nuclear size and number. Abundant glycogen can be visualized in the cytoplasm using PAS stains and there are scattered fine vacuoles of lipid. Interposed between the radial cords of hepatocytes are vascular sinusoids lined by fenestrated and discontinuous endothelial cells attached to which are scattered the Kupffer cells of the reticuloendothelial system.

3. The biliary system begins in the centrilobular regions as an elaborate network of canaliculi interposed between abutting hepatocytes. These are channels 1–2 microns in diameter formed merely by grooves along the external surfaces of abutting liver cells. These progressively join

and drain eventually into the larger bile ducts within the portal triads.

4. The lineup of hepatocytes about the portal tract is referred to as the *limiting plate*.

5. Cross sections of hepatic artery, portal vein and bile duct are seen within the portal tracts and there is a mild sprinkling of chronic inflammatory cells in normal portal tracts.

6. Functionally, liver parenchyma is divided into three zones, zone 1 being closest to the arterial and portal supply, zone 3 abutting the central vein and zone 2 being intermediate.

7. This explains why many forms of toxic injury to the liver are most severe in zone 1, means periphery of the lobule, because that is the area exposed to the greatest concen-tration of blood borne hepatotoxins. Analogously, hypoxic injury such as occurs with shock or cardiac failure is located in zone 3, most remote from arterial and portal supply.

Non-alcoholic Steatohepatitis

The key histological changes are fatty change and lobular inflammation with or without fibrosis. The *fatty change* is of large droplet in type and is predominantly seen around the central vein **(Fig. 58.14)**. The lobular inflammation may be predominantly neutrophilic or lymphocytic **(Fig. 58.15)**. *Mallory bodies* (eosinophilic cytoplasmic inclusions that take the form of candle drippings) have been described. The fibrosis is mainly pericellular and perivenular in pattern, although there may also be portal tract expansion. Semi-quantitative scoring systems have been proposed for assessing the severity of these changes.

Chronic Hepatitis

1. The morphology of chronic hepatitis ranges from exceedingly mild to severe to eventual cirrhosis. In the mildest form, an inflammatory infiltrate is limited to portal tracts, consisting of lymphocytes, macrophages, occasional plasma cells and a rare neutrophil or eosinophil.

2. The histological hallmark of progressive disease is piecemeal necrosis *(interphase hepatitis*) whereby the chronic inflammatory infiltrate spills out from portal tracts into adjacent parenchyma, with associated necrosis of hepatocytes in the limiting plate **(Fig. 58.16)**.

3. There may be lobular inflammation with focal necrosis of hepatocytes. Bridging necrosis may connect adjacent portal-portal, central-central and portal-central zones.

4. Continued loss of hepatocytes results in fibrous septum formation, which accompanied by hepatocyte regeneration results in cirrhosis. *‘Ground glass* *hepatocytes’* are sometimes present in chronic HBV hepatitis. *Lymphoid aggregates* in portal tracts and mild fatty change are seen

in about 50% of cases and bile duct damage is seen in more than 90% of chronic HCV hepatitis.

5. It is frequently impossible to identify the etiology of chronic hepatitis on tissue samples, so great reliance must be placed on clinical, virologic and serological observations.

Cirrhosis Liver

Interconnecting fibrous scars creating parenchymal nodules disorganize the architecture of the liver. The nodules vary in size, depending on causation, from micronodules (<3 mm in diameter) to macronodules (>3 mm to several centimeters in diameter).

The fibrous scars are infiltrated by lymphocytes and macrophages and in places where entire lobule has been destroyed, they may contain distorted portal triads along with irregular strands and nests of bile duct epithelium. Fat, Mallory bodies and other specific features may be found, but usually there would be no clue to the aetiology of the cirrhosis **(Fig. 58.17)**.

Metavir Score for Fibrosis in Liver Biopsy

n F0: Normal

n F1: Periportal fibrosis

n F2: Bridging fibrosis (few)

n F3: Bridging fibrosis (many)

n F4: Cirrhosis

Knodell Histological Activity Index in Liver Biopsy

**Periportal +/- bridging necrosis**

None 0

Mild piecemeal necrosis 1

Moderate piecemeal necrosis 3

(< ½ circumference)

Marked (> ½ circumference) 4

Moderate PN + bridging necrosis 5

Marked PN + bridging necrosis 6

Multilobular necrosis 10

**Interlobular degeneration and focal necrosis**

None 0

Mild (1/3 of lobules) 1

Moderate (1/3–2/3) 3

Marked (> 2/3) 4

**Portal inflammation**

None 0

Mild (< 1/3 of portal tracts) 1

Moderate (1/3–2/3) 3

Marked (> 2/3) 4

**Fibrosis**

None 0

Fibrous portal expansion 1

Bridging fibrosis 3

Cirrhosis 4

**Chapter 59.**

**Microbiology**

**Parasites**

1. Unicellular microbes: Protozoa

2. Larger multicellular organisms: Metazoa

**Classification of Parasites**

**Protozoa**

***Amoebae*** **(Fig. 59.1)**

*Of the alimentary canal*

*Pathogen*: Entamoeba histolytica

*Nonpathogenic commensals*

1. *Entamoeba coli, Entamoeba gingivalis, E. dispar, Endolimax nana, Iodamoeba butschlii*

*Potentially pathogenic freeliving amoeba*

1. *Naegleria, Acanthamoeba*

**Flagellates**

***Hemoflagellate***

1. *Trypanosoma, Leishmania*

***Intestinal Flagellate***

1. *Giardia lamblia*

2. *Dientamoeba fragilis*

***Genitourinary Flagellate***

1. *Trichomonas vaginalis*

**Sporozoa**

1. *Plasmodium spp*

2. *Toxoplasma gondii*

3. *Isospora belli*

4. *Cryptosporidium parvum*

5. *Cyclospora cayetanensis*

6. *Microsporidia*

**Ciliates**

*Balantidium coli*

**Helminths**

**Trematodes**: *Leaf-like flukes*

*Diecious blood flukes*: Live inside veins

1. *Schistosoma haematobium* in vesical and pelvic venous plexus

2. *Schistosoma mansoni* in the inferior mesenteric vein

3. *Schistosoma japonicum* in the superior mesenteric vein

*Hermaphroditic flukes* – Live in the lumen of various tracts

1. Biliary tract – Liver flukes

n *Clonorchis sinensis*

n *Fasciola hepatica*

2. Gastrointestinal tract – Intestinal flukes

n *Fasciolopsis buski*

n *Gastrodiscoides hominis*

3. Respiratory tract

n *Paragonimus westermani*

**Cestodes**:*Flat, tape like worms*

1. *Diphyllobothrium latum* (fish tapeworm)

2. *Taenia saginata* (beef tapeworm)

3. *Taenia solium* (pork tapeworm)

4. *Echinococcus granulosus* (dog tapeworm)

**Nematodes**

1. Based on the location of the adult worm in the body

**Intestinal nematodes**

*Small intestine*

*Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis, Trichinella spiralis*

*Large intestine*

*Enterobius vermicularis, Trichuris trichiura*

**Tissue nematodes**

*Lymphatic*

*Wuchereria bancrofti, Brugia malayi*

Subcutaneous

*Loa loa, Onchocerca volvulus,*

*Dracunculus medinensis*

*Conjunctiva*

*Loa loa*

2. Based on the mode of infection

*By ingestion of*

a) Eggs – *Ascaris, Enterobius, Trichuris*

b) Larvae within intermediate host – *Dracunculus*

c) Encysted larvae in muscle – *Trichinella*

*By penetration of skin*

*Ancylostoma, Necator, Strongyloides*

*By blood sucking insects*

Filariae

*By inhalation of dust containing eggs*

*Ascaris, Enterobius*

**Life Cycle of *Echinococcus granulosus***

**Common Name**

Dog tapeworm

**Mode of Infection**

Direct contact with infected dogs or via contaminated vegetables.

*In man*

*Wherever it is lodged, it develops into the hydatid cyst. Liver is the most common site; next common site is the lung.*

**Life Cycle of Hookworms (Fig. 59.4)**

**Species**

*Ancylostoma duodenale and Necator americanus*

**Mode of Infection**

By penetration of skin

**Life Cycle of Roundworms (Fig. 59.5)**

**Species**

*Ascaris lumbricoides*

**Mode of Infection**

Ingestion of embryonated eggs

With contaminated water and vegetables

**Gram stain**

Originally devised by Christian Gram.

**Principle**

When stained by this method certain organisms retain the violet primary stain and are called Gram-positive, whereas certain organisms are decolourized by the decolourizing agent and take up the pink counter stain and are called Gram-negative.

**Procedure**

1. Flood the smear with crystal violet and let it stand for 1 min.

2. Pour off the stain, wash with water.

3. Flood the smear with Gram’s iodine and let it stand for 1 min.

4. Pour off the stain, wash with water.

5. Flood the smear with acetone and keep for 2 sec.

6. Wash quickly with water.

7. Flood the smear with dilute carbol fuchsin for 30 sec.

8. Pour off the stain, wash with water.

9. Air dry the smear and see under oil immersion objective.

**Uses**

1. To differentiate between Gram-positive and Gram-negative organisms.

2. To study the size, shape, arrangement of bacteria.

3. For direct detection of organisms in clinical samples.

4. Rapid and simple method of tentative identification of bacteria.

5. The Gram reaction helps decide the antibiotic panel to which the susceptibility of the isolate is to be tested.

**Acid fast stains**

**Introduction**

Certain organisms are difficult to stain due to some features in their cell wall; however, once stained with basic dyes like strong carbol fuchsin they resist declarization with sulphuric acid and acid alcohol. These organisms are termed acid fast and the organisms, which are decolourized and take up the counter stain, are termed non-acid fast.

**Ziehl-Neelsen Stain**

1. Flood the smear with strong carbol fuchsin

2. Heat gently until steam rises; do not boil

3. Pour off the stain, wash with water

4. Flood the slide with acid alcohol (3% HCl in alcohol) and keep for 1–2 min

5. Wash with water and flood the slide with methylene blue

6. Let stand for 1 min

7. Pour off the stain. Wash with water.

8. Air dry the smear and see under oil immersion objective.

Instead of acid alcohol, sulphuric acid can also be used as decolourizing agent

1. 20% – *Mycobacterium tuberculosis*

2. 5% – *M. leprae*

3. 1% – *Nocardia*

4. 5% – Bacterial spores

**Modified Acid Fast Stain for Cryptosporidium**

1. Smears from the feces samples are made either directly from the stool or from the concentrated deposit.

2. Air dry and fix in methanol for 3 min.

3. Stain with strong carbol fuchsin for 20 min and rinse well with water.

4. Decolorize in acid alcohol (1% HCl in methanol) for 20 sec.

5. Rinse well with water and counterstain with 0.4% malachite green for 20 sec.

6. Rinse well with water and air dry.

7. Examine under high power and oil immersion objective.

8. Oocysts are red in colour, round or slightly ovoid, measuring 4.5–5.0 mm.

9. They may appear unstained, partially stained or completely stained.

**Other Sporozoa Stained by Acid-fast Stain**

1. Microsporidia

2. *Cyclospora*

3. *Isospora belli*

**Examination of feces**

**Sample Collection**

1. Collect in suitable, clean container

2. Avoid contamination with urine, water or disinfectants

3. Note the consistency, color, odor and presence of blood or mucus.

4. Also look for whole worms or tapeworm proglottides.

5. Fresh specimen needs to be examined for motility of protozoan trophozoites.

**Microscopy**

1. Direct microscopy

2. Concentration techniques

***Direct Microscopy***

*Examination of Wet Mounts*

1. Emulsify a small quantity of feces in a drop of saline placed on a slide and apply a coverslip.

2. Useful for detecting live motile trophozoites of *E. histolytica*, *B. coli* and *G.. lamblia* and eggs of helminths

*Temporary Stain*

1. Used with wet films and it helps to visualize the cysts better.

2. Stains used are eosin stain or iodine stain.

*Permanent-stained Smears*

1. It is used for identification of protozoa in feces.

2. It helps to store smears for future reference.

3. Stain used are iron hematoxylin stain and Wheatley’s trichrome stain.

***Concentration Methods***

When parasites are scanty in stools, routine wet mount may fail to detect them. Selective concentration of the protozoan cysts and helminth eggs and larvae is then attempted.

*These techniques are classified as:*

1. Flotation methods

2. Sedimentation methods

*Flotation Methods*

1. Feces is suspended in a solution of high specific gravity, so that parasitic eggs and cysts float up and get concentrated at the surface.

2. Simple flotation using saturated saline or zinc sulphate centrifugal flotation methods are used.

3. It is used to detect protozoan cysts and eggs of nematodes and *H. nana.*

4. It does not detect unfertilized eggs of *Ascaris*, nematode larvae, trematode and large tapeworm eggs.

*Sedimentation Methods*

1. Feces is suspended in a solution with low specific gravity so that the eggs and cysts get sedimented at the bottom.

2. Formol ether sedimentation is the most commonly used method.

3. Useful for all helminth eggs and protozoan cysts.

**Blood culture**

**Introduction**

1. A patient’s blood must be obtained by aseptic venipuncture and then incubated in culture media.

2. Bacterial growth is detected by using manual or automated techniques.

3. On detection of growth, organism is isolated, identified and subjected to antibiotic susceptibility testing.

**Specimen Volume**

1. 10 mL in adults per blood culture bottle

2. 1–5 mL in children

**Number of Blood Cultures**

1. If adequate volume of blood is cultured, two or three blood cultures are usually sufficient to ensure optimum blood culture sensitivity.

2. Blood for culture is to be collected before institution of antibiotic therapy.

**Media Used for Blood Culture**

1. Trypticase soy broth, brain heart infusion broth – aerobic culture

2. Thioglycollate broth – anaerobic blood culture

3. Bile broth – suspected salmonellosis

4. The bottles are incubated in the incubator at 350C, the aerobic culture bottle is subculture after 6 hr, 2 days and 7 days on a differential media like Macconkey’s agar and an enriched media like blood agar.

5. The anaerobic blood culture bottle is visually inspected for growth; if growth is detected, it is subcultured and incubated both aerobically as well as anaerobically.

**Automated Blood Culture Systems**

1. BACTEC

2. BacT/ALERT System

n They detect release of CO2 by the growing bacteria

n Advantage: rapidly and accurately detects organisms in blood cultures due to constant monitoring of the specimen incubated in the system.

**Enzyme-linked Immunosorbent assay (ELISA)**

**Introduction**

Most widely used procedure in clinical serology. It is used to detect antibody or antigen.

**Principle**

To measure antibody, known antigens are fixed to a solid phase, incubated with test antibody dilutions, washed and reincubated with an anti-immunoglobulin labeled with an enzyme. Enzyme activity is measured by adding the specific substrate and estimating the color reaction which is directly proportional to the amount of antibody bound. **(Fig. 59.6)**

1. Antibody detection in HIV infection

2. Positive and negative controls are also put up along with each run.

**Types of ELISAs**

1. Simple non-competitive sandwich ELISA (described above)

2. Competitive ELISA (serum antibody and enzyme labeled antibody compete for the binding sites on the antigen)

**Uses**

1. Effective screening tests for a variety of infectious agents.

2. Easy to perform, adaptable to automation.

3. Large number of samples can be tested at one time.

4. Designed to be very sensitive; a small number of false positives do occur.

**Cylinder or Cassette ELISA**

1. It is a modified ELISA.

2. The antigens are immobilized at special fixed sites on a nitrocellulose membrane in the cassette.

3. Used as a screening test

4. Each sample is tested in a separate, disposable cassette.

5. Rapid, takes about 10 minutes

6. No need for special equipment

7. Available for screening sera for HIV, HCV, etc.

**Normal microbial flora of the mouth and upper respiratory tract**

**The Flora of the Nose**

Corynebacteria, staphylococci (*S.epidermidis, S. aureus*) and streptococci.

**The Mucous Membranes of Mouth and Pharynx**

1. Sterile at birth, get contaminated during passage of baby through birth canal.

2. Within a few hours of birth, viridians streptococci become established as the most prominent members of the resident flora and remain so for life.

3. The other bacteria seen are aerobic and anaerobic staphylococci, neisseriae, *Moraxella catarrhalis*, diphtheroids, anae robic spirochaetes, *Prevotella* species, and *Fusobacterium* species.

**Normal flora of the intestinal tract**

1. At birth, intestine is sterile, but organisms are soon introduced with feeding.

2. In the normal adult, the microorganisms on the surface of the oesophageal wall are those swallowed with saliva and food.

3. Stomach’s acidity keeps microorganisms at a minimum. The normal acid pH of the stomach markedly protects against infection with enteric pathogens like *Vibrio cholerae*.

4. In patients with carcinoma of the stomach or achlorhydria or pyloric obstruction, there is proliferation of Gram-positive cocci and bacilli.

5. The bacterial numbers increase progressively beyond the duodenum to the colon:

n 103–106 bacteria per gram of contents in the duodenum

n 105–108 bacteria per gram in jejunum and ileum

n 108–1010 in cecum and transverse colon

n 1011 bacteria in the sigmoid colon and rectum.

6. In duodenum and upper ileum, lactobacilli and enterococci predominate.

7. Lower ileum and cecum flora resemble fecal flora.

8. In the normal adult colon, resident bacterial flora (96–99%) are mostly anaerobes – anaerobic streptococci, anaerobic lactobacilli, clostridia, bacteroides, *Fusobacterium* species – and about 1–4% aerobes – enterococci, coliforms and small numbers of *Proteus*, *Pseudomonas*, lactobacilli, *mycoplasma*, *Candida* etc.

**Role of Intestinal Bacteria**

1. Intestinal bacteria are important in synthesis of vitamin K.

2. Conversion of bile pigments and bile acids

3. Absorption of nutrients and breakdown products

4. Antagonism to microbial pathogens.

**Polymerase chain reaction (PCR)**

**Introduction**

1. Powerful amplification tool to enhance sensitivity of molecular diagnostic techniques.

2. The most widely used target nucleic acid amplification method.

3. A single copy of the nucleic acid target is multiplied to 107 or more copies within a relatively short period. These copies are then detected by various methods.

4. There are 30–50 repetitive cycles, each comprising three sequential reactions:

n Denaturation of target nucleic acid

n Primer annealing to single stranded target nucleic acid

n Extension of primer target duplex

**Denaturation of Target Nucleic Acid**

1. For PCR, target nucleic acid must be in the single stranded conformation for the second reaction to occur.

2. DNA of organism is released and denaturation to single strand is done in a single step by heating the sample to 94oC. For RNA targets, this step is not required as they are already single stranded.

**Primer Annealing**

1. Primers are short sequences of nucleic acid that are selected to specifically hybridize (anneal) to a particular nucleic acid target.

2. Primer nucleotide sequence design depends on the intended target such as genus-specific genes, species-specific genes, virulence genes or antibiotic resistance genes.

3. Primers are used in pairs that flank the target sequence of interest.

4. When primer pair is mixed with denatured target DNA one primer anneals to a specific site at one end of the target sequence of one target strand, the other primer anneals to a specific site at the opposite end of the complementary target strand. The distance between them on the target DNA is 50–1000 base pairs.

5. Annealing process is conducted at 50–58oC or higher.

6. Once the duplexes are formed, last step in the cycle, which mimics DNA replication process, begins.

**Extension of Primer Target Duplex**

1. Annealing of primers to target sequences provides the necessary template format that allows DNA polymerase

to add nucleotides to 3’of each primer and produce an extension sequence complementary to the target template.

2. Taq polymerase is the enzyme used for primer extension.

**Detection of PCR Products**

1. PCR amplification product containing target nucleic acid of interest is referred to as amplicon.

2. Amplicon may be detected by probe labeled with reporter molecules that generate radioactive, colorimetric, fluorimetric or chemilu-minescent signals.

**Derivatives of PCR Method**

***Multiplex PCR***

1. Two or more primer sets designed for amplification of different targets are included in the same PCR mixture.

2. Advantages:

n It can be used to provide an internal control during the test.

n Ability to search for different targets using one reaction, i.e., you can look for different organisms or genes in one reaction vessel.

3. Limitation – more complicated to develop and less sensitive than PCRs with single primer sets.

***Nested PCR***

1. Sequential use of two primer sets in two roun-ds of PCR.

2. First primer set amplifies a target sequence in the first round of PCR.

3. The products of first round of amplification are then subjected to a second round of amplification with a second set of primers that anneal to a sequence internal to the first amplicon.

4. Though extremely sensitive and with confirmed specificity, the procedure requires open manipulations of amplified DNA that can lead to aerosols and contaminate other reaction vials.

***Quantitative PCR***

1. Detects and identifies the infectious agent.

2. It also quantitizes the actual number of targets originally in the clinical specimen.

*Uses*

1. The ability to quantitate infectious burden helps study and understand the disease state, like AIDS.

2. Prognosis of certain infections, e.g., to predict disease progression

3. To assess effectiveness of antimicrobial therapy

***RT PCR (Reverse Transcriptase PCR)***

1. Developed to amplify an RNA target.

2. Enzyme reverse transcriptase directs synthesis of DNA from viral RNA template. DNA thus obtained is subjected to routine PCR technology.

3. Used for detection of HCV RNA and along with quantitative PCR for quantitation of HIV-1 and HCV RNA in clinical specimens.

***Real Time PCR***

1. Capable of detecting the presence of a target within 30–120 min.

2. This process is called “real time” PCR.

3. Rapid thermocycling and ability to detect target by fluorescent-labeled probes as the hybrids are formed in real time.

4. Advantages

n Multiplexing reactions

n Quantitation of target

n Online monitoring

**Current Applications of Molecular Diagnostics**

1. ***Detection of slowly growing and unculti-vable pathogens***

n For several diseases, nucleic acid based tests have replaced culture as the gold.

standard (hepatitis C, enteroviral meningitis, genital infection with *Chlamydia trachomati*, etc).

n Biggest impact of molecular methods is on clinical virology.

n Faster, more sensitive, more cost effective.

n Molecular diagnostics have led to the discovery of previously unrecognized or uncultivable pathogens.

2. ***Identification of bacteria and fungi by nucleic acid sequencing***

3. ***Disease prognosis***

n To predict disease progression, e.g., HIV-1 plasma viral load as a predictor of progression to AIDS and death in HIV-1 infected individuals.

n Estimation of level of CMV DNA to predict the development of active CMV diseas .

n Viral load assays have been used to monitor the response to therapy in patients chronically infected with HBV and HCV.

4. ***Response to therapy***

n Molecular methods have been used to detect genes responsible for drug resistance in methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, rifampin-resistant *Mycobacterium,* etc.

**Chapter 60.**

**Pharmacology**

**Proton pump inhibitors**

**Introduction**

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in gastroenterology practice and are considered a major advance in the treatment of acid-peptic diseases and gastroesophageal reflux disorders.

**Pharmacological Actions**

1. Proton pump inhibitors have a much greater potency in the suppression of gastric acid secretion than H2-receptor antagonists.

2. These drugs alter gastric acid secretion by inhibition of the final common pathway of acid secretion, the enzyme H+, K+ -ATPase (i.e., the proton pump) of the parietal cell.

3. These drugs form a covalent bond with the proton pump and acid secretion is suppressed until more acid is produced.

4. As PPIs inhibit only activated enzyme present in the canalicular membrane, the reduction of gastric acid secretion after an initial dose will probably be suboptimal.

5. After the second dose is given on the next day before meal, more H+, K+-ATPase will have been recruited and subsequently inhibited, and after the third dose, additional recruitment and further acid inhibition will probably occur.

6. Once-daily PPI dosing inhibits maximal acid output by about 66% after 4–5 days. Thus, the occasional use of a PPI taken on an ‘as needed’ basis would not be expected to reliably provide adequate acid inhibition.

**Pharmacokinetics**

1. PPIs are substituted benzimidazole, lipophilic, weak bases.

2. As PPIs are inactivated by exposure to gastric juice, they are available as enteric-coated tablets or capsules that pass through the stomach intact and are absorbed in the proximal small bowel.

3. All PPIs have a short plasma half-life (about 1–2 hrs), but their duration of action is much longer because (around 24–36 hrs) of their unique mechanism of action.

4. The pharmacokinetics of omeprazole is unaltered in renal failure.

5. Metabolism of omeprazole is through CYP 2C19, for which polymorphism has been described.

6. Esomeprazole is the s-isomer of omeprazole. Due to lesser first-pass effect and slower plasma clearance, its bioavailability is more than omeprazole.

**Dose**

1. Because the amount of H+,K+-ATPase present in the parietal cell is greatest after a prolonged fast, thus PPIs should be administered before the first meal of the day. Usually, once-daily dosing is sufficient and a second dose, which is occasionally necessary, should be administered before the evening meal.

2. PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release gelatin capsules containing enteric-coated granules (omeprazole and lansoprazole) or in delayed-release enteric-coated tablets (rabeprazole and pantoprazole).

n Omeprazole 10, 20 and 40 mg

n Lansoprazole 15 and 30 mg

n Pantoprazole 40 mg

n Esomeprazole 20 and 40 mg

n Rabeprazole 20 mg

**Indications**

1. PPIs are effective for treatment of all acid-related disorders like both gastric and duodenal ulcers and ZES (Zollinger Ellison syndrome).

2. Raising intragastric pH with PPIs improves antimicrobial efficacy of chemotherapeutic agents towards *H. pylori* through several mechanisms, thus increasing their bactericidal effectiveness. Thus, the combination of a PPI and two antimicrobials (mainly clarithromycin and amoxicillin or metronidazole) is now a well-established first-line regimen.

3. In patients with reflux esophagitis, the degree of mucosal healing is directly related to the proportion of time during the 24-hr period for which the intragastric pH is maintained above 4.

4. Prevention of NSAID-induced gastroduodenal ulceration.

5. Used for bleeding ulcers to maintain intra-gastric pH >6 to promote platelet aggregation, clot formation and stability. Combination of endotherapy with acid suppression is superior to monotherapy in reducing bleeding and surgery.

**Side Effects**

1. PPIs are generally well tolerated. The frequency of adverse effects associated with PPIs is similar to that of placebo or H2-receptor blockers.

2. Headache, diarrhoea, abdominal pain and nausea are the common side effects. Except for diarrhoea (incidence is <5%), the adverse effects of PPIs do not appear to be related to age, dosage or duration of treatment.

3. The diarrhoea is related to the profound acid suppression, which has been shown to alter the bacterial content of the gut.

4. Short-term and long-term safety of PPIs is well established.

5. The safety profiles of the newer agents, rabeprazole and esomeprazole, appear to be similar to omeprazole or lansoprazole.

6. PPIs are only contraindicated in patients with hypersensitivity to them.

7. PPIs are not recommended for use in breast feeding mothers.

**Drug Interactions**

1. PPIs cause significant increase in intragastric pH, which may alter the absorption of weak acids or bases (griseofulvin, ketoconazole, iron salts, vitamin B12, etc.)

2. PPIs increase the absorption of digoxin.

*Why are PPIs better than H2RAs?*

1. H2RAs have a relatively short duration of action. Multiple daily doses of these agents are likely to be required. H2RAs produce incomplete inhibition of postprandial gastric acid secretion.

2. Tolerance to standard H2RAs generally develops within 2 weeks of repeated administration, resulting in a decline in acid suppression.

**Novel PPIs**

The majority of novel PPIs are still in preclinical development. Only two drugs are actively being studied in humans. They are ilaprazole and tenatoprazole.

**Potassium Competitive Acid Blockers**

The next generation of drugs, which suppress gastric acid will most likely be P-CABs, which are K+-competitive inhibitors of the ATPase. P-CABs have a structural specificity for their target, the K+-binding region of the H+, K+-ATPase.

Dexlansoprazole (trade names Kapidex, Dexilant, available in 30 mg and 60 mg) is a proton pump inhibitor that is marketed by Takeda Pharmaceuticals, USA. Chemically, it

is an enantiomer of lansoprazole. Dexlansoprazole MR is a modified-release formulation of dexlansoprazole that employs an innovative dual delayed release delivery system designed to prolong plasma concentration of dexlansoprazole

**Prokinetic agents**

**Metoclopramide**

***Pharmacological Actions***

1. Metoclopramide is central as well as peripheral dopamine (D2) antagonist.

2. Central action of metoclopramide is also on chemoreceptor trigger zone (CTZ) in the area postrema. Its antiemetic property is superior to domperidone.

3. It has 5-HT4 agonist effect, thus enhances release of acetylcholine from myenteric plexus and thus accelerates gastric emptying.

4. At high concentrations, it can block 5-HT3 receptors in CTZ. Thus, large doses are used to prevent chemotherapy-induced vomiting.

***Dosage***

1. Metoclopramide 10 mg PO TID

2. Intravenous dose 0.3–1.0 mg/kg/day

***Side Effects***

1. Dizziness, diarrhoea, muscular dystonia.

2. Long-term use can cause parkinsonism, galactorrhea and gynecomastia.

**Domperidone**

***Pharmacological Actions***

1. Domperidone is a peripheral dopamine (D2) receptor antagonist with similar efficacy as metoclopramide for gastric emptying.

2. Domperidone does not cross blood-brain barrier, thus central nervous system side effects are negligible unlike metoclopramide.

3. It increases lower oesophageal sphincter pressure, gastric emptying and gastroduodenal coordination.

4. It has little prokinetic activity on colon.

***Dosage***

Domperidone 10–40 mg 3 times a day

***Side Effects***

1. Domperidone is very well tolerated.

2. It can cause dry mouth, loose stools, headache and galactorrhea.

**Cisapride and Mosapride**

***Pharmacological Actions***

1. It has major non-selective 5-HT4 agonist effects and enhances release of acetylcholine from myenteric plexus and accelerates gastric emptying.

2. Its antiemetic effects are negligible due to lack of D2 receptor and minimal 5-HT3 antagonism.

3. It facilitates motility throughout the gastrointestinal tract, including colon.

***Dosage***

1. Cisapride 10–20 mg PO TID

2. Mosapride 5 mg PO TID

***Side Effects***

1. Abdominal cramps, diarrhea, dizziness

2. Cisapride (not mosapride) prolongs QTc interval and predisposes to torsade de pointes.

**Erythromycin**

***Pharmacological Actions***

1. Migrating motor complex (MMC) is the fasting gastric and small intestinal motor pattern responsible for interdigestive transit of undigested residue.

2. Motilin, released from duodenal mucosal cells, is a mediator of MMC.

3. Erythromycin, a macrolide antibiotic, is a motilin receptor agonist.

4. It accelerates solid and liquid gastric emptying in dose-dependent manner.

**Dosage**

Erythromycin 1–2 mg/kg/day IV

***Side Effects***

Mild epigastric discomfort, diarrhoea, skin rash, cholestatic hepatitis

**Ondansetron/Granisetron**

***Pharmacological Actions***

1. It is a 5-HT3 antagonist on CTZ and the nucleus tractus solitarius (NTS).

2. Chemotherapy and radiotherapy produce vomiting by stimulating CTZ and NTS via 5-HT3. It blocks central and peripheral emetogenic impulse.

3. Used to control radiotherapy and chemotherapy induced vomiting and prevents postoperative vomiting.

4. Granisetron is 10 times more potent than ondansetron.

***Dosage***

1. Ondansetron 4–8 mg PO TID; 4–8 mg IV slowly half an hour before chemotherapy.

2. Granisetron 1–2 mg PO TID; 10 ng/kg IV half an hour before chemotherapy.

***Side Effects***

1. Well tolerated

2. Mild headache, abdominal discomfort and skin rash

**Tegaserod/Proculopride**

***Pharmacological Actions***

1. Tegaserod (5-HT4 partial agonist) and proculopride (5-HT4 agonist) stimulate peristalsis, accelerate gut transit, including colonic contractions.

2. Clinical trials showed their efficacy in constipation-predominant IBS.

***Dosage***

Tegaserod 2–6 mg PO BID

***Side Effects***

Diarrhoea, abdominal discomfort

**Neostigmine**

***Pharmacological Actions***

1. It is an acetylcholinesterase inhibitor, thus provides important stimulatory input for contractile activity in the gastrointestinal tract.

2. Role of neostigmine in acute colonic pseudo-obstruction (ACPO) is proved in clinical trials.

***Dosage***

1. In ACPO, 2 mg IV slowly; second dose can be repeated after 2 hrs

***Side Effects***

Abdominal discomfort, vomiting, bradycardia, bronchospasm

**Drugs that reduce motor activity**

Many pharmacological agents are available that delay intestinal transit. Most of the agents act on enteric nervous system. Major therapeutic roles of these drugs are in chronic diarrhoea and diarrhoea-predominant IBS.

**Opioid Agents**

***Pharmacological Actions***

1. Opioid drugs increase small bowel tone, reduce propulsive movement and reduce intestinal secretions by enhancing absorption.

2. Major action of opioid agents are mediated through opioid receptors situated on enteric nervous system.

3. This class of drugs is known to be active at µ opiate receptors that mediate their inhibitors effects on intestinal smooth muscle.

4. Both morphine and loperamide can inhibit chloride secretion induced by bacterial enterotoxins and prostaglandin E2. Loperamide may have some antisecretory activity; it would appear that the balance of opinion would attribute its anti-diarrheal action to its effects on gut motility.

***Dosage***

1. Codeine 60 mg PO TID

2. Diphenoxylate (2.5 mg) + atropine (0.025 mg) (Lomotil) PO TID

3. Loperamide 2–4 mg PO TID

***Side Effects***

Abdominal pain, constipation, paralytic ileus, abdominal distension

**Mebeverine**

***Pharmacological Actions***

1. Mebeverine is a smooth muscle relaxant similar to papaverine that inhibits ileal and colonic motility.

2. Its main use is in pain-predominant or diarrhoea-predominant IBS.

***Dosage***

Mebeverine 135 mg PO BID ½ hr before food

***Side Effects***

Well-tolerated drug with very few side effects like nausea

**Hyoscine/Dicyclomine**

***Pharmacological Actions***

1. Both are commonly used antispasmodic agents; act by muscarinic receptor antagonism.

2. Their anticholinergic activity inhibits gastrointestinal contractions.

***Dosage***

1. Hyoscine 0.2–0.4 mg PO TID

2. Dicyclomine 10–20 mg PO TID

***Side Effects***

Constipation, dryness of mouth, urinary retention, blurring of vision and palpitation

**Somatostatin Analogues (Octreotide)**

**Introduction**

1. Somatostatin-secreting cells and somatostatin receptor-expressing cells are distributed throughout the GI tract.

2. Somatostatin or its analogue octreotide result in the inhibition of the majority of gastrointestinal, including gastrin, motilin, secretin, cholecystokinin (CCK), vasoactive intestinal peptide and insulin.

3. Octreotide regulates gut motility, absorption of electrolytes and nutrients, gastric acid secretion, and pancreatic secretion of enzymes and bicarbonate.

4. It also reduces splanchnic arterial and portal blood flow.

5. Somatostatin and its synthetic derivative octreotide may have a role in treating multiple disorders of the gastro-intestinal tract.

**Role of Somatostatin Analogue in Gastroenterology**

1. Control of variceal bleeding

2. Control of non-variceal bleeding

3. Dumping syndrome

4. Postvagotomy diarrhoea

5. AIDS-related diarrhoea

6. Short bowel syndrome

7. Pancreatitis

8. Pancreatic fistula

9. Post-ERCP pancreatitis

10.Pancreatic neuroendocrine tumour

11.Hepatocellular carcinoma

**Role in Variceal Bleeding**

1. The somatostatin analogue octreotide inhibits the secretion of vasoactive hormones and reduces splanchnic blood flow and portal pressure in cirrhosis. Octreotide is used for control of acute variceal haemorrhage.

2. The role of octreotide in the prevention of early rebleeding has not yet been defined.

3. Octreotide reduces basal or postprandial portal blood flow.

4. Octreotide has some advantage over somatostatin. Octreotide has longer half-life, is relatively stable in ambient light, and can be administered subcutaneously.

5. Dose of octreotide in variceal bleeding is 100 µg intravenous followed by 50 µg/hr as a maintenance dose. Somatostatin is given as 250 µg initial bolus dose followed by continuous intravenous infusion at a rate of 250 µg/hr.

6. Current data indicate that octreotide has comparable efficacy to terlipressin, sclerotherapy and banding for control of acute variceal bleeding.

**Short Bowel Syndrome**

1. Somatostatin and its synthetic analogue, octreotide, have also been used in the management of diarrhea in the treatment of patients with short bowel syndrome.

2. The proposed mechanisms of action of octreotide in short-bowel syndrome include its antimotility effects, prolonged contact of luminal contents with the intestinal mucosa by delaying transit, and decreased pancreatic and biliary secretions.

3. Short-acting octreotide (100 mg 3 times daily) has been shown to be effective in reducing fluid and electrolyte requirements in patients with short bowel syndrome.

4. The role of the long-acting octreotide (LAR) depot (20 mg intramuscularly every 3–4 wks) is under evaluation.

**Dumping Syndrome**

1. Dumping syndrome is classified as early or late, depending on the timing of onset of symptoms after ingestion of a meal.

2. Early dumping syndrome occurs within 10–30 min of ingestion of a meal, whereas late dumping, occurs 2–3 hrs postprandially.

3. Octreotide is beneficial in early dumping because it slows gastric emptying, delays intestinal transit, and inhibits the release of gastrointestinal peptides. In late dumping, octreotide inhibits the insulin release and thus reduces reactive hypoglycaemia.

4. The dose of subcutaneous octreotide 50 mg 3 times daily, taken 30 min before a meal improves more than 90% of patients with dumping syndrome.

***AIDS-related Diarrhoea***

1. Refractory diarrhoea is a major problem among patients with HIV disease.

2. Idiopathic secretory diarrhoea, octreotide (500 mcg 3 times daily) may demonstrate an overall efficacy of about 45–50%.

**Hepatocellular Carcinoma**

1. Studies have shown that octreotide is a very potent inhibitor of vascular endothelial cell growth factor, the major factor for angiogenesis in most tumours. Thus, the antiangiogenic effects of octreotide may provide additional benefit for patients with HCC.

2. Around 50% of HCC tumours express somatostatin receptors, providing additional rationale for inclusion of somatostatin analogues in the treatment regimen.

3. Few trials suggest that octreotide therapy will have a survival benefit in patients with advanced HCC. However, the numbers enrolled were small in previously published data.

4. Additional trials are underway to further investigate the role of octreotide LAR depot (30 mg IM every 4–6 wks) in advanced HCC.

**Pancreatitis**

1. Somatostatin and its analogues octreotide are used in a variety of pancreatic indications:

n ERCP-induced pancreatitis

n Acute severe pancreatitis

n Pain in patients with chronic pancreatitis

n Pancreatic duct rupture

n Pancreatic surgery

2. Clinical trials till now failed to demonstrate positive effect of somatostatin and its analogue to prevent post-ERCP pancreatitis.

3. Clinical trials also failed to demonstrate a benefit of octreotide with respect to complications or mortality in established severe acute pancreatitis and pain in patients with chronic pancreatitis.

4. Retrospective data suggest that somatostatin and octreotide speed pancreatic fistula closure and control of pancreatic ascites.

5. Octreotide reduces the postoperative pancreatic fistulas following pancreatic surgery.

**Enkephalins and Enkephalinase Inhibition**

1. Enkephalins are endogenous opioids in the gastrointestinal tract that have pro-absorptive and anti-secretory activity in the small intestine.

2. Endogenous enkephalins are rapidly degraded by a membrane-bound metalloproteinase, enkephalinase. A potent inhibitor of enkephalinase has been developed as racecadotril. The clinical importance of this agent lies in its mode of action that appears to be exclusively anti-secretory without any effects on intestinal motility. Racecadotril has no central effects such as respiratory depression.

3. The dosage of racecadotril is 100 mg PO three times a day.

4. Racecadotril reduced the duration of diarrhea but, most importantly also dramatically, reduced stool output. The requirements for oral rehydration fluids were also lower in the racecadotril group.

**Role of 5-HT and 5-HT Receptors in Normal and Altered Bowel Functions**

1. Around 95% of 5-HT in the body is in the gastrointestinal tract, whereas the remaining 5% is localized in the central nervous system (mostly in the brain).

2. In the gut, two non-neuronal sources, *viz* the enterochromaffin (paracrine) cells and the enteric mast cells account for most of the available 5-HT.

3. Serotonin is known to markedly influence bowel motility by activating at least five receptor types, *viz* 5-HT1 to 5-HT5. Among all serotonin receptors, those belonging to the 5-HT3 and 5-HT4 type are the most extensively studied in gastroenterology, resulting in commercially available agonists and antagonists for the treatment of IBS and functional dyspepsia.

**Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors**

1. First generation tricyclic antidepressants such as amitriptyline, have been shown to be superior to placebo in treating IBS, with an 8-fold benefit from pain (tricyclics are potent analgesics) and a 4-fold benefit for global symptom improvement.

2. Tricyclic antidepressants tend to reduce colonic transit and therefore may exert a greater benefit in patients with diarrhea predominant-IBS.

3. SSRIs are class of compounds with a lower side effect profile than tricyclics. SSRIs tend to produce diarrhea (due to enhanced availability of 5-HT) and may be most efficacious in constipation predominant-IBS.

**Endogenous Opioids System and its Application in Gastroenterology**

1. Endogenous opioids are a family of peptides that include -endorphin, enkephalins, endomorphin and dynorphin.

2. Endogenous opioids are distributed throughout the body including the central and peripheral nervous systems and the gastrointestinal tract where they are present in myenteric and submucosal plexus and in endocrine cells of the intestinal mucosa.

3. Endogenous opioids modulate diverse biological processes including analgesia, motor activity, autonomic functions and stress response.

4. The effects of opioids are mediated by three main classes of G-protein coupled membrane receptors, the delta, kappa and mu opioids receptors.

5. In the gastrointestinal tract, mu opioids receptors are present predominantly in the mucosa, submucosa, and submucosal plexuses and they appear to be involved in analgesia and gastrointestinal motility. Kappa opioid receptors, on the other hand, are present in higher concentrations in the muscular layers in the myenteric plexuses and are also involved in analgesia and motility. Finally, delta opioid receptors appear to be present in the myenteric and submucosal plexuses and in nerve fibers extending to muscle and mucosa.

6. Endogenous opioids’ effects include altering motility, secretion, analgesia and inflammation. Exogenous opioid receptor agonists also share many of these effects depending on the opioid receptor binding affinity.

**Lamivudine**

**Pharmacological Actions**

1. Lamivudine, a nucleoside analogue, was the first effective oral agent for patients with chronic hepatitis B.

2. It competitively inhibits reverse transcriptase, thereby terminating proviral DNA chain extension.

**Dose**

Lamivudine 100 mg PO daily

***Efficacy in Chronic Hepatitis B***

Lamivudine in patient with chronic HBV infection (both HBeAg-positive and HBeAg-negative patients)

1. Lamivudine, 100 mg orally daily, results in loss of HBeAg in 18% of patients after 1 yr and 25% of patients after 2 yrs.

2. When treatment for 1 yr does not result in HBeAg to anti-HBe seroconversion, or in patients with HBeAg negative chronic hepatitis B infection, long-term therapy to suppress HBV DNA may be required.

***Lamivudine in Liver Transplantation Setting***

1. Lamivudine is effective as prophylaxis for de novo hepatitis in recipients of anti-HBc-positive grafts and for recurrent infection in recipients transplanted for acute or chronic hepatitis B with liver failure.

2. Lamivudine may stabilize graft function and retard histological progression in transplant recipients who have developed breakthrough HBV reinfection.

***Lamivudine Resistance***

1. The most common mutation leading to lamivudine resistance is a specific point mutation in the conserved tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase in which a methionine residue is changed to a valine or isoleucine.

2. Lamivudine-resistant mutants were detected in 14% and 32% of patients at the end of a 1-year course of treatment in the Asian and United States studies, respectively.

3. Lamivudine resistance is usually manifested as breakthrough infection, defined as reappearance of HBV DNA in serum after its initial disappearance.

4. It can be treated with adefovir.

***Advantages of Lamivudine***

1. Oral administration

2. High degree of tolerability

3. Safety in patients with decompensated cirrhosis

4. Lamivudine can be used as first-line therapy or following interferon failure.

***Disadvantages***

1. Uncertainty about the duration of therapy and the long-term durability of response.

2. Lamivudine-resistant strains of HBV develop at a rate of 15–20% per year of therapy.

**Adefovir Dipivoxil**

**Pharmacological Actions**

Adefovir dipivoxil is the oral prodrug of adefovir, which is converted to the active adefovir diphosphate by cellular adenylate kinase. This adefovir diphosphate causes termination of viral DNA chain by competitively inhibiting natural substrate (deoxyadenosine triphosphate of DNA polymerase).

**Pharmacokinetics**

1. Adefovir is absorbed rapidly following oral administration. Its biological half-life is 7.48 ± 1.65 hrs.

2. It is excreted by kidney. So, dosage and dosing interval should be adjusted in patients with impaired renal function.

**Dose**

Adefovir 10 mg PO once daily

**Side Effects**

1. Adefovir in the dose of 10 mg/day is generally well tolerated in patients with chronic hepatitis B infection.

2. Asthenia and diarrhoea are the most adverse effects encountered.

3. Risk of nephrotoxicity of adefovir in the dose of 10 mg/day for 48 weeks is very low.

4. Safety of adefovir has not been established in pregnant women.

**Efficacy in Chronic Hepatitis B Infection**

1. **Adefovir in HBeAg positive chronic he-patitis B infection** *(*Marcellin et al. *N Engl J Med* 2003; 348:808–16)

n HBe Ag loss occurred in 23%, whereas histological improvement was seen in 53% of patients.

n Higher baseline alanine aminotransferase (ALT) values are associated with good response.

n Efficacy of 10 mg/day dose was equal to 30 mg/day.

2. **Adefovir in HBeAg negative chronic hepatitis B infection** (Hadziyannis et al. *N Engl J Med* 2003; 348:800–7)

n Reduction of HBV DNA level – <400 copies/ml was observed in 51%, whereas histological improvement occurred in 64%.

n Long-term safety and efficacy of adefovir was evaluated for 72 weeks.

3. **Adefovir in patients with lamivudine-resistant chronic hepatitis B infection**

n Adefovir plus lamivudine had shown efficacy against lamivudine-resistant chronic hepatitis B infection.

n Marked reduction in HBV DNA levels once patient with lamivudine resistance was given adefovir with or without continuing lamivudine.

**Ribavirin**

**Pharmacological Actions**

1. Exact pharmacological action of ribavirin is not known. Ribavirin, synthetic nucleoside analogue, is assumed to activate Th1 cytokines.

2. Interferon augments the effect of ribavirin by increasing virus specific cytotoxic T-lymphocytes, preserving IL-2 and INF- activity.

**Dose**

1. Ribavirin 13–15 mg/kg/day

2. Dose of ribavirin depends on the genotype of HCV.

3. Genotype I: 1000–1500 mg/kg/day

4. Genotype II: 800 mg/kg/day

**Adverse Reactions**

1. Anaemia is the most important adverse reaction of ribavirin.

2. Incidence of anaemia, which is dose dependent, occurs in 9–10% of patients.

3. Dosage of ribavirin should be reduced if haemoglobin is less than 10 g/dL.

**Efficacy of Ribavirin in HCV Infection**

1. Monotherapy of ribavirin has no role in chronic HCV infection.

2. It should be given in combination with either conventional or peg-interferon.

3. Sustained virological response is better in genotype I with peg-interferon plus ribavirin combination than conventional interferon plus ribavirin.

4. In patients with non-genotype I, response to peg-interferon and conventional interferon is same in combination with ribavirin.

**Ribavirin-like Molecules**

1. Levovirin – A sugar analogue of ribavirin with similar Th1 modulation.

2. Viramidine – It is converted to ribavirin by adenosine deaminase in the body.

3. Newer molecules are in phase II trials and have not shown haemolysis.

**Interferon**

**Introduction**

1. It is a glycoprotein produced in vivo by leucocytes in response to viral infection.

2. Commercially manufactured by cell culture or recombinant technology

**Pharmacological Actions**

1. Reduce viral replication, through direct antiviral mechanisms

2. Decreased viral attachment and uncoating

3. Induction of intracellular protein

4. Amplications of CTLS and NK cells

5. Mechanism of interferon in HCV is poorly understood.

6. Interferon has anti-inflammatory activity, independent of antiviral activity.

**Pharmacokinetics**

1. Conventional interferon has short half life, so it should be given at least thrice a day.

2. PEG Interferon  polyethylene glycol is attached to the INF to reduce the clearance.

3. Pegylation leads to 10-fold increase in the half-life.

4. INF-2B 12 kd: excreted by kidney.

5. INF-2a 40 kd: metabolized by liver.

**Dose**

Conventional

3–5 MU SC daily

10 MU SC thrice a week

PEG-INF

*INF 2a (Pegasys)*

Liquid – ready to inject form

t½ life 80 ± 32 hrs

180 mg standard dose

Volume of distribution is equivalent to plasma volume; so fixed dose

*INF 2b (Fulford)*

Powder form

t½ 40 ± 13.4 hrs

1–1.5 mg/kg dose

Volume of distribution is larger, thus it is given in per kilogram dose

**Monitoring**

1. Baseline: Complete blood count, liver profile and thyroid function test

2. Complete blood count: Every 2–4 weeks

3. *Decrease dose of INF to half in following conditions*

n Total count < 1500/m3

n Absolute neutrophil counts < 750/m3

n Platelet counts < 80000/m3

**Side Effects**

1. Flu-like symptoms (slightly more with Peg INF)

2. Anorexia and erythema at injection site

3. Hair loss

4. Hypothyroidism/hyperthyroidism (5% develop antithyroid antibody; 3% develop hypothyroidism)

5. Depression; irritability; decreased concentration

6. Gastrointestinal side effects like nausea, vomiting and abdominal discomfort

7. Neutropenia occurs in 10% patients with standard INF and 18% with peg INF

**Ursodeoxycholic Acid**

**Introduction**

1. Ursodeoxycholic acid (UDCA) is a naturally occurring, hydrophilic bile acid that derives its name due to its presence in the bile of the black bear.

2. UDCA constitutes about 1–4% of the total bile acids in human bile.

**Pharmacological Actions**

1. UDCA suppresses hepatic synthesis and secretion of cholesterol; and inhibits intestinal absorption of cholesterol.

2. It has hepatoprotective effect by stabilizing liver cell membrane against damage by toxic bile acids.

3. UDCA has immunomodulatory activity, thus prevents hepatocyte apoptosis.

4. UDCA has direct and indirect antioxidant effects.

5. UDCA has hypercholerectic effect, thus it increases bile flow, and reduces cholestasis.

**Pharmacokinetics**

1. Around 90% of a therapeutic dose of UDCA is absorbed in the small bowel following oral administration.

2. After oral absorption, UDCA enters the portal vein and reaches the hepatocytes, where it is conjugated by either glycerin or taurine, and then secreted to hepatic bile ducts.

**Dose**

UDCA 600 mg PO in divided doses after meals

**Indications**

1. Primary biliary cirrhosis

2. Primary sclerosing cholangitis

3. Biliary microlithiasis

4. Intrahepatic cholestasis of pregnancy

5. Familial intrahepatic cholestasis

6. Non-alcoholic steatohepatitis

7. Alcoholic liver disease

**Contraindications**

Hypersensitivity to bile acids.

**Drug Interactions**

As cholestyramine binds with UDCA, concurrent administration of this drug with UDCA is not recommended.

**PROBIOTICS**

**Introduction**

Probiotics is a live microbial food supplement that beneficially affects the host animal by improving its intestinal microbial balance. The microorganisms involved are usually lactobacilli and bifidobacteria. An effective probiotic should:

1. Exert a beneficial effect on the host

2. It should be nonpathogenic and nontoxic

3. It should contain a large number of viable cells and capable of surviving and metabolizing in the gut

**Pharmacological Actions**

Commercial probiotic preparations are usually mixtures of lactobacilli and bifidobacteria although yeasts such as saccharomyces have also been used.

**Indications**

1. Viral diarrhoea

2. Antibiotic-associated diarrhoea

3. Nosocomial diarrhoea

4. Traveller’s diarrhoea

5. Inflammatory bowel disease

6. Functional bowel disease

**Mechanism Probiotic microorganism**

Production of *L. reuteri*

pathogen – inhibitory *L. rhamnosus GG*

substances

Inhibition of pathogen *S. boulardii*

attachment *L. acidophilus*

Inhibition of action of *S. boulardii*

microbial toxins

Stimulation of *S. boulardii*

immunoglobulin A *L. rhamnosus GG*

Tropic effects on *S. boulardii*

intestinal mucosa

**PREBIOTICS**

**Introduction**

Prebiotics have demonstrated an ability to increase the concentrations of friendly gut bacteria. ‘Prebiotics’ refers to short-chain polysaccharides (carbohydrates), not completely digested by the human intestinal tract, that serve as a food supply for the friendly bacteria of the large bowel (bifidobacteria), enhancing their growth and cell division rate.

Prebiotics are defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon.

Prebiotics must be:

1. Neither be hydrolyzed nor absorbed in the upper part of the gastrointestinal tract.

2. Be able as a consequence to alter the colonic microflora towards a more healthier composition.

Fructooligosaccharides are the most commonly used prebiotics and have an energy value of 6 kJ/g; they have no genotoxic, carcinogenic or toxicological effects.

**SYNBIOTICS**

A symbiotic formulation is a mixture of the selected probiotic strains, and prebiotics (fructooligosaccharides). The rationale of this formulation is to exploit a complementary probiotic action and the promotion of bifidobacterial growth due to oligosaccharides.

**Treatment of constipation**

**Bowel Training**

The optimal times to have a bowel movement typically are soon after waking and after meals, when colonic activity is greatest. Patients should be encouraged to attempt defecation first thing in the morning, when the bowel is more active, and 30 min after meals, to take advantage of the gastrocolic reflex.

**Dietary Fibre Intake**

Studies have shown that increased dietary fibre intake leads to decreased colonic transit time and to bulkier stools. The

daily recommended fibre intake is 20–30 g daily such as bran, fruits, vegetables and nuts. Adding fibre to the diet too quickly may cause excessive gas and bloating. Weekly increment in the fibre supplementation prevents bloating and gas formation.

**Fluid Intake**

Fluid intake is the key to treatment. Patients should be advised to drink at least 8 glasses of water daily. Counselling may be required to achieve this goal. Milk and milk products should be minimized if these prove constipating.

**Regular Exercise**

Prolonged bed rest and immobility are often associated with constipation.

**Pharmacotherapy**

Failure to control constipation on a regimen of fibre supplementation and increased water intake should prompt an analysis of patient compliance and a search for other physical causes (e.g., altered colonic transit time, outlet obstruction and psychological causes). These patients need laxative to relieve constipation.

Medications to treat constipation include bulk-forming agents (fibres), emollient stool softeners, rapidly acting lubricants, prokinetics, laxatives, osmotic agents and prosecretory drugs.

Fibre is arguably the best and least expensive medication for long-term treatment. It is important to convey to patients that bulk-forming agents generally do not work rapidly and must be used on a long-term basis.

Rapidly acting lubricants and laxatives like bisacodyl and sodium picosulfate are used for short- to medium-term use in chronic idiopathic constipation. However, their long-term use is limited, because of the risk of habituation or toxicity. Emollient stool softeners are easier to use, but they lose their effectiveness with long-term administration. Polyethylene glycol is simple to use and lest side effect.

Osmotic agents lubiprostone and linaclotide, which stimulate intestinal fluid secretion by acting on the intestinal epithelial chloride channel and the guanylate cyclase receptor, respectively. Lubiprostone and linaclotide are FDA approved for chronic idiopathic constipation and constipation caused by irritable bowel syndrome. Lubiprostone is also approved for opioid-induced constipation in patients with chronic, noncancer pain.

Newer therapies for constipation include prucalopride, a prokinetic selective 5-hydroxytryptamine-4 (5-HT4) receptor antagonist that stimulates colonic motility and decreases transit time.

Renzapride, a mixed 5-HT4 receptor agonist and 5-HT3 receptor antagonist, has been tested to assess its efficacy and safety in the treatment of chronic constipation.

Neurotrophin-3 stimulates the development, growth, and function of the nervous system and has been used to treat functional constipation. Stem cells have been suggested as a means of repopulating dysfunctional neurons.

**Further Reading**

1. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis: enhanced efficacy of proton pump inhibitor therapy for peptic ulcer bleeding in Asia – a post-hoc analysis from the Cochrane Collaboration. *Aliment Pharmacol Ther* 2005;21:1055–61.

2. Chong E, Ensom MH. Pharmacogenetics of the proton pump inhibitors: a systematic review. *Pharmacotherapy* 2003;23:460–71.

**Chapter 61.**

**Nutrition**

INTRODUCTION

Nutritional evaluation and supplementation is extremely important in all gastrointestinal and liver-related disorders. The art and science of nutrition has been evolving over the last two decades. To understand the nutritional needs in different disorders, we first have to have a better under-standing of the normal mechanisms of digestion and absorption of different nutrients.

MACRONUTRIENTS

1. **Proteins**:Proteins are made of chains of amino acids joined by peptide bonds and are considered “building blocks” of human body. There is a constant turn over of proteins in our body at a rate dependent on multiple factors like age, exercise and disease processes. The largest source of proteins resides in the muscles. The major sources of dietary protein are meats, eggs, cereals, legumes, nuts and pulses. Protein is also essential in the production of enzymes and hormones. The daily requirement of protein significantly increases in conditions like burns, sepsis and trauma. There are eight essential amino acids, which can only be obtained from food, while the nonessential amino acids are synthesized in our body and if not consumed in the diet, health will not be impaired.

Protein is degraded into amino acids by the peptides secreted by the stomach, pancreas, and proximal small bowel. Absorption of amino acids occurs throughout the small bowel.

2. **Carbohydrates**: Nutrients that have a formula containing CHO are called carbohydrates. They include simple sugars (glucose, galactose and fructose), disaccharides (sucrose, maltose and lactose), and complex plant starches. They are the main energy source for immediate use in day to day metabolism. In developing countries, it is the major source of energy. Complex carbohydrates have to be broken down by amylase secreted by saliva and the pancreas, and the brush border disaccharides into monosaccharides before they can be absorbed by the small intestines. Once absorbed, glucose is highly regulated by pancreatic hormones and liver.

3. **Lipids**:Lipids (fats) provide most of the energy due to their high caloric density and are the energy reservoirs in our body, accounting for 15–25% of our body weight depending upon body type. Most of the fat is stored in the subcutaneous tissue and surrounding body organs. The main dietary sources of lipids are animal fat and vegetable oils. Lipids are present in the form of triglycerides, fatty acids, cholesterol and phospholipids.

Fats require pancreatic lipase and bile acids for it to break down into monoglycerides and fatty acids to form hydrophilic micelles before they are transported through the intestinal mucosa to the liver by the portal venous system. Besides providing insulation to the body, fats are also essential for hormone production, absorption of fat soluble vitamins, and cell membrane integrity. Fat can be mobilized for energy during starvation or stressful medical conditions requiring significant daily energy needs.

Micronutrients

Vitamins (organic) and minerals (inorganic) make up the micronutrients essential in small quantities for different metabolic activities in our bodies and its deficiency can result in complex clinical syndromes. There are 2 kinds of vitamins – fat soluble (A, D, E, K) and water soluble (B complex, C). RDA (recommended dietary allowance) is defined as average daily intake level that is sufficient to meet the nutrient requirement of all healthy individuals. It is important to note that the RDA may not be adequate in different diseases and also depends on the dietary habits of different parts of the world. Age and sex also impacts the RDA.

Nutritional Assessesment

A person’s body reflects life time nutrient and energy balance. Maintaining optimal health requires maintenance of adequate tissue levels of essential nutrients and source of energy. Poor oral intake, poor absorption of nutrients and multiple medical conditions leads to malnutrition. Early detection and intervention of malnutrition can significantly improve the over all morbidity and mortality. Over the years, multiple nutritional assessment tools have evolved each one with its own pros and cons. A detailed diet history is very crucial and compliments different nutritional assessment measures.

Risk Factors for Nutritional Deficiencies

There are numerous risk factors for poor nutritional status,

including major trauma, burns, sepsis, substance abuse, recent weight loss and many gastrointestinal disorders. Additional information learned through a careful medical history can also suggest possible risk factors for malnutrition. The factors listed below may place a patient at risk for developing, or may denote the presence of, nutrient deficiencies.

n Age < 18 yrs or >65 yrs (increased risk age >75 yrs)

n Recent significant, unintentional weight loss: > 5% in 1 month or >10% in 6 months

n Weight loss calculated as follows:

**Percent weight loss = (UBW-CBW)/UBW**

Where: UBW = usual body weight, CBW =current body weight

n Excessive alcohol intake, other substance abuse

n Homelessness, limited access to food

n Limited capacity for oral intake (dysphagia, odynophagia, stomatitis, mucositis)

n NPO > 3 days

n Increased metabolic demands: extensive burns, major surgery, trauma, fever, infection, draining, abscesses, wounds, fistulae, pregnancy.

n Protracted nutrient losses: Malabsorption syndromes, short gut syndrome, draining abscesses, wounds, fistulae, effusions, renal dialysis.

n Intake of catabolic drugs: corticosteroids, immuno-suppressants.

n Protracted emesis: Anorexia nervosa, bulimia, hyperemesis gravidarum, radiation, cancer chemotherapy.

n Chronic disease (especially AIDS, diabetes, cystic fibrosis, stroke, cancer).

Diet History

A detailed diet history provides insight into a patient’s baseline nutritional status and may detect subclinical nutrient deficiencies or toxicities. Assessment includes questions regarding chewing or swallowing problems, avoidance of eating related to abdominal pain, changes in appetite, taste, or intake, as well as use of a special diet or nutritional supplements. Twenty-four hour caloric count is very helpful in hospitalized patients.

Medical History

A review of past medical history includes identifying existence of conditions resulting in increased metabolic needs, altered gastrointestinal function and absorptive capacity, chronic disease states, organ failure and levels of physical activity. A review of current medications may further elucidate at-risk nutrient status.

Physical Examination

Physical examination should focus on assessment of muscle mass and strength, evidence for chronic liver disease and signs of vitamin or mineral deficiency. With the improvement in overall nutrition of the Indian population, it is uncommon, though not rare, to find patients with classical manifestations of far-advanced vitamin or mineral deficiencies although short term; acute vitamin deficiencies are more common than appreciated.

***The following are the most widely used Nutritional assessment tools***

1. **Anthropometry**:It is the science of estimating body composition based on measurements of weight, stature, height, body circumference and subcutaneous fat thicknesses. It is one of the oldest and well studied modes of evaluating for malnutrition.

n Height and weight: In a stable state, body weight and height is an indirect marker of protein mass and energy stores. While many variables impact the weight of a patient (oedema, ascites tumor mass, etc), it is still the simplest way to detect malnutrition. For hospitalized patients, daily weight is strongly recommended, to be taken with minimal variables like time of the day, clothing and oral or IV intake. Height and weight of a person also is used to calculate other anthropometric indices.

n BMI (Body Mass Index): The use of BMI measured by Wt.(kg)/Ht.(m)2 is now a well accepted measure of protein energy malnutrition and obesity. It is widely used for studying different body types and the impact on intervention. It also has some limitations in acutely ill patients who are hospitalized and have fluctuating weights.

n Skin fold thicknesses: Body composition can be assessed by measuring skin fold thickness measured at multiple sites (triceps, bicep, subscapular). This will estimate submucosal fat reserve. Although it is more sensitive than BMI, it does require a measuring tool and there is a learning curve associated with the accurate and reproducible measurement. The triceps is the preferred area for this measurement.

n Mid arm circumference (MRC): Along with skin fold measurement, MRC can be used to estimate the amount of muscle and fat with in the body. Again, it has wide range of normal values and varies with different ethnic groups. Nevertheless, in the same individual, serial measurements can be very helpful in assessing the impact of nutritional supplementation.

n Bioelectrical impedance analysis (BIA): This is an easy-to-use non-invasive and reproducible technique to evaluate changes in body composition. It depends on the principle that lean tissue conducts electricity much better than fat. It requires a commercially available machine and a trained personal. It has been shown to detect malnutrition much earlier than other measures, especially in oncology patients.

2. **Biochemical measures**: This involves the measurement of circulating various proteins secreted by the liver. In a thermodynamically stable state and in absence of any inflammatory processes, these are very sensitive indicators of protein energy malnutrition.

n Albumin: Albumin is a very non specific indicator of protein stores and can be abnormal in many other conditions. It has a longer half life (20 days) and thus not a good assessment tool for hospitalized patients.

n Pre-albumin.: It has much shorter half life (2 days) and thus is more sensitive in predicting protein calorie malnutrition in acutely ill patients. It also has many variables that impact its serum levels.

n Retinol-binding protein: A rarely used protein measure, it has a half life of 0.5 day. It is may be useful in measuring the daily impact of aggressive nutritional intervention in intensive care unit patients.

n Transferrin: It is the main iron storage protein and a good indicator of total body protein stores. It is a better indicator than albumin.

n Nitrogen balance: By measuring the urinary creatinine, nitrogen balance can be measured by calculating the difference between the intake and output of nitrogen. This helps determine the protein and caloric needs of hospitalized patients who have very high energy needs due to acute insult like burns, trauma and severe sepsis.

n Immunological test: Malnutrition may depress the immune system and cause delayed hypertensive reaction to antigen abstracts like mumps and candida. Lymphocyte count in the blood is also decreased with malnutrition.

3. **Patient Generated Subjective Global Assessment (PG-SGA)**:PG-SGA is more recent assessment tool, which involves a scoring system that relies on 4 features. Overall, the patients are ranked into 3 categories - (a) Well nourished. (b) Moderately malnourished. (c) Severely malnourished. This has been used very successfully in Oncology and HIV population. Besides being a very simple patient generated measure, controlled studies have shown the results to be sensitive and reproducible. It does not require any equipment or technical expertise. Unfortunately, since it is patient generated measure, the level of literacy of the patient population could

be a limiting factor in certain parts of developing coun-

tries, especially in the rural areas of India.

Nutritional Management of Gastrointestinal (GI) Disorders

Nutritional challenges in various GI disorders vary depending on what part of the digestive tract is affected by the disease process. The best way to understand these challenges is to systemically discuss disorders of each part of the digestive tract.

oEsophagus

Dysphagia/Odynophagia

Difficulty (dysphagia) or pain (odynophagia) in swallowing could be caused by mechanical, physiologic or infectious disorder of the swallowing process. There are three phases of swallowing – oral phase, pharyngeal phase and oesophageal phase. Defect in any of these phases can cause serious nutritional deficiencies as well as risk of aspiration and pneumonias. The most common causes of dysphagia include infectious, mechanical or motility disorders. Some of the causes of the dysphagia and odynophagia can be easily treated with appropriate antibiotics for infections or by endoscopic interventions like dilatation of benign strictures or radiation treatment and/or oesophageal stents for malignant strictures.

The role of the speech therapist for oropharyngeal dysphagia is very crucial. The dietary recommendations will depend on the ability of the patient to swallow certain consistencies of foods. Usually thick, soft and pureed foods are safer to prevent aspiration. Nasogastric tubes can be used for feeding in patients with short-term dysphagia.

With the advances in enteral feedings, placement of a percutaneaous endoscopic gastrostomy (PEG) tube can easily fulfill the nutritional needs of most of the patients with dysphagia. PEG is a very simple, safe and easy procedure that should be considered early in most of the patients with dysphagia who is likely not to eat adequate calories for more than 2 weeks. In patients with complete esophageal obstruction, surgical or radiological placement of gastrostomy tube can be considered.

Jejunostomy tube placed surgically or by an interventional radiologist may be necessary in patients with gastroparesis or previous gastric resection. Most of the commercially available tube feedings contain adequate amounts of macro and micronutrients, if the patient receives a liter to a liter and a half of feeding. In patients who cannot afford expensive tube feedings, pureed foods can be given through the PEG/PEJ tubes under the supervision of a dietitian. It is important to make sure that the patient not only gets adequate calories,

but also fluids. In case of a tube feeding, clear water flushes can be given in between the bolus feedings.

Stomach

Dyspepsia

Dyspepsia or indigestion includes a combination of multiple symptoms like burning, bloating in the stomach, heart burn, nausea, burping, vomiting, early satiety and post prandial fullness.

The aetiology of dyspepsia includes systemic, psycho-logical and local gastric disorders.

Nutritional intervention for dyspepsia can be frustrating. Some of the interventions include:

1. Well cooked foods with limited use of seasonings.

2. Evaluate for any food allergies.

3. Review the medications since some of them could contribute to the symptoms.

4. Low fat high fiber diet may help patients with delayed gastric empting.

5. Try antacids, H2 blockers or proton pump inhibitors (PPIs).

6. Avoid non-steroidal anti-inflammatory drugs (NSAIDs).

Gastritis and Peptic Ulcer Diseases

Most common causes of inflammation of the gastric mucosa (gastritis) could be from bacteria (*Helicobacter pylori*), autoimmune gastritis (pernicious anemia), erosive gastritis (NSAIDS or alcohol) and atrophic gastritis. Nutritional interventions include:

1. Omit foods that cause gastric irritation, i.e., fatty and spicy foods.

2. Avoid NSAIDS, alcohol and caffeine.

3. Treat the primary condition.

4. Discuss the replacement of calcium, vitamin B12 and folate.

5. Evaluate the side effects of medications.

6. Careful handling and cooking of foods is very crucial to avoid super infections.

7. Milk and other daily products may increase the symptoms.

Gastroparesis

The most common symptoms of gastroparesis are abdomen pain and fullness, nausea and emesis, heartburn and weight loss. The causes include diabetes, hypothyroidism, autonomic neuropathies, parkinsonism, scleroderma, vascular insufficiencies and gastric surgeries.

The nutritional management that has been proven to be effective includes:

1. Decrease volume of meals.

2. Strict diet in diabetics to assure good blood sugar control.

3. Low fat, low residue diet.

4. Correct dehydration or any electrolyte imbalance with oral intake.

5. Multiple frequent meals.

6. Remove and prevent gastric bezoars.

7. Jejunostomy tube feeding should be considered in severely malnourished patients.

8. Stay upright during the meals.

9. Ginger products can help nausea.

10. Cuminum cyminum is an Ayurvedic product widely used in India for many upper gastrointestinal symptoms.

Small intestines

Celiac Disease

Celiac disease is a common, yet most under diagnosed autoimmune disease. Once diagnosed, diet plays the key role in the treatment of this condition. A diet free of gluten (wheat, barley, rye and oats) can completely reverse the small bowel pathology, and resolve all the signs and symptoms of Celiac disease. The challenge is educating the patient to follow a strict diet. Wheat being the staple part of the Indian diet, many patients find it difficult to avoid it for rest of their lives. Regular nutritional counseling is helpful in keeping patients compliant with their diet.

There currently are “gluten-free foods” available in some urban grocery stores. Replacement of nutrients like iron, folate, calcium and vitamin D may be necessary in severe cases until the small bowel regenerates on the gluten free diet. Oats have been found to be safe in mild cases of Celiac disease and can be incorporated into a vegetarian diet as a good source of protein. Secondary lactose intolerance is not uncommon in acute cases of celiac disease and thus dairy should be avoided.

Malabsorption Syndrome

Fat malabsorption can occur with diseases affecting the pancreas or small bowel mucosa. The etiologies could be auto immune or infectious. Major nutrition challenges include providing adequate calories, fat and fat-soluble vitamins. Besides treating the underlying condition, predigested tube feeding formulas and even parenteral nutrition may be necessary to stabilize the patient. Medium-chain triglycerides (MCT) have been used as a good source of fat that may alleviate steatorrhea. Vegetable proteins, complex carbohydrates and limited fat intake may help maintain nutritional needs in these patients. Limit dietary oxalate containing foods to prevent renal stones. Recently some data suggests benefit of probiotics and thus use of curds and buttermilk should be encouraged. Fat-soluble vitamins should be supplemented orally or parenteraly to avoid serious irreversibly complications.

Colon

Colitis (infectious or inflammatory) can cause severe dehydration and electrolyte imbalance. Main goals for the treatment include:

1. Aggressive oral rehydration with electrolyte and glucose containing solution that is easily available. UNICEF/WHO recommends oral rehydration solution containing sodium chloride – 3.5 g, sodium bicarbonate - 2.5 g, potassium chloride – 1.5 g and 20 g of glucose mixed with 1 liter of water. Intravenous therapy may be needed in the presence of vomiting.

2. Low fibre diet in presence of severe diarrhoea. Avoid nuts legumes and whole grains.

3. Low fat, high carbohydrate diet to achieve 30–35 kcal/kg.

4. Vitamin and mineral supplementation – mainly thiamin, folic acid,vitamin B12, vitamin E zinc, calcium, vitamin D and iron.

Gallbladder

Gallstones

Individuals with gallstones typically present with symptoms of abdominal pain after eating high fat foods or bloating, gas and/or indigestion with meals. A diet recall to evaluate for symptoms with consumption of high fat foods or a history of resuming oral intake after receiving total parenteral nutrition (TPN) should be completed. Long-term use of TPN is a risk factor for the development if gallstones.

Nutrition intervention may help control symptoms until gallstones or gallbladder can be removed. The following interventions may help decrease gallbladder contraction and control symptoms:

1. A low fat diet with <30% energy from fat.

2. Moderate amount of protein from low fat sources.

3. Small, frequent meals may help improve intake.

4. Weight loss may help prevent formation of gallstones.

Pancreas

Pancreatitis

Nutrition intervention for pancreatitis depends on the severity of the disease. Individuals with moderate-to-severe pancreatitis may be hypermetabolic and demonstrate insulin resistance with increased gluconeogenesis and lipolysis. In the past, the recommendation for those with pancreatitis was to make them NPO to rest the pancreas. Newer research has shown the benefit of enteral nutrition support compared with NPO status or parenteral nutrition for those with severe pancreatitis.

Interventions should be tailored to the severity of pancreatitis, as determined by APACHE or Ranson’s criteria, as follows.

Mild-to-moderate Pancreatitis

1. NPO with progression to oral diet as symptoms improve & amylase & lipase trend down.

2. Intravenous fluids.

3. A low fat diet may or may not help, but can be tried if patient experiences steatorrhea and/or abdominal pain to see if help with symptoms.

4. Pancreatic enzyme replacement may be needed for individuals with chronic pancreatitis.

5. If patient has history of alcohol abuse, supplement with Thiamin (100 mg/d), folate (1 mg/d), and a multivitamin. If fat malabsorption present, may also need supplementation with fat-soluble vitamins.

6. Pancreatic enzymes may help if patient has steathorrhea.

7. If patient fails oral nutrition & has been NPO for more than 7 days, may need to consider alternate form of nutrition.

Severe Pancreatitis

1. Initiate enteral nutrition within 24–48 hrs if expect patient to not be able to tolerate oral feedings within 5–7 days. Feed into jejunum at a continuous rate.

2. Try a polymeric formula first. If not tolerated, try a hydrolyzed formula.

3. Parenteral nutrition not indicated unless patient fails enteral nutrition and the patient has not received any nutrition for more than 5–7 days.

In all cases of pancreatitis, patients should be counseled to abstain from alcohol.

Liver

Hepatitis

Generally, individuals with hepatitis will be able to eat a regular diet. They may experience anorexia, early satiety and fatigue, which may make it difficult to eat. These individuals may need to be evaluated to avoid malnutrition from suboptimal intake of calories, protein and micro-nutrients. Patients may benefit from oral, liquid nutritional supplements. In severe, acute cases or chronic cases with progression to cirrhosis, some may require enteral or parenteral nutrition. Individuals with chronic hepatitis that progresses to cirrhosis may need diet restrictions to control symptoms. These restrictions will follow in the next section on cirrhosis. Individuals with a history of alcohol abuse that develop hepatitis may already be malnourished. They may need more aggressive oral, liquid supplements or enteral or parenteral support. These individuals may need

Thiamin (100 mgs/d), folate (1mg/d) and multivitamin supplements.

Cirrhosis

Assessing nutritional status in patients with cirrhosis can be complicated. Weight may be hard to assess with ascites, as weight gained from ascites may mask loss of muscle mass and adipose tissue. In addition, visceral proteins, which are

generally not good indicators of nutritional status, become even less reliable when synthesis is decreased due to altered liver function. The following may be helpful to identify individuals at nutritional risk:

1. Physical assessment for signs of loss of muscle mass – look for signs of muscle wasting such as squaring of the shoulders and temporal wasting.

2. Assess body composition using one of the methods described in the previous section on assessment and anthropometry.

3. Diet history for signs of inadequate intake due to anorexia, early satiety from ascites, nausea, vomiting or bowel changes.

4. Signs and symptoms of vitamin and mineral deficiency **(Table. 61.1)**.

In addition to adequate calories and protein, patients with cirrhosis may require restriction of some nutrients to help manage complications from cirrhosis.

The following may need to be considered:

1. Sodium restriction of 2000 mg/day to help reduce fluid accumulation.

2. 4–6 meals/day with liquid nutritional supplements as necessary to help meet calorie and protein needs.

3. Supplementation of vitamins and minerals if deficiency symptoms present.

4. Fat restriction of < 30% of calories if steatorrhea present. In these patients, supplementation with medium-chain triglycerides (MCT oil) may help provide calories that are more easily absorbed. Generally, start with 1 tablespoon per day mixed in salad dressings or other foods, and work up to 3 tablespoons per day as tolerated. MCT oil can also be added to enteral feedings in patients that require this method of nutritional support.

5. Patients with hyponatremia (serum sodium < 128 mEq/L) may require a fluid restriction. Usually, a restriction of 1200–1500 mL/day fluid is recommended. If serum sodium is < 125 mEq/L, a restriction of 1000–1200 mL/d may be needed. Individuals should be instructed to avoid liquids with a high sodium content & encourage to drink liquids with a high nutritional value that provide calories & protein, such as liquid supplements, milk or soymilk.

6. Patients with difficult to manage ascites may also need a modest fluid restriction.

A word about protein in cirrhosis – There is no evidence to support the use of a protein restriction in patients with cirrhosis. Protein restrictions should be reserved for individuals with refractory encephalopathy that is not responding to medical intervention.

Hepatic Encephalopathy

Protein restriction is not indicated in hepatic encephalopathy except in severe acute decompensated liver condition. Daily and vegetable proteins are better tolerated and should be given at 0.8–1 g/kg of body weight. Replacing vitamins and electrolytes is also essential. Branched chain amino acids (leucine, isoleucine and valine) containing oral and parenteral solution have been used in chronic encephalopathy but recent literature questions their benefit. Adequate energy is necessary to prevent further catabolism. Carbohydrates are recommended as a primary source of energy in chronic encephalopathy. Salt and fluid restriction may be necessary to prevent anasarca.

Nutrition in gastrointestinal cancer

Oncologic nutrition is extremely complex and beyond the scope of this book. Nevertheless, we will discuss the salient features:

1. Nutritional needs depend on the type of the cancer. Gastric and pancreatic cancers are more challenging than other cancers.

2. Early detection and aggressive intervention is the key to maintaining optimal nutritional status in these patients.

3. PG-SGA (Patient Generated Subjective Global Assessment) and BIA (Bioelectric Impedance Analysis) have been found to be very sensitive nutritional assessment tools in detecting early malnutrition in cancer patients.

4. Early recognition and management of the side effects of the cancer therapy (loss of taste/appetite, nausea, vomiting, diarrhoea and pain) may improve the nutritional status.

5. Placement of enteral feeding (naso-gastric, naso-jejunal, gastrostomy or jejunostomy) tubes in patients with oesophageal, gastric and pancreatic cancer patients help them fulfill their caloric and fluid needs.

6. Perioperative nutritional intervention in moderately to severely malnourished patients with either immuno-nutritents (omega-3 fatty acids, arginine, glutamine and dietary nucleotides-RNA) or parenteral nutrition for even 10 days before major GI cancer surgery has been shown to reduce morbidity and mortality.

7. Herbal and dietary supplements are widely used in cancer patients to help with side effects of the therapy and may have some anti neoplastic properties. Some of the most widely used supplements include cloves, flaxseed oil, turmeric, saffron, green tea, curcumins, bay leaves, ginger, fennel, pomegranate, garlic, ginseng, kava, licorice, milk thistle, noni juice, etc. Ayurvadic and homeopathic products are also widely prescribed in India and are getting more popularity in the western world. Such alternative therapies should be used with caution to prevent any harmful side effects.

8. Antioxidants are also widely used in cancer patients. Vitamin C, selenium, beta-carotene, vitamin E, zinc and coenzyme Q-10 are most studied antioxidants. Benefit of these products is still controversial.

The nutritional goals many times are to improve quality of life and reduce metabolic and septic complications. The role of a dietitian is very crucial in managing these patients. New standards for nutritional interventions continue to be established to better serve these patients.

Conclusion

The impact of malnutrition in different GI diseases is serious and with recent advances, is now much better understood.

Early detection of malnutrition is important in all patients. Ideally, every hospital should have a nutrition and metabolic support team to manage complex nutritional needs. Early nutritional intervention has been shown to

reduce morbidity, mortality, and duration of hospital stay with a positive impact on overall health care cost. Whenever possible, enteral feeding should be implemented early in malnourished patients. Parenteral Nutrition, though

expensive, is beneficial in acutely ill patients who have a non-functioning GI tract.

Physician leadership in managing nutritional needs of their patients can be improved by implementing nutrition support as a part of Medical school curriculum. We have

seen a lot of progress in this field over the last two decades and will continue to evolve over the years to come. More research needs to be done to determine if nutrition support can actually modify the outcome of various gastrointestinal diseases.

**Chapter 62.**

**Gastrointestinal Procedures**

**Vishal Ghevariya**, MD, Consultant Gastroenterologist, Eden Medical Center, USA

**Sedation and Analgesia for Gastrointestinal Procedures**

Sedation is a drug-induced depression in the level of consciousness. The goals of inducing sedation for an invasive procedure are relief of patient anxiety, discomfort, diminishes memory of the procedure and improving outcome of the procedure **(Table 62.1)**.

**Pre-procedural Assessment**

1. Pertinent history taking, allergies and current medication list to drug interaction and physical examination.

2. Oral airway assessment including history of snoring, sleep apnea, stridor.

3. Patients should fast for 2 hrs after consuming clear liquids and 6 hrs after consuming solid foods. Impaired gastric emptying may require longer fasting.

4. American Society of Anesthesiologists (ASA) classification can be used to risk stratify patients for endoscopy. Patients with a higher score on this classification may benefit from using an anaesthesia provider during a procedure.

5. Mallampati classification can be used to identify potential obstructive airway and difficult endotracheal intubation. Patients with a higher score on this classification may benefit from using an anaesthesia provider during a procedure **(Tables 62.2 & 62.3)**.

**Intra-procedural Patient Monitoring**

1. Patients should be monitored during sedation to detect variations in pulse, blood pressure and respiration rate and oxygen saturation.

2. The use of exhaled carbon dioxide monitoring (capnography) predicts insufficient ventilation much earlier than drop in oxygen saturation and therefore its use is encouraged.

3. The assessment of patient’s level of consciousness and vitals should be monitored before initiating sedation, every 5 min during the procedure, during recovery and just before discharge.

**Sedation Administration**

Mild and moderate conscious sedation typically utilizes a short acting opioid for pain control and short acting benzodiazepine to minimize anxiety and slight amnestic effect. The most common agents used are Midazolam or Diazepam (Benzodiazepines) and Fentanyl or Meperidine (Opiates). Due to their short acting properties and better safety profile, most endoscopist use a combination of Midazolam and Fentanyl. A typical starting dose for moderate sedation is Midazolam 2 mg IV and Fentanyl 50 Micrograms IV and depending upon the length of the procedure and need for sedation, it is repeated at Midazolam 1 mg IV and Fentanyl 25 micrograms IV every 2–3 min. Repeated administration of these agents in shorter period should be avoided as they accumulate in adipose tissue first and are released later resulting in prolonged sedation effect. Patients with significant alcohol use may benefit from administration of 25–50 mg of intravenous Diphenhydramine for added effect of sedation. Antagonists of opiates (Naloxone) and benzodiazepine (Flumazenil) should be readily available for reversal during the procedure. Clinical effects of these antagonists are typically shorter than the effects of opiates and benzodiazepines and therefore patients should be monitored longer if reversal is used.

Monitored anaesthesia care (MAC) utilizes a dedicated anesthesia provider who typically administers Propofol in small boluses to achieve sedation for GI endoscopies. The use of MAC results in reduced distraction for the endoscopist, better patient satisfaction and allows longer procedure to be performed without the risk of prolonged sedation with higher doses of benzodiazepine-opiate combination.

**Upper endoscopy**

**Introduction**

Upper GI endoscopy, also called EGD (esophago gastro duodenoscopy), is a visual examination of the mucosal surfaces of the oesophagus, stomach and proximal duodenum using a lighted, flexible fibreoptic or video endoscope.

**Endoscope Instrument**

Endoscope instruments are of two types. The original fibre optic instrument has a flexible bundle of glass fibres that collect the lighted image at one end and transfer the image to the eyepiece. The newer video endoscopes have a tiny, optically sensitive computer chip at the end. Electronic signals are then transmitted up the scope to the computer, which then displays the image on a large video screen.

Upper endoscope is available in 8.7 mm and 9.4 mm outer diameter. An open channel in these scopes (2.2–2.8 mm in diameter) allows the passage of accessories like biopsy forceps, cytology brushes, sclerotherapy needles, diathermy snare, etc. Channel size depends on the outer diameter. Therapeutic scopes with larger outer diameter have large channels (up to 6 mm wide), which allow better suction and larger accessories. Dual channel endoscopes are also available allowing multiple accessories to be used at the same time. An ultra slim video gastroscope is available with 5.4 mm outer diameter and 140 degrees field of view allowing for unsedated trans nasal EGD as well as safe passage through oesophageal strictures.

**Procedure**

Upper GI endoscopy is usually performed on an outpatient basis. The throat is rinsed with Lidocaine or Benzocaine Gel or Spray for numbing effect. For some individuals who can relax on their own and whose gagging can be controlled, the exam is done without intravenous medications. The patient is positioned left lateral with head end of bed elevated at about 30 degrees. A plastic mouthpiece (also known as bite block)

is often used to minimize the risk of injury to the scope from patient’s teeth.

Once the gastroscope is inserted into the oral cavity, visualization of the tongue is kept at 12 o’clock and the scope is advanced further. At about 5–7 cm, posterior pharynx and epiglottis along with the vocal cord is typically visualized. The scope is then turned at 5 o’clock and posterior to align its tip with the cricopharyngeus. Once advanced further, the scope enters the proximal oesophagus. Care should be taken during this maneuver and blind push should be avoided as cricopharyngeal diverticulum (Zenker’s diverticulum) can be present and blind push can result in intubation of the diverticulum and potentially, its perforation.

*There are several landmarks from incisor teeth in EGD*

1. 15 cm - Cricopharyngeal constrictor (upper oesophageal sphincter)

2. 25 cm - Aortic/bronchial impression

3. 40 cm - Diaphragmatic hiatus (squamo-columnar junction or oesophago-gastric junction)

While in the gastric lumen the tip of the scope is turned 180 degrees to visualize the cardia, fundus of the stomach (retroflexion maneuver). The initiation of this maneuver also visualized the incisura angularis (body-antrum junction along the lesser curve). The scope is then advanced to duodenal bulb, duodenal sweep and the second portion.

Accessories that can be passed through the endoscope channel to perform additional procedures, if necessary. For example, a biopsy can be done in which a small tissue specimen is sent for histopathological examination. A polyp or tumor can be removed using a thin wire snare and electrocautery (electrical heat). Other therapeutic procedures can be performed like control of upper gastrointestinal haemorrhage, dilating the stricture of oesophagus and pylorus, deployment of metallic stent to palliate dysphagia in patients with inoperable oesophageal tumour, etc. The examination takes from 10 to 20 min, after which the patient is taken to the recovery area. There is no pain with the procedure and patients seldom remember much about it.

**Indications**

***Diagnostic***

1. Unexplained upper abdominal pain

2. Persistent vomiting

3. Dysphagia

4. Evaluation of severity of gastroesophageal reflux disease

5. Suspecting acid peptic disease or upper gastrointestinal malignancy

6. Dyspepsia (upper endoscopy is indicated in patients with age more than 45 years or dyspepsia with alarming symptoms like anorexia, weight loss or anaemia)

7. Familial adenomatous polyposis syndromes

8. In patients with suspected portal hypertension to document or treat oesophageal and gastric varices

9. To assess the extent of injury following corrosive ingestion

10. Chronic acid reflux-evaluation for metaplasia/dysplasia of esophageal mucosa (Barrett’s esophagus)

**Therapeutic**

1. Control of upper gastrointestinal bleeding (variceal and non-variceal bleeding)

2. Balloon dilatation of oesophageal stricture, pyloric stricture and achalasia cardia

3. Bougie dilation of benign oesophageal stricture

4. Foreign body removal

5. Deployment of metallic stents to palliate dysphagia in patients with inoperable oesophageal malignancy

6. Placement of nasojejunal tube

7. Placement of percutaneous endoscopic gastrostomy (PEG)

8. Endoscopic mucosal resection (EMR) for early oesophageal and gastric cancer

**Complications of Upper Endoscopy**

***Complications in general***

n Diagnostic upper endoscopy 0.2%

n Oesophageal dilatation 0.5%

n Endoscopic sclerotherapy 8.0%

***Perforation***

n Diagnostic upper endoscopy 0.4%

n Oesophageal dilatation 8–10%

n Endoscopic sclerotherapy 20–30%

***Bacteremia***

n Diagnostic upper endoscopy 4%

n Oesophageal dilatation 45%

n Endoscopic sclerotherapy 18%

**Antibiotic Prophylaxis**

Life-threatening complication like bacterial endocarditis (BE) is possible in high risk with cardiac pathology following procedure related bacteremia. Procedure-related bacteremia is high with therapeutic procedure. High-risk patients need antibiotic prophylaxis to prevent bacterial endocarditis.

***High-risk Patients for BE (need antibiotic prophylaxis)***

1. Prosthetic heart valves

2. Past history of BE

3. Surgically constructed systemic pulmonary shunt

4. Vascular synthetic graft of less than 1 year

***Intermediate Risk (role of antibiotic prophylaxis is debatable)***

1. Valvular dysfunction

2. MVP with MR

3. Congenital heart disease

4. HOCM

***Low Risk (antibiotic prophylaxis is not needed)***

1. Coronary artery bypass graft

2. Pacemaker

3. Past history of rheumatic fever

4. Implantable cardioverter defibrillator (ICD)

***Prophylactic Antibiotic Regime***

*For high-risk Patients*

1. Ampicillin 2.0 g IM or IV + Gentamicin 1.5 mg/kg 30 min before procedure followed by Ampicillin 1 g IM or IV 6 hrs later.

2. Patients allergic to penicillin: Vancomycin 1.0 g IV over 1–2 hrs; infusion should be completed within 30 min of starting procedure.

*For moderate-risk Patients*

1. Ampicillin 2.0 g IM or IV 30 min before procedure or Amoxicillin 2.0 g orally 30 min before procedure.

2. Clindamycin 600 mg PO or IV 30 min before procedure.

3. Cephalexin 2.0 g PO 1 hr before procedure.

4. Vancomycin 1.0 g IV over 1–2 hrs; infusion should be completed within 30 min of starting procedure.

For all kinds of patients, antibiotics are required before PEG placement. Antibiotics are not needed for prosthetic joints.

***Procedures with High Risk of Bacteremia***

1. Oesophageal sclerotherapy

2. Oesophageal or colonic balloon dilatation

3. Therapeutic ERCP

***Procedures with Low Risk of Bacteremia***

All diagnostic endoscopies with or without biopsy.

**Sigmoidoscopy and colonoscopy**

**Introduction**

Flexible sigmoidoscopy is used to examine the rectum, sigmoid, and a variable length of descending colon using flexible instrument. Colonoscopy allows examination of the entire colon and frequently, the terminal ileum.

**Indications of Flexible Sigmoidoscopy**

1. Evaluation of fresh bleeding per rectum.

2. Persistent or recurrent left iliac fossa pain.

3. Evaluation of suspected distal colonic disease when there is no indication for colonoscopy.

4. Evaluation for anastomotic recurrence in rectosigmoid carcinoma.

**Indications of Colonoscopy With or Without Ileoscopy**

***Diagnostic***

1. Unexplained gastrointestinal bleeding and anaemia.

2. Inflammatory bowel disease – to evaluate the nature and the extent of the disease.

3. Patients with colorectal cancer to evaluate synchronous lesion.

4. Screening and surveillance for colorectal cancer (age >45, family history).

5. Chronic diarrhoea of unknown origin (for random colon biopsies for microscopic colitis).

**Therapeutic**

1. Colonoscopic hemostasis of bleeding vascular lesion, tumour, ulcer or polypectomy site

2. Excision of polyp

3. Foreign body removal

4. Colonoscopic decompression of acute colonic pseudo-obstruction or sigmoid colon volvulus

5. Balloon dilatation of colonic stricture

6. Palliative treatment of stenotic neoplasm

**Contraindications of Colonoscopy**

***Absolute***

1. Acute diverticulitis

2. Suspected peritonitis/perforation

3. Toxic megacolon

***Relative***

1. Myocardial infarction 3 weeks prior to the procedure

2. Severe pulmonary oedema

3. Exacerbation of obstructive airway disease

***Colonoscopy with Extreme Care***

1. Acute and severe inflammatory process like ulcerative colitis, Crohn’s disease or ischemic colitis. Rectal retroflexion should be avoided if any inflammation is present in the rectum.

2. Chronic stage of irradiation colitis

3. Large, deep ulceration seen in the colon

All above mentioned conditions increase the risk of perforation.

**Patient Preparation**

Limited preparation is often adequate for flexible sigmoidoscopy. Patient should be prepared by giving enema 20–30 min before the procedure. Colonoscopy requires full preparation for better visualization of proximal colon and distal ileum. Failure of bowel preparation occurs in elderly patients, patients with chronic constipation and patients with diverticular disease. Patients should avoid high residual food 24 hrs before colonoscopy. Patients with constipation should be primed with laxative one night prior to the test.

There are two types of oral lavage available for complete colonic preparation:

1. Polyethylene glycol solution (PEG)

2. Sodium phosphate (Fleet’s phosphosoda) - Avoid in elderly, chronic kidney disease patients.

***Pre-procedure Sedation***

Sedation is often administered in patients before procedure. Ideal sedation should be short acting with strong analgesic effects without cardiopulmonary depression.

Intravenous antispasmodic in the form of either hyoscine N-butyl bromide or glucagon produces short-term colonic relaxation. Hyoscine has ocular side effects like precipitating glaucoma, but glucagon, although costlier than hyoscine, has no side effects. Dilute Simethicone is instilled through biopsy channel of the colonoscope to reduce fog and air bubbles with in the colonic lumen.

**Instruments and Methods**

The 70-cm instrument is used for flexible sigmoidoscopy and more than 160 cm instrument for colonoscopy. Outer diameter of the scope is 11.3–12.9 mm, while channel diameter is 3.7 mm.

Usual accessories like biopsy forceps, polypectomy snares, dilating balloons, cytology brushes, etc, can pass through the channel. Colonoscopy is done with air or CO2 insufflations. Details of colonoscopy technique are outside the scope of this book.

Colonoscope tip should reach to the cecum. The cecum is identified by the three taenia coli joining down into the appendix (Mercedes-Benz sign). The ileocecal valve is situated on the medial part encircling the cecum about 5 cm from its pole. Success rate of cecal intubation is more than 97% for skilled endoscopist. Ileoscopy is required in case of unexplained abdominal pain, inflammatory bowel disease

and evaluation of gastrointestinal bleeding and unexplained diarrhoea.

**Complications**

1. Complications related to sedation.

2. Bacteremia – Rate of bacteremia for diagnostic colonoscopy is around 3–4%.

3. Perforation – 0.002–0.02%. Balloon dilation is associated with high risk of perforation (4.6%).

4. Hemorrhage – post polypectomy bleeding is the most common; occurs in around 0.7–2.5% of patients.

**Push enteroscopy**

Push enteroscopy is done using 170–250 cm length enteroscope. Stiff over tube is used to reduce gastric looping and facilitate deep intubation of the proximal small intestine. Once the tip of the enteroscope is in the second part of duodenum, over tube is passed to reduce gastric loop and thereafter, scope is passed into the jejunum with minimal air insufflations. Average duration of the procedure is 30–45 min.

**Sonde enteroscopy**

It is basically a passive fiberoptic bundle without tip deflection or a therapeutic channel.

The length of Sonde enteroscope is 270 cm. A balloon is situated at the tip, which allows the passive propulsion of the instrument into the jejunum and ileum. It takes around 6–8 hours to reach the ileum. Examination of small intestine is done while withdrawing the scope.

**ERCP**

**Introduction**

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive endoscopic procedure to evaluate and manage various pancreaticobiliary diseases. In the era of non-invasive imaging like spiral CT scan, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS), use of ERCP is mainly for therapeutic purpose.

**Indications**

***Biliary Disease***

***Diagnostic***

1. Evaluation of sphincter of Oddi dysfunction -Should be performed at expert centre only.

2. Biliary aspiration for diagnosis of microlithiasis.

3. Cytology brushing of suspected bile duct malignancy.

***Therapeutic***

1. Treating cholangitis or choledocholithiasis by relieving obstruction

2. Removal of common bile duct stones

3. Postoperative or traumatic biliary complications such as bile leak, stricture or fistula

n Palliation of malignant biliary stricture with a stent.

***Pancreatic Disease***

***Diagnostic***

1. Pancreas divisum - EUS can detect pancreas divisum easily and should be used as the test of choice if MRCP is negative.

2. Suspected chronic pancreatitis - EUS can identify changes of chronic pancreatitis with greater sensitivity and specificity and should be the test of choice.

***Therapeutic***

1. Pancreatic endotherapy for chronic pancreatitis

2. Evaluation and treatment of pancreatic trauma

3. Endoscopic pseudocyst drainage, either transpapillary or transgastric

***Contraindications***

1. Absolute

n Acute cardiopulmonary complication

n Suspected perforation or peritonitis

2. Difficult passage of duodenoscope

n Zenker’s diverticulum

n Esophageal diverticulum

n Tight esophageal stricture

**Techniques**

Detailed technique of ERCP is out of the scope of this book. Technique of ERCP is mentioned in brief. Disinfection of the duodenoscope is the most important aspect to prevent infective complications. Patient should be kept nil per orally for at least 6 hrs. Procedure is performed in fluoroscopy room with patient’s position prone. Conscious sedation is given with the help of midazolam with pethidine or fentanyl. Use of propofol and general anaesthesia is often required. Administration of supplemental oxygenation through nasal cannula (around 2–5 L/min) is necessary to prevent desaturation. Prophylactic antibiotic is not always necessary.

Following transoral passage of side-viewing scope (duodenoscope), scope is advanced into the stomach along greater curvature loop. Once the scope reaches the second part of duodenum, the scope is gradually withdrawn and clockwise rotated to make shaft straight along the lesser curvature, and is called “short position.” Most of the time, with the short route, the papilla is usually visualized. The normal papilla varies considerably in size, shape and appearance. It is mostly oval shaped, 10–12 mm long and 8 mm wide. The common channel is around 1–10 mm long. Selective cannulation of the relevant duct is the most difficult part of ERCP. For selective cannulation of bile duct, catheter should aim towards the 11’O clock axis and for pancreatic duct, 1’o clock axis. After selective cannulation, cholangiogram or pancreatogram is obtained.

Following etiological diagnosis, therapeutic ERCP is performed by cutting either biliary or pancreatic sphincter (sphincterotomy). After adequate sphincterotomy, therapeutic endotherapy is performed by using stone extraction balloon, dormia basket, stricture dilator or various endoprothesis (plastic as well as metal).

**Complications of ERCP**

Overall complication rate is 9.8%, severe complications require prolonged hospitalization in 1.6% and mortality rate is 0.4%.

1. ***Post-ERCP pancreatitis***

n Pancreatitis is the most common post-ERCP complication.

n It is defined as new or worsened abdominal pain with elevation of amylase or lipase level more than three times, occurring 24 hours after the procedure that requires at least 2 days of hospitalization.

n Frequency of post-ERCP pancreatitis is around 5.4%.

n Repeated attempt to cannulate bile duct, precut “papillotomy,” repeated pancreatic duct opacification and associated sphincter of Oddi dysfunction are the risk factors for post-ERCP pancreatitis development.

n Pathogenesis of post-ERCP pancreatitis involves papillary oedema, mechanical duct trauma and thermal injury during sphincterotomy.

n Many pharmacological agents like diclofenic sodium, somatostatin, octreotide, gabexate (protease inhibitors), IL-10 (anti-inflammatory activity), glyceryl trinitrate, etc are tried. But none of them show consistent benefit to prevent post-ERCP pancreatitis.

2. ***Haemorrhage***

n Post-ERCP haemorrhage is related to sphincterotomy.

n It is defined as the presence of melena, haematochezia, or haematemesis associated with a haemoglobin decrease of at least 2 g/dL or needs blood transfusion.

n The incidence is around 0.76–2%.

n Coagulopathy and precut papillotomy are the risk factors for haemorrhage.

3.***Perforation***

n Incidence of perforation is 0.3–0.6%.

n It is associated with wide sphincterotomy incision.

n Majority of perforations are managed conservatively.

4.***Cholangitis***

n Incidence of cholangitis is less than 1%.

n Inadequate ductal drainage is the most important cause of cholangitis.

5.***Cholecystitis***

n Incidence of cholecystitis is 0.2–0.5%.

n This complication develops following filling of gallbladder with contrast agent. Role of routine, prophylactic antibiotic is not proven.

**Liver biopsy**

**Indications**

In the era of modern imaging the indications of liver biopsy are narrowed. In view of inherent risk of percutaneous *liver biopsy,* it should be performed only when benefit of liver biopsy outweighs the risks to the patient. With the improvement in molecular and serological diagnosis, liver biopsy in patients with hereditary hemochromatosis, Wilson’s disease, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) is less indicated. Risk of tumour dissemination along the needle tract and hemoperitoneum make role of liver biopsy more controversial in patients with hepatocellular carcinoma (HCC) with underlying cirrhosis liver. Despite all these, liver biopsy plays important role in diagnosis and management of certain situations:

1. Grading and staging of chronic hepatitis B and C infection

2. Unexplained hepatomegaly

3. Unexplained elevation of liver enzyme

4. Infection of the liver like granulomatous hepatitis

5. Copper estimation in the liver biopsy when all the tests are equivocal in patients with suspected Wilson’s disease

6. Grading and staging of non-alcoholic steatohepatitis (definite role of liver biopsy is still controversial)

7. Post-liver transplantation to assess acute rejection, invasive cytomegalovirus infection and in assessing recurrent disease.

**Contraindications**

1. Abnormal coagulation profile

n Prothrombin time is prolonged by 4 sec

n Platelet count below 60,000/mm3

2. Extrahepatic biliary obstruction

n Patients with extrahepatic biliary obstruction develop more complications following liver biopsy like pain, biliary peritonitis, septicaemia and death.

3. Bacterial cholangitis

n It is relative contraindication as it increases the risk of septicemia and peritonitis.

4. The uncooperative patients

5. Ascites: More chances of complications like hemoperitoneum

6. Cystic lesions in the liver

n Suspected echinococcal cyst with the risk of anaphylaxis.

**Methods**

Liver biopsy can be performed by four ways: percutaneous liver biopsy, transvenous, endoscopic ultrasound-guided and by laparoscopy.

1. **Percutaneous liver biopsy**

n Percutaneous liver biopsy can be performed by either transthoracic route or subcostal route.

n It is very much ideal to perform liver biopsy under ultrasonography guidance. In case of blind liver biopsy it is better to have pre-biopsy ultrasonography.

n Transthoracic liver biopsy is performed in the intercostal space in the mid-axillary line just about the costal margin.

n Patients with hepatomegaly, liver biopsy can be performed via subcostal route.

n Complication rates are slightly more with the transthoracic (4.1%) than the subcostal route (2.7%).

n Target area is infiltrated with local anaesthetic, and a small incision is made through the dermis. The biopsy needle is then advanced into the intercostal space. The patient then holds his/her breath in expiration and the procedure is completed.

2. **Transvenous liver biopsy**

n Transvenous liver biopsy (TJLB, transjugular liver biopsy) is indicated in patients with abnormal coagulation profile.

n It can be performed through a transjugular approach (most preferred one) or via a femoral route.

n The right internal jugular vein is cannulated and a sheath inserted via a Seldinger technique.

n A 45-cm long catheter is then guided under fluoroscopic control through the right side of the heart to the inferior vena cava.

n The catheter is then loaded with the transvenous biopsy needle and advanced into the hepatic veins and the position checked by injection of contrast medium. The needle is then advanced rapidly 1–2 cm past the tip of the catheter with the patient holding his/her breath.

n The livertissue is retained in the needle by aspiration on a syringe attached to the other end of the needle.

3. **Laparoscopic liver biopsy**

n Liver biopsy can be preformed during laparoscopic surgery.

4. **Endoscopic ultrasound-guided liver biopsy**

n EUS can readily image left lobes of the liver along the gastric wall and right inferior lobes along the duodenal bulb wall. Fine needle biopsy (FNB) can be performed if a lesion is located in the liver through EUS or general biopsy from the liver is needed.

**Complications of Liver Biopsy**

1. Pain at biopsy site (30%)

2. Vasovagal episodes

3. Significant hemorrhage (0.35–0.5%)

4. Haemobilia (0.05%)

5. Rarely, puncture of other viscera

**Percutaneous biliary decompression**

**Causes of Malignant Biliary Obstructions**

1. Carcinoma gallbladder

2. Carcinoma pancreas

3. Cholangiocarcinoma

4. Ampullary carcinoma

5. Lymph node metastasis at porta hepatitis leading to bilary obstruction

Only 20–30% of malignant biliary obstruction is resectable at the time of diagnosis.

**Indications of Percutaneous Biliary Decompression**

1. Failed endoscopic drainage

2. Previous Billroth II surgery

3. Inability to intubate duodenum due to duodenal obstruction

4. Inability to negotiate guide wire by ERCP due to tight biliary obstruction

5. Large periampullary diverticulum

6. Large ampullary growth

7. To deploy transhepatic brachytherapy

8. To treat cholangitis when ERCP fails

9. ? Preoperative biliary decompression (controversial)

**Relative Contraindications**

1. Bleeding disorders

2. Tense ascites

3. Segmental, isolated intrahepatic obstruction

**Methods**

1. There are two types of biliary drainage, external drainage and internal drainage.

2. External drainage is achieved following transhepatic cannulation of the biliary system. If the malignant obstruction is very tight, it is difficult to cross the stricture. Thus, only external catheter is placed.

3. Internal drainage is achieved to deploy an endoprosthesis with proximal and distal side-holes across the stricture.

4. Procedure should be done under fluoroscopy with ultrasonography guidance.

5. Right hepatic duct is short unlike left, which is 2–3 cm long until its bifurcation into the segmental duct.

6. A percutaneous puncture is made in the intercostal space in mid-axillary line. A right duct is punctured on fluoroscopy.

7. Following successful puncture, a J guide-wire is inserted through the sheath and maneuvered towards or through the obstruction, if possible. The wire is exchanged for a more rigid Lunderquist guide-wire and over this dilators are passed to facilitate passage of the catheter/endoprothesis.

8. An endoprothesis or catheter is deployed through the stricture. Internal drainage is instituted by side holes in the endoprothesis or catheter.

9. It is always ideal to cross the stricture and put internal catheter. If crossing of stricture is impossible, external drainage is instituted.

10. Draining of around 25% liver volume is sufficient to palliate the jaundice.

**Complications**

1. Mortality is around 0–2.8%

2. Overall complications rate3.5–9.5%

3. Higher complications rate is seen in malignant disease

**Immediate complications**

1. Sedation related

2. Haemobilia

n Around 16% of patients develop mild haemobilia while 3% develop severe haemobilia.

n Mainly it is a venous blood and usually self-limiting.

n Arterial haemobilia needs embolization of the vessels to arrest the bleeding.

3. Sepsis

4. Pericatheter leak occurs in 15% of patients

5. Pneumothorax develops rarely

6. Pericarditis (0–4%)

7. Contrast reaction (< 2%)

**Delayed complications**

1. Cholangitis

n Rate can be decreased by using larger 10–12F drain

2. Catheter dislodgement

3. Peritonitis (1–3%)

4. Biliopleural fistula

5. Metastatic abscess

**Efficacy of Percutaneous Biliary Drainage in Malignant Biliary Obstruction**

1. Technical success 86–100%

2. Adequate drainage 81–96%

3. 30-day mortality is 1–49%

**Plastic versus Metallic Stent in Percutaneous Biliary Drainage**

1. Occlusion rate lower in metallic stents – 19 vs 27%

2. Longer patency in metallic stents – 272 vs 96 days

3. Decreased 30-day mortality as compared with plastic stents – 10% vs 24%

4. Decreased overall hospitalization compared with plastic stents

**Endoscopic approach to enteral nutrition**

**Indications**

1. Poor volitional intake

2. Permanent neurological impairment

3. Oropharyngeal dysfunction

4. Short gut syndrome

5. Severe malnutrition before elective surgery

6. Intensive anticancer chemotherapy

**Types**

1. Endoscopic nasoenteric tube placement

2. PEG (Percutaneous Endoscopic Gastrostomy)

3. PEG J

4. DPEJ – Direct endoscopic jejunostomy

EUS-guided gastrojejunostomy using Axios Stent (Lumen apposing stent)

**Nasoenteric Tube Placement**

1. Nasoenteric tube of 8–12 F size and 120 cm long is passed under fluoroscopy.

2. Successful enteral intubation is in around 90% of patients.

3. Endoscopically there are various techniques of nasoenteric tube placement, including nasoenteric tube placement over the guide wire, through the channel of endoscope or by the side of the endoscope.

***Complications of Nasoenteric Tube Placement***

1. Epistaxis 1.8–4.7%

2. Tube migration 12–16%

3. Tube occlusion 9–20%

4. Aspiration

**Percutaneous Endoscopic Gastrostomy**

**Absolute Contraindications**

1. Inability to transluminate abdominal wall

2. Inability to oppose anterior gastric wall

**Relative Contraindications**

1. Ascites

2. Coagulopathy

3. Gastric varices

4. Prior gastric surgery

5. Morbid obesity

6. Neoplastic gastric infiltration

**Technique of PEG Placement**

***The Standard ‘Pull’ Technique***

1. A standard endoscope is passed into the stomach and thorough examination of stomach and oesophagus is made. The stomach is distended with air, in dark room.

2. The tip of the endoscope is directed towards the anterior wall of the stomach and the abdominal wall is observed for transillumination and the assistant indents the site with a finger **(Fig. 62.1a)**.

3. The endoscopist checks that the indentation is seen and it is in an appropriate part of the body of the stomach. This is one of the most important steps in the technique of PEG placement.

4. After marking the point of maximum indentation, that area is prepared with povidone iodine and local anaesthetic agent is infiltrated up to subcutaneous tissue.

5. A short skin incision extending up to subcutaneous fat is made.

6. An 18-gauge needle catheter is pushed through the anterior abdominal wall and the endoscopist, who has meanwhile placed a polyp snare under the area of indentation and maintained gastric distension, observes its entrance into the stomach **(Fig. 62.1b)**.

7. Commercially available guide wire (comes in the kit of PEG set), at least 150 cm long, is passed through the needle and grasped with the snare.

8. The endoscope and snare are withdrawn through the mouth, carrying the guide wire, ensuring that the free end of the wire remains outside the abdominal wall **(Fig. 62.1c)**.

9. The wire at the mouth is then tied to the PEG catheter with figure-of-8 patterns, which is pulled down the oesophagus and through the anterior abdominal wall. This position is checked after the endoscope is replaced **(Fig. 62.1d and Fig. 62.2)**.

10. The tube is anchored at the skin by various disc devices available with kit of PEG set.

11. Feeding can be started on the day after the procedure if there are no complications.

***Technique of Percutaneous Endoscopic Jejunostomy (PEJ)***

In view of prevention of gastroesophageal reflux disease, there is increasing role of PEJ for enteral nutrition. The jejunostomy tube may be inserted under endoscopic guidance through an established gastrostomy tract.

**Procedure-related Complications**

1. Overall complications rate 1.5–4.0%

2. Aspiration 0.3–1.0%

3. Haemorrhage < 1.0%

4. Transient pneumoperitoneum 40%

5. Prolonged ileus 3%

PEG placement related complications are higher in HIV, malignancy and neurologically impaired patients.

1. **PEG site infection**

n It is a common complication following PEG, particularly in absence of prophylaxis antibiotics.

n Risk factors

n Diabetes mellitus

n On steroid

n Obesity

n Malnutrition

***Most of the PEG site infection are minor and can be well treated with antibiotics***

n Pre-procedure cefazoline decreases the chances of local infection.

n Proper placement of external bolster is very important to prevent infection.

n Peritonitis occurs in around 0.4–1.6% of patients.

n Necrotizing fasciitis occurs very rarely.

2*.* **Excessive leakage of feed**

n Frequency is around 1–2%.

n Risk factors include use of corrosive agent (hydrogen peroxide) for local dressing, cutaneous fungal or bacterial infection.

n Absence of external bolster or buried bumper syndrome can also cause increased leakage.

3.**Buried bumper syndrome**

n Frequency is around 20%.

n Incomplete buried bumper syndrome may be higher.

n It can be simple ulceration beneath the internal bolster, to complete erosion of tube through the gastric and abdominal walls.

n May be due to excessive tension between external and internal bolsters.

n Other causes include stiff internal bolster, poor wound healing and malnutrition.

n It is presenting as leakage, infection, tube immobility, resistance to infusion or abdominal pain while feeding.

n Management is by insertion of new PEG.

4. **Tumour implantation**

n Rarely metastasis occurs at PEG site

5. **Gastrointestinal bleeding**

n It rarely occurs; around 0.6–1.2% of patients.

7. **Gastro-colo-cutaneous fistula**

n Insufficient insufflations, inadequate illumination, previous abdominal surgery

n Presents with peritonitis, fasciitis

8. **Other complications**

n Subcutaneous emphysema

n Gastric volvulus

n Subcutaneous neuralgia

n Left lower part liver laceration

n Persistent gastrocutaneous fistula after removing PEG

**TIPS (transjugular intrahepatic portosystemic shunt)**

**Introduction**

A transjugular intrahepatic portosystemic shunt (TIPS) is a percutaneously created connection within the liver between the portal and systemic circulations. A TIPS is placed to reduce portal pressure in patients with complications related to portal hypertension. The goal of TIPS placement is to divert portal blood flow into the hepatic vein, so as to reduce the pressure gradient between portal and systemic circulations.

**Indications**

1. Acute variceal bleeding that cannot be successfully controlled with medical treatment as well as endotherapy.

2. Recurrent and refractory variceal bleeding or recurrent variceal bleeding in patients who cannot tolerate conventional medical treatment, including endotherapy (band ligation and sclerotherapy) and pharmacologic therapy (Terlipressin or non-selective beta blocker).

3. Therapy for refractory ascites.

4. Portal decompression in patients with hepatic venous outflow obstruction (Budd-Chiari syndrome).

5. Hepatic hydrothorax

6. Hepatorenal syndrome – mainly in type II hepatorenal syndrome as a bridge to liver transplantation.

**Relative Contraindications**

1. Active intrahepatic or systemic infection as bacteria can colonize the stent, causing persistent infection.

2. Severe hepatic encephalopathy poorly controlled with medical therapy.

3. Hypervascular hepatic tumours.

4. Portal vein thrombosis (Although portal vein thrombus may make the procedure more technically demanding, it is not an absolute contraindication to TIPS placement.)

**Prosthesis**

Two types of prosthesis are available: Uncover (Wall stent) and Cover stent (Gore VIATORR TIPS Endoprosthesis). Polytetrafluoroethylene graft lining of cover stent reduces bile and mucin permeation, thereby improving patency. It also reduces in growth of tissue into the graft, which can be advantageous for subsequent liver transplantation.

An 8-mm diameter stent is usually acceptable in patients with refractory ascites, whereas a 10–12 mm shunt may be needed in patients with life-threatening hemorrhage. Wall stents can be over dilated to about 10% larger than their nominal diameter to allow further gradient reduction. Nitinol stents cannot be over dilated in this way.

**Complications**

1. Uncommon - Pneumothorax, injury to hepatic artery and bile duct, capsular tear leading to life-threatening haemorrhages.

2. Hepatic encephalopathy (HE) - New-onset or worsened encephalopathy, which occurs in about 25% of treated patients. Preprocedural HE or Child class C cirrhosis is more likely to have this complication. Shunt diameter and degree of portosystemic gradient reduction are related to the development of encephalopathy. Most often, HE can be medically treated with lactulose and dietary protein restriction although shunt revision to a smaller diameter or intentional shunt thrombosis may be necessary. Frequencies of HE were similar with covered and uncovered stents.

3. Shunt stenosis and occlusion - Early shunt thrombosis (often within 24 hrs) is usually believed to be secondary to extension of the intrahepatic tract across a bile duct. Such early shunt occlusions can be treated with balloon dilation of the stent. Late stent occlusion is related to pseudointimal hyperplasia within the stent or, more commonly, intimal hyperplasia within the hepatic vein. The use of covered (polytetrafluoroethylene [PTFE], polyester) stents to improve primary and secondary shunt patency may prove helpful.

4. Haemodynamic complications - Acute increases in cardiac output and central venous and pulmonary wedge pressures can result in acute pulmonary oedema and congestive heart failure.

**Doppler Criteria for Stent Occlusion**

Surveillance ultrasonography is performed for TIPS patency at 3 and 6 months after the procedure and twice yearly thereafter. There are certain criteria for stent occlusion on Doppler study.

1. Absent flow

2. Low peak shunt velocity (<50–90 cm/sec)

3. High peak shunt velocity (190 cm/sec)

4. Low mean PV velocity (<30 cm/sec)

5. Return of antegrade flow in the intrahepatic PVs

6. Significant change in shunt velocity (>50 cm/sec) compared with the immediate post procedural result

**FIBROSCAN**

Ultrasound elastography is radiologic technique to assess hepatic fibrosis have been studied. Both rely on assessment

of the effect of liver stiffness (fibrosis) on the velocity of

transmission of a shear wave through the liver. Ultrasound elastography (Transient Elastography), commercially known as FibroScan®, uses a modified ultrasound probe to measure the velocity of a shear wave created by a vibratory source. Estimates of stiffness of the liver by ultrasound correlate with fibrosis stage. Ultrasound elastography can be performed in approximately 95% of patients; although older patients and patients who are obese can be more difficult to study (XL probe may be helpful). This technique has been evaluated most consistently in patients with chronic HCV disease. Second, magnetic resonance elastography assesses images of an acoustic wave generated by a sound source as it passes through the liver to determine hepatic stiffness.

Ultrasound elastography is strongly correlated with advanced fibrosis in patients with chronic hepatitis, and values above (LSM, liver stiffness measurement) 12.5 kPa are indicative of cirrhosis (F4). If fibroscan value is less than 6 kPa, it excludes significant fibrosis (F0–F1). Value between 6–12.5 kPa is a gray zone (F2). This technique works best for separating patients with minimal or no fibrosis from those with significant fibrosis. A linear correlation with increasing fibrosis has not been demonstrated, and 15% discordance between elastography scores and histologic fibrosis has been observed. Advanced fibrosis may be underestimated and patients with macronodular cirrhosis may be classified as noncirrhotic. Fibrosis may be overestimated in patients with extrahepatic cholestasis or acute hepatocellular injury due to the effects of these conditions on liver stiffness. Ultrasound elastography does not distinguish patients with no fibrosis from patients with minimal fibrosis. Ascites can interfere with the generation of a shear wave through the liver.

Fibroscan with CAP (controlled attenuation parameter) simultaneously estimate the quantity of fat and fibrosis in patients with NAFLD. Value of CPA is classified as S0 no steatosis, whereas S3 indicates high steatosis.

**Occupational Health Hazards for the Gastroenterologist**

Innovative advances in the field of gastrointestinal endoscopy have presented a practicing gastroenterologist with prolonged endoscopic procedures using a variety of complex equipment. Increasing health awareness and healthcare availability has placed additional burden on the physician for increasing work hours. All of the above has steadily increased occupational health hazards for the practicing gastroenterologist.

**Further Reading**

1. Guidelines: Appropriate use of gastrointestinal endoscopy. American Society for Gastro-intestinal Endoscopy. *Gastrointest Endosc* 2000;52:831–7.

2. Mallery JS. Complications of ERCP. *Gastrointest Endosc* 2003; 57:633–8.

3. Hirota WK. Guidelines for antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2003;58:475–82.

4. Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001;54:425–34.

5. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; 335:909–18.

6. Loperfido S, Angelinip G, Benedetti G, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; 48:1–10.

8. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. *Gut* 1999;45 (Suppl 4):IV1–IV11.

9. Gulati MS, Srinivasan A, Agarwal PP, et al. Percutaneous management of malignant biliary obstruction: the Indian perspective. *Trop Gastroenterol* 2003;24:47–58.

10. DiSario JA. Endoscopic approaches to enteral nutrition support. *Gastrointest Endosc* 2002;55:901–8.

11. Colombato L. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. *J Clin Gastroenterol* 2007;41 Suppl 3:S344–51.

12. Ofori E, Ramai D Occupation-associated health hazards for the gastroenterologist/endoscopist. *Ann Gastroenterol* 2018; 31:448–455.

**Chapter 63.**

**Instruments**

**Sengstaken-Blakemore tube**

1. A Sengstaken-Blakemore tube has three channels **(Fig. 63.1)**

n One to inflate the gastric balloon

n One to inflate the oesophageal balloon

n One to aspirate the stomach

2. The tube is placed and maintained in the correct position as evidenced by:

n Injecting air into the gastric aspiration channel and auscultating over stomach.

n Aspiration of gastric contents (blood in case of active bleeding) via the above channel.

n pH testing of the aspirate.

n X-ray confirming that the part of the tube where the oesophageal and gastric balloons meet is at the level of the xiphoid process.

**Indications**

Balloon tamponade should be considered in those who have active ongoing variceal bleeding despite endoscopic attempts to control bleeding or in whom endoscopy is not possible due to massive bleeding.

**Contraindications**

1. Pharyngeal/upper oesophageal obstruction

2. Severe maxillofacial injury

3. Basal skull fracture

4. Following precautions should be taken in patient with Sengstaken tube:

n To prevent aspiration, airway should be secured before placement of tube to prevent aspiration pneumonia.

n Oesophageal balloon pressures should never exceed 45 mmHg.

n Fully deflate both balloons prior to extubation.

n Clamp the tube before extubation to prevent liquid escaping from distal end and being aspirated into lungs to prevent aspiration.

n Traction (if ordered) must be maintained constant at all times.

n Scissors are kept near the patient at all times in case the tube migrates superiorly and the balloons cause respiratory obstruction in non-intubated patients. The tube can be immediately cut to deflate the balloons rapidly, remembering to grasp the tube between the patient and scissors.

n The used tube should be washed and dried, once removed, and placed in a paper bag.

5. Balloon tamponade should be considered as a salvage procedure

**Outcome**

1. Tamponade is 90% successful at stopping haemorrhage.

2. Around 50% patients rebleed within 24 hrs of removal of tamponade.

**Minnesota tube**

The Minnesota tube is a modification of Sengstaken-Blakemore tube, providing a fourth port for oesophageal suction, thus eliminating the need for a nasogastric tube to be placed in the oesophagus. With the gastric balloon inflated, blood and salivary secretions accumulating in the oesophagus need to be sucked out to prevent aspiration.

**Linton-Nachalas tube**

1. Single large gastric balloon (400 mL air)

2. No oesophageal balloon

3. Oesophageal suction port to prevent aspiration

4. Mainly used for gastric varices bleeding

**Complications of Balloon Tamponade**

1. Ulceration – if left for more than 24 hrs

2. Asphyxia

4. Obstruction of the pharynx

**Rigid Sigmoidoscope**

**Introduction**

1. Anoscopy, proctoscopy, and sigmoidoscopy tests allow to examine the anus, rectum, and part of the sigmoid colon.

2. Sigmoidoscopy is a thorough examination of the last 2 ft (0.6 m) of the lower colon (sigmoid colon).

3. Sigmoidoscopy is most commonly used to screen for colon cancer.

4. About half of all colon tumours and polyps can be found using sigmoidoscopy.

**Indications**

1. Symptoms referable to anorectum: Bleeding, discharge, protrusion or swelling, anorectal pain, diarrhoea or constipation.

2. Evaluation of patients prior to anorectal surgery (flexible sigmoidoscopy is preferred).

3. Foreign body removal from the rectum.

4. Screening for colorectal cancer.

5. Rectal biopsy (e.g., to evaluate for proctitis, amyloidosis).

6. Treatment of internal hemorrhoids (e.g., banding, infrared coagulation with flexible sigmoidoscopes).

**Contraindication**

No absolute contraindication except for caution in patients with anal stenosis and painful anal lesions like fissures.

**Preparation**

1. Most patients can be examined without prior preparation.

2. Enema or laxative can be used, if stool precludes the adequate examination.

3. Premedication is rarely necessary.

**Instruments**

1. **Anoscope**

n Short, rigid, hollow tube that may also contain a light source.

n It is used to look at the last 2 in (5.1 cm) of the colon (anal canal/lower rectal mucosa).

n It does not require preparations (enemas or laxatives) to empty the colon.

2. **Proctoscope (Fig. 63.2)**

n Slightly longer than the anoscope

n Used to view more of the rectum

n Proctoscopy rarely requires the use of enemas or laxatives.

3. **Rigid Sigmoidoscopy** **(Fig. 63.3)**

n It is about 10 in (25.4 cm) to 12 in (30.5 cm) long and 1 in (2.5 cm) wide rigid sigmoidoscope

n Air insufflators

n Suction

n Sigmoidoscopy spoon

**Patient Position**

1. Left lateral with knees drawn up toward chest (Sim’s position)

2. Knee-chest position

3. Prone, inverted (jack-knife) position on sigmoidoscopy table

**Rectal Biopsy**

Rectal biopsy can be performed, mainly from the posterior

rectal wall below the peritoneal reflection (within 7–10 cm of the anal verge) to minimize the risk of free peritoneal perforation.

**Guide wire (for ercp)**

**Use**

1. To negotiate stricture prior to stricture dilatation or stent placement.

2. Guide wire cannulation is the preferred method of cannulation for bile duct or pancreatic duct cannulation.

3. For wire-guided sphincterotomy.

4. To position catheter in transpapillary drainage for pancreatic pseudocysts.

5. For placement of sheath prior to biliary or pancreatic duct cytology.

6. For guiding manometry catheter to diagnose sphincter of Oddi dysfunction.

7. For unilateral drainage of right or left intrahepatic ducts without contaminating the other side with contrast; guide wire can be used to gain access over which an ERCP catheter is advanced into the unilateral side and then contrast injected.

**Classification of Guide Wire**

**Non-Hydrophilic Distal Full Hydrophilic**

**Hydrophilic Tip Wire**

Zebra type Hydra Jag Wire Terumo type

Standard Stainless Pathfinder

steel wire

Road Runner Metrotracer Wire

**Characteristics of Hydrophilic Wires**

Hydrophilic wires become highly slippery in contact with biliary or pancreatic juice because of their hydrogel coating.

**Standard Guide Wire (Fig. 63.4)**

1. Make up of stainless steel with Teflon coating to reduce surface friction

2. Size 0.018–0.038 inch; length 260–450 cm

3. Kinks easily

4. Either curved tip; floppy tip; or stiff tip

5. Mark V system means distal end has markings at 5 cm interval to allow measurement of length of the stricture

**Zebra Wire Boston Scientific (Fig. 63.5)**

1. Non-hydrophilic

2. Made up of nitinol with TFE

3. Distal 60 cm has endoglide property

4. Zebra pattern makes it easy to visualize movement across the papilla, reduces fluoro-scopic exposure

5. Kink resistance, slippery, torquable; platinum radio-opaque tip

6. Straight end and J-shaped end

7. Size – 0.025, 0.035 inches; length – 260–450 inches

8. Catheter exchange is possible

9. 7F stent can easily be mounted on the guide wire

10. Easy to handle

**Protector Plus**

1. Nitinol + TFE coating

2. Suited for wire guided sphincterotomy

3. Kink resistance

4. Mark V system

**Radiofocus (Terumo)**

1. Nitinol with polyurethane coating

2. Extremely hydrophilic

3. Tip is highly flexible

4. Good for stricture negotiation, but not suitable for catheter exchange

5. Available straight and curved type

**Jag Wire (Fig. 63.6)**

1. Hybrid of Zebra and hydrophilic guide wire

2. Distal tip is hydrophilic; rest is similar to Zebra guide wire

**Tracer Wire**

1. Made up of nitinol with TFE coating

2. Distal 60 cm is hydrophilic

3. Has a mark V system

4. Torquable and kink-resistance

**Road Runner**

1. Nitinol + Teflon

2. Tip platinum

3. Non-hydrophilic

4. Slippery, torquability

5. Used for both negotiating stricture as well as catheter exchange

5. Size – 0.18 inch; diameter – 480 mm

**Glide Wire**

1. Nitinol + Polyurethane

2. Hydrophilic

3. Size 0.018, 0.025, 0.35

4. Length 260 cm, 450 cm

5. Platinum tip

6. Straight and angled

7. Hydrophilic for access and exchange

**Pathfinder**

1. Non-hydrophilic except distal 11 cm

2. Nitinol + Endoglide

3. Platinum

4. Size 0.018; length 450 cm

***Precaution Taking Using Hydrophilic Wire***

1. Metal tip cannula may damagehydrophilic coating.

2. Prior to introducing guide wire to ERCP cannula, cannula should be flushed with saline to remove any contrast materials and to keep the wire wet.

3. Saline should be injected through the hub of the guide wire holder in order to keep the wire wet.

**Sclerotherapy needle**

1. Needle that can be retracted into the flexible sheath **(Fig. 63.7)**.

2. 21/23G needle and 5/4 mm shaft

3. Used for oesophageal varices injection, injecting bleeding peptic ulcer and bleeding sites after procedures like sphincterotomy, polypectomy, etc. It can also be used to inject saline submucosally for mucosal resection and to inject tattoo ink.

4. Sclerosants agents:

n 5% Ethanolamine oleate

n Sodium morrhuate

n Absolute alcohol

n 50% dextrose

n 0.5–2% Polidocanol

n 3% Sodium tetradecyl sulfate

n Hypertonic saline

5. **Epinephrine** – Most commonly used sclerosing agents for bleeding peptic ulcer

n It causes vasoconstriction, compression of vessels due to effect of injected volume, and platelet aggregation.

n Recommended maximum dose is 10 mL (1:10000 dilution), but 30 mL also can be tolerated.

n Metabolized by liver.

n Repeat injection can be done within 24 weeks.

n Combination with heater probe gives better results than alone.

6. **Polidocanol**: Hemostasis by bowel wall spasm and acute edema followed by inflammation and sclerosis.

7. **Alcohol**: Rapid dehydration and tissue fixation lead to arterial coagulation. Maximum volume 2 mL can be used. There are more chances of perforation.

**Methods of Sclerosant Injection in Oesophageal Varices**

1. **Intravariceal**: Thrombosis and inflammatory reaction within the varices eventually obliterates the variceal channel

2. **Paravariceal**: Fibrosis of oesophageal mucosa overlying the varices.

3. Dose of sclerosant agent for oesophageal varices sclerotherapy

n Dose varies with the type of sclerosant used (0.5–3.0 mL sclerosant at each site)

n Weekly injection till eradication

n Efficacy of intravariceal injection is more than paravariceal injection.

**Complications of Sclerotherapy**

1. Ulceration

n Depends on the type and volume of sclerosant agents, method of injection, size of varices and interval between injections.

n Incidence ranges from 10 to 80%.

n Increases with increased volume of sclerosant agent

n No difference in incidence of ulcer with intravariceal or paravariceal injection.

n Ulcer >1 cm is likely to be symptomatic.

n Prevented by H2 blocker/Sucralfate/proton pump inhibitors.

2. Bleeding

n Early recurrent bleeding occurs in 15–55%.

n Urgent re-treatment achieves control of bleeding in more than 70% of patients.

n Bleeding from post-sclerotherapy ulcer is usually self-limited.

3. Perforation

n 2–5% free perforation

4. Intramural haematoma – rare

5. Stricture

n 10–50%

n Associated with frequency and volume of injection

n Short stricture; localized to lower 5 cm of the oesophagus

6. 2–3 session of dilatations are sufficient to relieve the stricture in more than 85% of patients.

7. Bacteremia

n Incidence is around 0–50%.

8. Intramural hematoma – rare

9. Esophago-aortic fistula – rare

**Multiband Ligator (Fig. 63.8)**

**General Information**

1. It is a variceal ligation system used for endoscopic ligation of oesophageal varices.

2. Efficacy to control bleeding is as good as sclerotherapy with less complications.

3. One band is used per varix.

4. Ligation of grade I varices is difficult.

5. Two-three sessions are required to obliterate the varices.

6. Banding should begin at the gastroesophageal junction and proceed up the oesophagus spirally.

7. Avoid passing endoscope over a previously placed band to avoid dislodgement of the band.

**Complications**

1. Ulceration at the banding site

2. Chest pain

3. Perforation

4. Oesophageal stricture

5. Aspiration

6. Oesophageal obstruction

**Contraindications**

1. Cricopharyngeal or oesophageal stricture

2. Banding with caution

n Oesophageal diverticula, rings or webs

n Tortuous oesophagus

**OEsophageal dilators**

1. Peptic stricture is common in Western world and corrosive stricture of oesophagus is more common in India.

2. The symptom of dysphagia occurs if oesophageal diameter decreases to <12 mm. So the aim of oesophageal dilatation is to maintain diameter >12 mm post procedure.

3. Aims of oesophageal dilatation

n Alleviate dysphagia

n Reduce the risk of aspiration

n Prior to placement of oesophageal stents in some patients

n To pass endoscopic ultrasound scope in those with tight narrowing

4. Absolute contraindication of oesophageal dilatation

n Acute or incompletely healed oesophageal perforation

n Tracheoesophageal fistula

5. Relative contraindication of oesophageal dilation

n Bleeding disorder

n Severe cardiorespiratory disease

n Severe pharyngeal/cervical deformity

n Large thoracic aneurysm

6. Presence of varix is not a contraindication.

There are two types of dilators.

1. **Push dilators**: Give radial and axial force

2. **Balloon dilators**: Give radial force

**Push Dilators**

***Wire-guided Dilators***

1. Eder-Puestow–type metal olives

2. Savary-Gillard dilator

3. Celestin dilators

4. Keymed advanced dilators

5. American dilators

***Non–Wire-Guided Dilators***

Mercury-filled bougie; suitable for simple and wire stricture

**Balloon Dilators**

***Over-the-guide Wire (OTW)***

1. Wilson-Cook 8–15 mm dilators; 8 cm diameter

2. Rigiflex balloon (Boston Scientific, Boston, MA)

***Through the Scope (TTS)***

1. Through tapered tip extending 2–3 cm beyond the distal end for negotiation of stricture.

2. Balloon should be lubricated through silicon jelly.

3. Inflation pressure of the balloon is specified by the manufacturer.

4. Pressure unit is psi (pounds per square inch) or atm (atmospheres).

***Recently Introduced TTS Balloons***

*CRE (Controlled-radial-expansion)*

1. Each balloon can be inflated to 3 incremental diameters with three different inflation pressures.

2. Special polymer

3. Low-compliant balloon

4. Negligible “waisting” effect, unlike Rigiflex balloon

***Principles of Dilatation***

Push dilators radial vector of an axillary directed force dilates progressively from the proximal to the distal end of the stricture. Unlike balloon dilators, the operator can get a “feel” of the resistance offered by the strictures and then determine when to stop.

1. Role of “3” for esophageal dilatation by Savary dilators

2. To reduce the risk of perforation

Once mild to moderate resistance is encountered, no more than three dilators of progressively increasing diameter should be passed in a single session.

***Complications***

1. Mortality 0.01%

2. Perforation 0.2%

3. Bleeding 0.07%

4. Others: Chest pain, nausea, vomiting

5. Bending, kinking or malposition of guide wire leads to perforation.

**Savary-type Dilators (Fig. 63. 9)**

(Wilson Cook Medical Inc., Winston-Salem, NC)

1. Polyvinyl dilator

2. Tapered tip 20 cm

3. Size: 70–100 cm

4. Radiopaque point at widest diameter

5. 5 to 20 mm

6. American dilator system is similar except that dilators are impregnated with barium sulfate for better fluoroscopic visualization and distal tapered end is shorter.

7. **Advantages:** Smooth and easy passage through pharynx and stricture

8. **Disadvantages**

n Require multiple passages

n Long non-dilating end

n Difficult to use in children and in post gastrectomy state

Balloon is directing entire force radially and simultaneously over the entire length of the stricture, leads to stricture dilatation. Since the operator does not get a “feel” of the stricture, fluoroscopy is recommended to monitor the disappearance of the stricture waist with slow increments of inflation pressure.

Two forces are responsible for stricture dilation:

1. Circumferential force

2. Radial force

n Relieving of dysphagia is comparable with both the Savary dilators and TTS balloons

3. No more than three dilators of progressively increasing diameter (3 x 1 mm increments) should be passed in a single session

***Indications for Surgery in Corrosive Oesophageal Stricture***

1. 10% of corrosive strictures require surgery.

2. Young patients who require continuous dilatation for 1–2 yrs.

3. Stricture requires frequent dilatation

4. Oesophagus is irretrievably damaged

5. Oesophageal perforation

**Rigiflex Balloon (Fig. 63.10)**

1. OTW balloon for pneumatic balloon dilation in achalasia cardia

2. 10 cm long

3. Available in 3 sizes: 30 mm, 35 mm and 40 mm diameter (when fully inflated)

4. **Non-compliant balloon**: Balloon inflated maximally to its designated diameter only. Further inflation will not increase the diameter, but will rupture.

**ERCP cannula**

Special cannulae are available for special indications. A typical cannula is:

1. 150–200 cm long

2. Made up of Teflon

3. 5F wide

4. Tip is either tapered or blunt, carries radiopaque marker or can be metal tipped

4. Can take 0.018", 0.021", 0.025", 0.035", 0.038" guide wire **(Fig. 63.11)**

**Sphincterotome**

**Classification of Sphincterotomy**

***Conventional Classification***

1. Standard or non-wire guided

2. Wire guided

3. Precut sphincterotome

4. Billroth-II sphincterotome

5. Needle knife papillotome

***Classification According to Length and Type of Cutting Wire***

1. Long cutting wire: Disadvantage is leakage of current and difficulties in bowing the sphincterotome as the cutting wire may still be partially in the channel of the scope.

2. Shorter cutting wire: Advantage is higher current per unit surface area.

3. The cutting wire can be braded or monofilament for higher current per unit surface area.

***Classification According to Length of Nose***

1. Long nose: Maintain orientation during cutting, but needs deep cannulation

2. Short nose: Dose not require deep cannulation but cannot maintain orientation

3. No nose: pre-cut sphincterotome

**Standard/Non–Wire-Guided (Fig. 63.12)**

1. Bowstring type

2. Single lumen

3. Cutting wire: 15–35 mm

4. Nose length: 5–30 mm

5. Size of tip: 5 Fr

6. Usually distal 1/3rd of cutting wire is used to cut the superior wall of the sphincter.

**Wire-Guided Sphincterotome**

1. Bowstring type

2. 7 Fr size

3. Tip: 4–5.5 Fr

4. Cutting wire: 20–35 mm

5. Nose: 5–30 mm

6. Calibration in distal part of sphincterotome – length of the CBD

7. Can take up to 0.035 inch guide wire (Some can only take 0.021" or 0.025" guide wires)

8. Either double/triple lumen catheter

9. Can have wire and injecting capability

**Needle Knife Papillotome (Fig. 63.13)**

1. Huibregtse needle knife papillotome

2. 5 mm needle knife

3. Used for common bile duct cannulation when standard cannulation methods fail

4. Papillotome can also be used for transgastric pseudocyst drainage

5. Some are double lumen for passing wire or injecting contrast

**Stone extraction basket**

1. Biliary basket made up of Nitinol wire **(Fig. 63.14)**

2. Wilson- Cook Mini basket

3. Used for endoscopic removal of biliary/pancreatic stones or foreign bodies (e.g., migrated stents, parasites)

4. Basket is constructed of monofilament wire

5. Some are designed to crush stones (mechanical lithotripsy) and some have a guide wire channel

6. Reusable

**Stone extraction balloon**

1. Triple lumen balloon – one for balloon inflation, second for guide wire and third for contrast injection **(Fig. 63.15)**.

2. Some can be inflated to three diameters

3. Endoscopic removal of biliary stone

4. Occlusion cholangiogram

**Soehendra Lithotriptor**

1. Around 90% of the biliary stone can be removed by conventional methods of stone extraction (adequate sphincterotomy followed by usage of either balloon or basket).

2. Mechanically crush biliary stones when above mentioned methods of endoscopic removal have failed.

3. This device can be used to crush a stone when a regular basket gets impacted with a stone in the common bile duct. By doing so, the basket can be disimpacted. This is a salvage lithotripter **(Fig. 63.16)**.

**Biliary Stricture Dilation Balloons**

1. Through-the-scope balloons

2. Have guide wire 0.035" channel

3. Radiopaque markers to localize fluoroscopic positioning

4. Various diameters (4 mm, 6 mm, 8 mm) and lengths 2 cm, 3 cm, 4 cm)

5. Pressure (psi or atm) specifications reflect bursting pressures

6. Aim is to obliterate the stricture waist slowly.

**Plastic stents**

1. Straight stents

2. Single pigtail stents **(Fig. 63.17)**

3. Double pigtail stents **(Fig.63.18)**

**Pigtail Stents**

1. Used mainly for dilated system with no stricture

2. Stent can be held properly.

3. More chances of clogging

4. Double pigtail used mainly for biliary system, single pigtail can be used in pancreatic endotherapy.

**Straight Stents**

1. Good flow because of no pigtail

2. Easily migrated

3. Not used in non-strictured system as they tend to migrate if there is not stricture to anchor the stent

**Self-Expanding Metallic Stents (SEMS)**

**Types of SEMS**

1. Z-stents

2. Wall stents

3. Ultraflex stents (oesophageal)

4. Antireflux Dua stent (oesophageal)

5. Polyflex (this is a self-expanding plastic stent; oesophageal)

**Z-Stents (Fig. 63.19)**

1. Stainless steel with zigzag fashion and covered with polyurethane (fully covered or partially uncovered)

2. Measure: 16–18 mm

3. Length: 6, 8, 10, 12, 14 cm

4. Medium radial force

5. Tends to buckle in angulated strictures

6. Success rate: 80%

7. Palliation of dysphagia: 90%

8. Chest discomfort: 85%

9. Stent migration: 27%

**Wall Stents (Fig. 63.20)**

1. Most widely used

2. Made up of elgiloy – cobalt-chromium based non-magnetic metal

3. Strong radial force, high resilience, fatigue resistance and radiopaque

4. MRI is safe with minimal image distortion.

5. Success rate: 95–100%

6. Mortality: 1.4%

**Ultraflex Stents (Fig. 63.21)**

1. Made up of nitinol (nickel and titanium) – rubber like

2. Constant radial expansion force

3. Fatigue resistance, prevent recoiling

4. Can be used in long and tortuous stricture

5. Success rate more than 95%

6. Less migration or foreshortening

**Antireflux Dua Stent**

1. Oesophageal Z-stent

2. 8-cm windsock valve distally, which prevents reflux

**Polyflex Stent**

1. Self-expanding plastic stent

2. Diameter: 16 mm, 18 mm, 21 mm

3. Various lengths

4. Can be removed, hence can be used for benign strictures and T-E fistula also

**Self-Expanding Metal Enteral Stents**

1. Similar design to Wall stent but diameter 22 mm

2. Can be passed through the channel of a therapeutic upper scope

3. Can be used for proximal small bowel and colon

**Self -expanding Metal Colon Stents**

***Types:***

Wall stent as described above.

Z-stent (35mm diameter): cannot be passed thro-ugh the scope channel

**Self-Expanding Metal Biliary Stents**

**Types**

1. Wall stent (Microvasive Boston Scientific)

2. Zilver Stent (Wilson-Cook Medicals)

3. Mamotherm (Bard Medicals)

4. Others (e.g., Z-Stent, Za-Stent, Diamond Stent).

5. These stents expand to 10 mm in diameter and hence remain patent for a longer time compared to plastic stents.

6. Once deployed, they cannot be removed and hence are recommended only for palliating malignant biliary obstruction.

7. They can be covered or uncovered.

Although covered stents prevent tumor in-growth, there is a higher incidence of cholecystitis in those with patent cystic duct. Also covered stents should not be deployed for hilar strictures as they can cover intrahepatic ducts.

**Endoscopy Cap**

Endoscopy cap of various shapes are very useful for third space endoscopy **(Table 63.1)**

**Name Normal cap Oblique cap ST hood**

**Picture**

Company Olympus Olympus FUJI

Advantage n Can be used n Very good n Very easy for

for both ESD for clipping initial entry

and POEM because you into

for any can press submucosa

situation mucosa with

n No need to tapered tip

change cap

during

procedure

Disadvantage n Little bit n Too long for n Need to

difficult to submucosalo change cap

enter into tunneling when you

submucosa need to

apply clip

**Triangular Tip Knife – J Type**

Most widely used in POEM procedure. It is used for mucosal incision and submucosal tunnel entry **(Fig. 63.22)**.

**Hybrid Knife – T and I Types**

Has a special Waterjet generator **(Fig. 63.23)** – helps to injects fluid under high pressures, leads to good submucosal lift. It is used in cases of very tight GE junction of severe fibrosis in ESD.

**HemoStat – Y-Bipolar Coagulation Forceps**

It is flexible bipolar forceps **(Fig. 63.24)** for initial haemostasis without causing damage to the deeper tissue through thermal degeneration. It is useful for long term prevention of re-bleeding.

**Apollo Overstitch**

The only device used yet for closure of large mucosal and full thickness defects in the world. It has steep learning curve. It is very useful for full thickness resections **(Fig. 63.25)**.

**Chapter 64.**

**Suture Materials**

**Definition**

Suture is a thread, which brings into apposition two tissues or surfaces.

**Classification of Sutures**

1. ***Absorbable***

n Natural

- Catgut

- Fascia lata

- Beef tendon

n Synthetic

- Polyglactin 910 (vicryl)

- Polyglycolic acid (dexon)

- Polydiaxinone (PDS)

2. ***Non-absorbable***

a) Natural – Silk, cotton, linen

b) Synthetic – Monofilament, polyfilament (braided)

c) Metals – Stainless steel, platinum, silver wire

**Ideal Suture Material**

1. Should have uniform diameter

2. Should produce secure knots without cutting or slipping

3. Should have adequate tensile strength

4. Should not fray at the ends

5. Should excite minimum tissue reaction

6. Should facilitate easy handling

7. Should not create situation favorable for bacterial growth

8. Should be non-allergic, non-carcinogenic

9. Should be freely available and cheap

**ABSORBABLE MATERIALS**

**Catgut**

***Historical Aspect***

Catgut is a misnomer of ‘kitgut,’ which means medieval three-stringed violin like instrument, strings of which were used by the ancient people as suture material.

Joseph Lister hardened this material and minimized the tissue reaction invoked by this, by treating catgut with carbolic acid. Later on, Lister found that chromic acid delayed the absorption of the catgut and thus chromic catgut was discovered.

***Manufacture***

It is prepared from the submucosa of the sheep’s intestine. Sheep’s submucosa has a rich content of elastic tissue which accounts for the tensile strength of catgut. Sheep’s intestine is frozen and is scraped, with the submucosa left behind. Submucosa is dried and cut into ribbons. These ribbons are then subjected to water jet and there after rolled out. The rolled out ribbons are made fat free by chemical treatment with fat solvent and matched by computers in order to meet the most exacting demands for diameter and tensile strength. These ribbons are chromisized by treating with chromic acid before they are spun. Then an electronic spinning process creates a strand. The strands are then polished and uniform suture material is produced.

***Sterilization***

Catgut is sterilized during its preparation and kept in a preservative solution. The preservative solution is ethicon fliud containing 2.5% formaldehyde and 87.5% denatured absolute alcohol. Previously, iodine method and chromic acid method were used.

***Absorption***

Catgut is absorbed by proteolytic digestive enzymes, which are released from the inflammatory cells collected around the catgut. That is why in the presence of infection, catgut is rapidly absorbed.

***Duration in Bloody Tissues***

Plain catgut retains its tensile strength for 10 days and chromic catgut for 20 days.

***Uses***

1. **Plain catgut**

n To suture subcutaneous tissue

n Ligate small blood vessels

n In circumcision, for ligating the bleeding points and apposing the skin with submucosa

2. **Chromic catgut**

n Size 1–0: ligating the pedicles in hysterectomy

n Size 2–0: hydrocele in eversion of Sac or Lord’s plication, for closure of bladder

c) Size 3–0: intestine anastomosis – inner layer

d) Size 4–0 or 5–0: used in plastic surgery

**Polyglactin (Vicryl)**

It is a synthetic absorbable suture material. It is a copolymer of glycolin and lactide. It is a poly-filament braided suture.

**Advantages**

1. Minimal tissue reaction

2. No fraying

3. Excellent handling

4. Can be used in presence of infection

**Disadvantages**

1. Roughness

**Absorption**

Disintegrated by hydrolysis and then the filaments are phagocytosed by the polymorphonuclear cells and macrophages.

*Absorption Time*

Absorption is minimal until 40 days and is complete between 60 to 90 days.

***Uses***

1. Intestinal anastomosis

2. Ligation of pedicles, e.g., ligation of superior thyroid pedicles

3. Closure of laparotomies

**Polyglycolic Acid (Dexon)**

It is a synthetic absorbable suture material. It is a non-protein polymer of glycolic acid.

*Absorption*: By esterase enzyme system.

*Absorption time*: 100 days

**Advantages**

1. Minimal tissue reaction

2. Less oedema

3. Uniform absorption

4. Can be used in presence of infection

5. Secure knots

6. Less fraying

***Uses***

1. Intestinal anastomosis

2. Ligation of pedicles

**Polydioxinone (PDS)**

It is a synthetic absorbable.

***Absorption***

Disintegrated by hydrolysis and then the filaments are phagocytosed by the poly morphonuclear cells and macrophages.

***Absorption Time***

240 days

Due to its delayed absorption and minimal tissue reaction, it is favoured in intestinal anastomosis nowadays.

**Polyglecaprone (Monocryl)**

It is a newer monofilament absorbable suture material. It is a polymer of glycolide and capro-lactone.

*Absorption*: It is broken down by hydrolysis.

***Advantages***

1. Good tensile strength

2. Inert

3. Smooth surface, hence glides easily through the tissues

4. Not affected by infection

***Disadvantage***

1. It is expensive

***Uses***

1. Subcuticular sutures

2. Subcutaneous sutures

**Silk**

It is a non-absorbable polyfilament suture material. It is obtained from cocoon of silkworm. It is available in sterile foil overwrap pack. Sutupac–pre cut lengths of sterile sutures in a pack of 6 pieces of suture material, without a needle.

***Advantage***

1. It ties down smoothly and securely.

***Disadvantages***

1. Stitch granuloma

2. Infection rate is high.

***Uses***

1. Ligate the blood vessels and pedicles

2. Fixing skin grafts

3. Skin suturing

4. Suturing tendons

5. Fixing drains

**Nylon**

It is a non-absorbable, synthetic material.

***Advantages***

1. Cheaper

2. Less irritant

3. High tensile strength which is retained for long period

***Disadvantages***

1. Slippery knot

2. Infection

***Uses***

1. Skin suturing

**Prolene**

It is made up of polymer of propylene. It is a synthetic non-absorbable suture material. It is available in presterilized foil overwrap pack as eyeless needle sutures.

***Advantages***

1. It is inert.

2. Does not harbour microorganisms and hence no chance of infection

3. It is pliable and can be easily handled.

4. It is smooth and so it requires much less force to draw through the tissues.

5. Least thrombogenic

6. More elastic

***Uses***

1. Plastic surgery

2. Vascular surgery for anastomosis

3. Tendon repair

4. Hernia repair – to fix the prolene mesh

5. Laparotomy closures

**Newer non-absorbable synthetic suture materials**

They are available in different brand names – Dacron, PTFE, Marlex, Ethibond, Polyester and Polyethylene.

**Chapter 65.**

**Recent Advances**

**Magnetic Resonance Cholangio-pancreato-graphy (MRCP)**

**Introduction**

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive, radiation free imaging technique for evaluation of intra and extrahepatic biliary tree and pancreatic ductal system.

MRCP utilizes T2-weighted pulse sequences, in which stationary/slow moving fluid appears bright compared to rapidly moving blood flow and adjacent solid tissue. MRCP does not require contrast administration. Newer rapid acquisition with relaxation enhancement (RARE) and Half-Fourier acquisition single-shot turbo spin-echo (HASTE) techniques yield superior images in a single breath holding period of approximately 20 seconds **(Fig. 65.1)**.

Accuracy is more in dilated system than in non-dilated system **(Tables 65.1, 65.2)**. Accuracy is better for biliary tree than pancreatic tree.

**Indications**

1. In some centres, MRCP is the initial imaging tool for the biliary system and ERCP is reserved for therapeutic indications.

2. Contraindication to ERCP: Known or suspected primary sclerosing cholangitis (PSC) (to avoid contrast injection related cholangitis).

3. MRCP is the imaging of choice to evaluate biliary enteric anastomosis.

**Sensitivity Specificity Accuracy**

MRC 89% 78% 87%

MRP 77% 67% 75%

MRC- Magnetic Resonance Cholangiography MRP- Magnetic Resonance Pancreatography

**Sensitivity Specificity Accuracy**

MRC 96% 96% 90%

Dilated

duct

MRP 100% 100% 90%

**Clinical Indications**

1. Post surgery biliopancreatic injury

2. Hilar cholangiocarcinoma for roadmap for palliation

3. Recurrent pancreatitis – for pancreas divisum

4. Chronic pancreatitis (secretin-enhanced MRCP preferred)

5. Cystic lesions of the pancreas

6. Post traumatic pancreatic duct injury

7. Choledochal cysts

**Contraindications**

1. Claustrophobia

2. Metal foreign body

3. Large amount of ascites (signal artifact from stationary fluid)

**Limitations of MRCP**

1. Increased cost and motion artifact

2. Less availability

3. Lack of therapeutic ability

4. Metallic clips and gastrointestinal/biliary air create artifacts

5. Poor sensitivity for small biliary stones (<4mm)

**MRCP in Various Pancreatobiliary Conditions**

***Biliary Obstruction***

1. MRCP is comparable with ERCP in detection of obstruction with accuracy more than 94%. In ERCP, ductal caliber may be over estimated due to contrast injection pressure, but MRCP ductal caliber is more accurately assessed.

***Choledocholithiasis***

1. Common bile duct calculi appear as dark filling defects within the high-signal-intensity fluid at MRCP.

2. Thin section images increase the sensitivity for small bile duct stone.

***Benign Biliary Stricture***

1. Like ERCP, MRCP accurately demonstrates the location and extent of extrahepatic biliary stricture. Accuracy of MRCP to detect intrahepatic stricture is limited due to narrow ductal diameter (such as in PSC).

***Malignant Biliary Stricture***

1. MRCP is highly accurate in evaluation of the extent of hilar stricture and forms a road map of biliary anatomy before any intervention.

2. Dilation of both pancreatic duct and common bile duct (double duct sign) suggests pancreatic neoplasm.

***Bilio-enteric Anastomosis***

1. MRCP is 100% sensitive to detect anastomotic stricture and 90% sensitive to detect biliary stone proximal to anastomosis.

***Chronic Pancreatitis***

1. Dilatation of main pancreatic duct, pancreatic duct stone and side-branch ectasia suggest chronic pancreatitis.

**Capsule endoscopy**

**Introduction**

Capsule endoscopy permits examination of small intestinal mucosa using wireless image capturing technology.

**Capsule**

Size 2.6 cm **(Fig.65.2)**

Weight 3.5 g

Field of view 140°

**Compartments**

1. Metal oxide silicon image sensor

2. Light Emitting Diode (LED)

3. Aerial belt with 8 aerials, which collects signal from the capsule

4. Software for analysis

**Methods**

1. Overnight fasting for at least 10 hours. Water mixed with dilute Simethicone can be used to minimize gas bubble related interference during image capturing.

2. The capsule is activated and swallowed with small quantity of water.

3. Tighten the belt, which contains eight aerials and patient can do normal activity.

4. Total time taken for procedure is around 8 hrs.

5. Capsule endoscopy takes around 50,000 images.

6. The images can be downloaded to a computer and viewed on software for interpretation. The software indicates approximate location of the capsule in the small intestine; this is beneficial in locating the lesion and planning deep enteroscopy accordingly.

**Indications of Capsule Endoscopy**

1. Crohn’s disease

2. Celiac sprue

3. Immunoproliferative small intestinal disease (IPSID)

4. Polyposis

5. Small intestinal tumour such as carcinoid and lymphoma

6. Recurrent abdominal pain with diarrhoea

7. Obscure gastrointestinal bleeding (after negative upper endoscopy and colonoscopy)

8. Recurrent iron deficiency anaemia

**Advantages**

1. Non-invasive

2. Disposable

**Disadvantages**

1. Cost (capsule costs approximately 500 US dollars)

2. Inaccurate localization of the site of the lesion

3. Capsule retention due to normal anatomic narrowing or pathologic narrowing such as stricture due to Crohn’s disease

**Contraindications**

1. Suspected bowel perforation.

2. Suspected bowel obstruction/ileus.

3. Patients with pacemaker.

**Radiofrequency ablation (RFA)**

**Introduction**

Barrett’s esophagus develops when stratified squamous epithelium of the distal oesophagus is replaced by columnar (gastric type) epithelium due to chronic acid exposure. This is a risk factor for oesophageal adenocarcinoma. RFA utilizes a network of bipolar electrodes on a balloon that generate radiofrequency-induced tissue ablation. Subsequently, healing occurs with squamous epithelium (>90% ablation of dysplastic Barrett’s epithelium). RFA is indicated for Barrett’s mucosa with dysplasia or intramucosal carcinoma.

**Advantages**

1. Controlled tissue ablation (effect limited to the mucosal layer).

2. Can be applied to small patches or long-segment diseases using focal or circumferential ablation.

3. Several studies report improved quality of life with ablation of BE.

**Disadvantages**

1. Can cause chest pain.

2. No tissue available for histologic analysis.

3. Oesophageal stricture resulting in dysphagia.

4. May need multiple procedures for long-segment disease.

5. Healing with squamous mucosa after RFA can hide untreated Barrett’s epithelium. This can later develop cancer and are difficult to identify endoscopically (buried glands).

**Chromoendoscopy**

**Introduction**

Chromoendoscopy or vital staining refers to staining of endoscopic tissue or topical application of chemical stains

or pigments to alter tissue appearance and thereby improving

localization, characterization and staging of the diseased mucosa.

**Vital Stains**

1. **Lugol’s solution**

Lugol’s solution (1.5–4%) contains iodine and potassium

iodide.Once the solution is sprayed on the esophagus, within minutes the normal whitish squamous mucosa will change to dark brown colour (binding of iodine to glycogen in squamous epithelium), while inflamed, dysplastic, or malignant mucosa will not stain **(Fig. 65.3 and Fig. 65.4)**.

n It is used to screen early squamous cell carcinoma.

n It also improves the diagnosis of Barrett’s oesophagus by highlighting columnar metaplastic epithelium, which remains pink or unstained, from squamous mucosa, which will turn brown in colour.

2. **Toluidine blue**

n Toluidine blue (1%) stains nuclei (absorptive stain).

n It does not stain squamous epithelium. Can be used as screening for early oesophageal cancer in tobacco users.

n It stains squamous cell carcinoma and both gastric and intestinal metaplasia.

3. **Methylene blue**

n Methylene blue is actively absorbed by small intestinal and colonic epithelium (vital stain).

n It will not stain nonabsorptive epithelium such as squamous or gastric mucosa.

n It is useful in diagnosis of early gastric cancer, Barrett’s oesophagus **(Figs 65.5 and 65.6)**, subtle mucosal changes in colon particularly in flat adenomas and carcinomas and dysplasia in patient with chronic inflammatory bowel disease **(Figs 65.7 and 65.8)**.

n It requires pretreatment mucolytic agents to remove surface mucus.

n Methylene blue-guided endoscopic biopsy improves results of surveillance in Barrett’s oesophagus and dysplasia in inflammatory bowel disease.

n Can be used with Congo red to improve visualization.

4. **Indigo carmine**

n Indigo carmine is a contrast stain.

n It is nonabsorbable blue stain, which pools in crevices between mucosal projections.

n It highlights mucosal irregularities in Barrett’s oesophagus and flat colorectal tumours.

n It can be used with magnification or high-definition endoscopy.

5. **Congo red**

n Changes colour from red to dark blue/black in acidic environment.

n It is used to distinguish acid-producing epithelium from non-acid producing areas in the stomach (early gastric

malignancy, intestinal metaplasia and to assess effectiveness of vagotomy).

**NARROW BAND IMAGING (NBI)**

NBI or electronic chromoendoscopy utilizes high-resolution endoscopy using diverse wavelengths of the light. Blue light

has superficial penetration and red light has deepest mucosal penetration. This change from normal white light endoscopy is achieved by a microprocessor. The pattern of Red, Green and Blue (RGB) illumination can be selected by the endoscopist. NBI improves characterization of GI epithelium including Barrett’s oesophagus.

**Advantages**

1. Requires no special dyes or chemicals.

2. Can rapidly change from white light to NBI and vice versa.

3. Allows assessment of superficial vascular pattern, which can improve targeted biopsies.

4. High sensitivity (96%) and specificity (94%) for high-grade dysplasia in Barrett’s oesophagus.

**Disadvantages**

1. Standardized classification of image characteristics not yet available.

2. May not improve interobserver agreement.

3. No added advantage of improved detection of lesions compared to chromoendoscopy.

**PROBE BASED CONFOCAL LASER ENDOMICRO SCOPY (pCLE)**

This technique utilizes a low power laser beam that detects fluorescence of GI tissue at a specific depth. The beam of reflected light is passed through a confocal aperture to improve spatial resolution. The area under examination can be scanned in various planes to achieve real time microscopic

imaging of the tissues in vivo. Intravenous Fluorescein 10% solution, 3 mL is required prior to imaging. The probe with laser and imaging module is passed through the endoscope channel and guided using endoscope camera to the area of interest.

**Advantages**

1. Can be used with current endoscopic equipment.

2. Allows targeted sampling or resection (i.e., focus of early cancer in a large area of intestinal metaplasia in the stomach).

3. Probes are available for examination of intestinal, biliary and pancreatic mucosa.

4. Can be used to differentiate benign from malignant biliary strictures.

5. Can identify dysplastic lesions in Barrett’s oesophagus.

**Disadvantages**

1. Operator dependent technique.

2. Cannot scan large areas such as long segment Barrett’s oesophagus.

3. Interference from luminal mucus, debris.

4. Limited probe life requiring replacement.

5. Lack of standardization in imaging classification.

**CHOLANGIOSCOPY AND PANCREATOSCOPY**

These procedures involve per oral or through the duodenoscope channel insertion of a slim fiberoptic endoscope into the bile (Spy scope) or pancreatic duct. These techniques provide visualization of bilopancreatic ductal epithelium and allow sampling using cytology, brushing and focused biopsy. New, digital cholangioscopes with higher resolution CCD chips are under development.

**Indications**

1. Difficult bile or pancreatic duct stones requiring Electrohydraulic or laser lithotripsy.

2. Evaluation and sampling of indeterminate biliopancreatic strictures.

3. Removal of impacted intrahepatic duct stones.

4. Evaluation of primary sclerosing cholangitis (PSC).

**Limitations**

1. Insertion can be challenging in a nondilated ductal system.

2. Visualization impaired by blood, mucus, sludge/stone fragments.

3. Constant water irrigation is required to maintain adequate visualization.

4. Risk of cholangitis is higher than standard ERCP.

5. Pancreatoscopy can lead to acute pancreatitis following the procedure.

**Endoscopic Mucosal resection**

**Introduction**

Endoscopic mucosal resection (EMR) is a minimally invasive endoscopic technique used in treating superficial cancers or premalignant lesions in the gastrointestinal (GI) tract. EMR can be combined with chromoendoscopy to accurately assess lateral margins of the lesion prior to resection.

**Indications**

EMR is indicated for the removal of both benign and malignant lesions limited to the mucosa.

***Oesophageal Lesions***

Dysplastic area presents in squamous epithelium, dysplasia in Barrett’s oesophagus, early oesophageal cancer.

***Gastric Lesions***

Early gastric cancer is defined as gastric cancer limited to mucosa. Other use of EMR in stomach is for adenomatous polyps and gastric carcinoids.

***Colonic Lesions***

EMR is normally used for depressed or flat-type lesions such as serrated adenomas.

**EMR Techniques**

1. ***Strip biopsy technique* (Fig. 65.9)**

n Saline injection into the submucosal layer is the most effective technique to avoid muscle entrapment in the snare and perforation.

n A snare is then advanced through endoscope channel and the lesion is pulled while the snare is positioned at its base. Complete resection is achieved by electrocauterizing the mucosa beyond the margin of the lesion.

2. ***EMR cap technique (EMRC)***

n EMRC requires a special transparent plastic cap fitted onto the tip of an endoscope.

n Superficial lesion is sucked in the plastic cap and then is snared by the forceps.

3. ***EMR with variceal ligation (EMRL)***

n EMRL uses a standard endoscopic variceal ligation device fitted onto the tip of an endoscope.

n The lesion is sucked into the cap and a band is deployed to create a polypoid target.

n The polypoid target is snared at its base above or below the rubber band and resected by electrocautery using a standard polypectomy snare.

**Patient Evaluation before EMR**

Endoscopic ultrasound (EUS) using a 20 MHz high-frequency probe is most suited to exclude submucosal invasion. Depth of tumor invasion, involvement of lymph nodes and vascular structures are the most important parameters evaluated by 7.5 MHz EUS. EMR is contraindicated if EUS suggest submucosal invasion (approximately 10% chance of lymphovascular invasion) and involvement of muscularis propria (increased risk of perforation).

EMR is not ideal for lesions larger than 15mm due to potential incomplete resection. Piecemeal resection results in loss of anatomical configuration and accurate assessment of depth of invasion.

**Complications of EMR**

Bleeding and perforation are the most common complications of EMR. Careful assessment of resection margins, adequate timing of electrocauterization during resection and detailed examination of resection bed to exclude perforation, deep wall layer injury and bleeding vessels can minimize above complications. Resection bed can be approximated using endoscopic clips if indicated.

**Endoscopic submucosal dissection (ESD)**

Endoscopic submucosal dissection involves use of a specialized endoscopic knife to dissect submucosal or deeper lesions. This technique allows en bloc resection of large lesions while achieving negative lateral and deep margins. ESD is extensively studied in early gastric cancers and now being increasingly extended for the removal of esophageal, duodenal and colonic lesions.

The lesion for resection is first examined using EUS to exclude exophytic extension or deep muscularis propria invasion. Circumferential marking of the lesion is achieved using cautery marks to ensure negative margin resection (R0). Volume expanding agents such as saline or artificial tear is injected to achieve expansion of submucosa. The lesion is then resected using a knife and electrocautery in its entirety.

**Advantages**

1. Higher en bloc resection rate compared to EMR.

2. Excellent cure rate and long-term outcome in selected patients.

3. Can remove larger (>2 cm) lesions with negative margins.

4. ESD knife can be used for coagulation of submucosal blood vessels during the procedure.

5. Newer ESD knives have non-conducting tip allowing lateral resection without deeper tissue injury.

6. Some ESD knives have high pressure fluid injection port allowing lifting of the submucosa during the procedure as needed. This minimizes accessory change and reduces operating time.

7. ESD can be performed as outpatient procedure in hands of an expert.

**Disadvantages**

1. This technique has steep learning curve and may require training in animal models initially.

2. Higher rate of complications such as bleeding, perforation, stricture and injury to adjacent organs.

**endoscopic full thickness resection (EFTR)**

This technique is applied to the GI tract lesions arising from muscularis propria, most commonly for the removal of stromal tumours. Using ESD knives, full thickness resection of the lesion (usually <3 cm) is performed. The wall layer defect is approximated using various endoscopic suturing devices or clips. Carbon dioxide is used as insufflating agent instead of air; this allows rapid absorption and excretion from the body thus minimizing the risk of tension pneumoperitoneum.

**Advantages**

1. Allows en-bloc resection of muscularis based tumors endoscopically.

2. Minimally invasive endoscopic technique obviating the need for laparoscopy.

3. Comparable operative time in experienced hands.

4. Ideal for tumours for exo-endophytic components.

5. Shorter hospitalization compared to standard surgical procedures for such lesions.

**Limitations**

1. Steep learning curve, requires significant experience in endoscopic resection technique, haemostasis and perforation closure.

2. Limited use for the tumours >3.5cm in size and high mitotic rate.

3. Possible creation of tension pneumoperitoneum requiring percutaneous decompression.

**submucosal tunneling endoscopic resection (STER)**

This technique is used for resection of muscularis based tumors of the gastroesophageal area without creating a full thickness resection. Submucosal injection of volume expander is performed a few centimeters above the lesion and the mucosa is breached. A tract is then created in the submucosa in the direction of the lesion (submucosal tunnel). This tract is further deepened with submucosal dissection using a knife or balloon into the muscularis propria layer and the lesion is encountered. This creates a double flap Z tunnel, which prevents entry of luminal contents into outer wall layers and promotes immediate closure. The lesion is resected using endoscopic knife and removed through the tunnel. The mucosal entry point of the tunnel is then closed using endoscopic clips. Limited clinical studies demonstrate excellent safety profile and completeness of resection. This technique is particularly useful in the lesions of the esophagus, gastroesophageal junction and cardia area, where laparoscopic resection is challenging. This technique is also utilized in creating disruption of pylorus in patients with gastroparesis (endoscopic pyloromyotomy).

**peroral endoscopic myotomy for achalasia (POEM)**

POEM is a variant of natural orifice transluminal endoscopy (NOTES), where a myotomy of the lower esophageal sphincter (LES) is performed endoscopically for the treatment of achalasia. A submucosal tunnel is created as in STER technique and circular muscle fibres and LES fibres

are incised using an ESD knife. The submucosal tunnel is then closed.

**Advantages**

1. Minimally invasive technique for long-term treatment of achalasia.

2. Shorter hospitalization and no major complications noted in limited clinical trials.

3. Heller myotomy and balloon dilation can be performed safely if this technique does not improve dysphagia.

4. Can be performed in patients with failed Heller’s myotomy, pneumatic balloon dilation and botox injection.

**Limitations**

1. Identical oesophageal reflux related symptoms compared to laparoscopy.

2. Limited availability of the operators trained to perform POEM.

3. Lack of availability of long-term efficacy and safety data.

**Endoscopic ULTRASONOGRAPHY (EUS)**

**Introduction**

Endoscopic ultrasonography (EUS) provides sonographic visualization of gastrointestinal wall layers as well as

periluminal organs **(Fig. 65.10)**. EUS is used for T and N cancer staging and evaluation of lesions of gastrointestinal wall layers. EUS-guided fine needle aspiration (FNA) allows accurate histologic diagnosis of pancreatic cystic lesions, primary and metastatic lesions, and permits accurate TNM staging (tumour, regional lymph node and metastasis).

**Equipment**

EUS is either radial or linear echoendoscope and high frequency mini probe EUS. Radial EUS **(Fig.65.11)** provides a 360° cross-sectional image oriented perpendicularly to the shaft of the endoscope. Viewing frequency in most systems is between 7.5 and 12 MHz Linear array EUS provides images along the axis of the scope **(Fig. 65.12)**. The frequency used is 5 and 7.5 MHs. Linear EUS is used for EUS-guided FNA, celiac plexus neurolysis and Doppler study. Probe based EUS system allows examination of GI wall layers using high-frequency at up to 20 MHz. EUS probes designed to work over a guidewire can be used for examination of the bile and pancreatic duct and strictures.

**Applications of EUS**

***Diagnostic***

1. Local staging of oesophageal cancer

2. Diagnosis of early gastric cancer, evaluation of thickened gastric folds

3. Following EMR in early gastric cancer and anti-*H.pylori* therapy in low-grade MALT lymphoma

4. Evaluation of subepithelial lesions along the GI tract

5. Local staging of periampullary carcinoma

6. To evaluate cystic lesion of the pancreas

7. Diagnose choledocholithiasis (higher sensitivity and specificity than MRCP and ERCP)

8. Diagnosis of chronic pancreatitis and biliary microlithiasis

8. Local staging of rectal cancer

***Therapeutics***

1. Celiac plexus block in treating pain of chronic pancreatitis

2. Transenteric drainage of pancreatic pseudocyst

3. Botulinum toxin injection in primary achalasia

4. EUS-guided radiofrequency ablation therapy in patients with hepatocellular carcinoma

5. EUS-guided transrectal abscess drainage

6. EUS-guided antegrade biliary access and drainage

7. EUS-guided glue or coil instillation for obliteration of gastric varices

8. EUS-guided fiducial placement in the malignant pancreatic lesions for stereotactic radiation

**Double-balloon enteroscopy**

**Introduction**

The 6-meter length of the small intestine is difficult to assess endoscopically. Capsule endoscopy permits only diagnostic evaluation. Ability of pleating the small bowel over an overtube using balloons now permits real time diagnostic and therapeutic interventions in the small intestine.

**Equipment**

There are two balloons; one is on the tip of the endoscope and the other is on sliding overtube **(Fig. 65.13)**. The endoscope is first inserted into the stomach with both the balloons deflated.

When the scope reaches the stomach, overtube is advanced. Then the scope is inserted to the second part of duodenum. The balloon on the endoscope is then inflated so that it maintains a stable position within the intestinal lumen. The overtube is advanced along the endoscope until the overtube tip enters the duodenum. With both balloons inflated, the endoscope is gently withdrawn together with the overtube to straighten it. The balloon on the endoscope tip is then deflated.

The endoscope is advanced along the overtube, which is being held by the assistant, until the distal end of the scope reaches the ligament of Treitz. At this point, the overtube tip is fixed in a stable position in the duodenum, so that the scope advances further without becoming looped again in the stomach.

After the balloon at the tip of the scope is inflated and fixed in a stable position in the intestine, the balloon on the overtube tip is deflated so that the overtube can be advanced again along the scope up to the balloon at the distal end. Such repetitive maneuvers allow pleating of small bowel over the overtube and deep intubation of small intestine by the primary endoscope.

**Indications**

1. Obscure gastrointestinal bleeding

2. Small intestinal Crohn’s disease

3. Suspected small bowel malignancy

4. Radiographic abnormalities in the small intestine

5. Unexplained chronic diarrhea and chronic abdominal pain

6. Polyposis syndrome

**Signle-balloon enteroscopy**

Detailed features of the single balloon entero-scope can be seen in **Fig. 65.14**.

1. **Reduced examination times**

Set-up consists of simply wetting the inner surface of the splinting tube, which is attached to the balloon control unit, with water and passing the scope through it. The system is controlled by repeatedly inflating and deflating a single balloon via a remote controller. This eliminates the need for complex operations, thereby reducing the time required for examinations.

2. **High image resolution, improved insertability and larger channel diameter**

Use of CCD allows higher image resolution. The outer diameter of the enteroscope is 9.2mm, which permits flexibility to percolate through unanchored small bowel. This endoscope features 2.8mm accessory port, which can be used for biopsy/polypectomy/hemostasis.

3. **Support for NBI**

This system is supported by narrow band imaging (NBI).

4. **Splinting tube made from silicone rubber**

The splinting tube is made up of silicon rubber, thus biocompatible. To facilitate insertion deep into the small bowel, the inner surface of the tube has been treated with a hydrophilic lubricant coating to allow the insertion section of the endoscope to move freely.

**Spirus overtube enteroscopy**

This instrument features soft, spiral network over the over tube, which allows pleating and maintains pleated small bowel while an enteroscope achieves deep intubation.

Pleating of the small bowel is achieved by gentle rotating motion of the over tube, which results in backward rotations of the spiral and pleating of the bowel. This is undone by rotating the overtube in the reverse direction while withdrawing. This technique can be used as an alternative to single/double balloon enteroscopy. Successful use is described in patients with bariatric surgeries such as Roux n y gastric bypass where bariatric (roux) limb is created longer (approximately 140 cm).

**Contraindications of Small Bowel Enteroscopy**

1. Extensive adhesions of small bowel from multiple surgeries increases risk of perforation

2. Known small bowel stricturing disease

**Argon plasma coagulation**

**Introduction**

The argon plasma coagulator (APC) is a non-contact method of delivering high-frequency monopolar current through ionized and electrically conductive argon gas, which is called argon plasma. Generally, the zone of coagulation is 1–3 mm.

**Clinical Applications**

1. Adjuvant therapy after piecemeal resection of gastrointestinal polyps

2. Vascular lesion like angiodysplasia or gastric antral vascular ectasia (GAVE)

3. Ablation of Barrett’s oesophagus

4. Bleeding peptic ulcer disease

5. Radiation proctitis

**Positron emission tomography**

**Introduction**

Positron emission tomography (PET) is used in gastrointestinal oncology for staging of various cancers.

**Principles of PET**

FDG (18F-fluorodeoxyglucose) is a radiotracer that is the most clinically used in PET. FDG has high uptake in most cancers. FDG competes with glucose for transport into the cell and for enzymatic phosphorylation by hexokinase. Once FDG is phosphorylated into FDG-6-phosphate, it is trapped inside the cell and does not undergo further metabolism and is detected by PET.

**Role of PET in Gastroenterology**

FDG uptake is mostly seen in the large bowel and to a lesser extent in the small bowel and stomach. Activity in the cecum is usually higher than in the other colonic segments, which has been attributed to abundant lymphoid tissue in that area.

There is usually a normal homogeneous uptake in the liver, and to a lesser extent in the spleen.

1. **Role of PET in colorectal cancer**

PET can be used to exclude hepatic/other metastasis preoperatively in patients with colorectal cancer. Numerous studies have demonstrated a strong role for FDG-PET in identifying recurrences of colorectal carcinoma. For diagnosing recurrent colon carcinoma, FDG-PET has been found to be more sensitive than CT at all anatomic sites except the lung, where the both CT and PET are equivalent.

Whole-body PET is especially useful for detecting distant metastatic disease because one-third of PET-positive metastases in the extrahepatic abdomen and pelvis are CT-negative.

2. **Oesophageal and gastric carcinoma**

Approximately one-third of the patients undergoing surgery are found to have occult metastases. Published reports with oesophageal and gastric carcinoma suggest that FDG-PET is highly sensitive to detect the primary tumors as well as liver and distant metastases.

3. **Pancreatic cancer**

FDG-PET can differentiate benign from malignant lesions. The rate with which FDG-PET results may lead to alterations in clinical management is not defined in pancreatic malignancy. PET is useful in patients with suspected pancreatic cancer in whom CT fails to identify a discrete tumour mass.

4. **Hepatobiliary tumour**

The accumulation of FDG in hepatocellular carcinoma is variable. All benign tumours, including fibronodular hyperplasia, adenoma and regenerating nodules, have FDG

uptake similar to normal liver. In patients with hepato-cellular carcinomas PET can detect unsuspected metastases and lead to a change in management.

**Pillcam ESO**

**Introduction**

Although the oesophagus is readily visualized during esophagogastroduodenoscopy (EGD), many patients may not undergo this procedure because of concerns about invasiveness, discomfort and sedation issues. Esophageal capsule endoscopy serves as an alternative imaging procedure to traditional upper endoscopy.

**Instrument**

The Given Diagnostic System (Pillcam ESO) is comprised of three major components:

1. An ingestible oesophageal capsule

2. A data recorder, which includes a recorder belt and sensor array

3. A RAPID workstation

4. The ingestible, disposable Pillcam ESO is an 11 x 26 mm capsule and is able to acquire images from both ends of the device during passage through the oesophagus at a rate of 7 frames/sec (2 frames/sec for capsule endoscopy for small bowel) from each end of the capsule.

5. After completion of the 20-min examination, the accumulated data can be transferred from the recording unit to the RAPID workstation for processing and interpretation.

6. Pillcam ESO is developed to visualize the oesophagus, although both the stomach and proximal duodenum may be visualized. The capsule battery life may end before the capsule passing through the pylorus. Thus, Pillcam ESO is used mainly for the evaluation of oesophagus.

**Uses**

1. Evaluation of chronic GERD.

2. Screening for oesophageal varices in patients with chronic liver disease.

**Advantages of Pillcam ESO**

1. Convenience

2. Patient acceptability

3. Safety

4. Tolerability

5. Administration by a non-physician provider

6. Potentially increased adherence to screening recommendations

**Disadvantages**

1. Inability to insufflate air in Pillcam ESO lead to underestimate the “true” size of oesophageal varices.

2. Pillcam ESO is unable to assess the presence or absence of gastric varices.

3. Pill retention if stricture of small bowel is present

**Endoscopic Procedures for Weight Loss**

Endoscopy is used as minimally invasive approach to attain significant weight loss for patients with BMI <40. One of the most common approaches is insertion of air or saline filled silicon balloon into the gastric lumen to restrict caloric intake. The patients are able to loose approximately 10–15% total body weight in six months; the balloon is removed at that point. Common side effects of this procedure include worsening acid reflux, hiccups, nausea and vomiting and rarely perforation and bowel obstruction. With the availability of endoscopic suturing devices, endoscopic sleeve gastroplasty has emerged as promising approach.

Using permanent suture material, gastric lumen is restricted by creating a sleeve along the greater curve of the stomach endoscopically. Current data indicate approximately 50% less caloric ingestion and up to 50% loss of excess weight in 9 months.

**Further Reading**

1. Fergus V Coakley, Aliya Qayyum. Magnetic resonance cholangiopancreatography. *Gastrointest Endosc* 2002;55: S2–12.

2. Ginsberg GG. Wireless capsule endoscopy. *Gastrointest Endosc* 2002;56:621–4.

3. Isenberg GA. Virtual colonoscopy. *Gastrointest Endosc* 2003; 57: 451–4.

4. Gregory Monkewich, Gregory Haber. Novel endoscopic therapies for gastrointestinal malignancies: endoscopic mucosal resection and endoscopic ablation. *Med Clin of North Am* 2005; 89: 159–86.

5. Iqbal Sandhu, Manoop Bhutani. Gastrointestinal endoscopic ultrasonography. *Med Clin North Am* 2002;86:1289–317.

6. Delbeke D, Martin WH. Positron emission tomography imaging in oncology. *Radiol Clin North Am* 2001;39:883–917.

7. Gralnek IM, Rabinowitz R, Afik D, et al. A simplified ingestion procedure for esophageal capsule endoscopy: initial evaluation in healthy volunteers. *Endoscopy* 2006; 39:913–18.

8. Zhang B, et al. Endoscopic full-thickness resection of gastric stromal tumor arising from the muscularis propria. *Chinese Med J* 2013;126:2435–9.

9. Liu BR, Song JT, Kong LJ, et al. Tunneling endoscoic muscularis dissection for subepithelial tumors originating from the muscularis propria of the esophagus and gastric cardia. *Surg Endosc* 2013;14:4354–9.

11. Tate CM, Geliebter A. Intragastric balloon treatment for obesity: Review of recent studies. *Adv Ther* 2017;34:1859–75.

12. Stavropoulos SN, Modayil R, et al. Current applications of endoscopic suturing. *World J Gastrointest* *Endosc* 2015; 7:777–89.

**Chapter 66.**

**Focal Points**

**Esophagus**

**Los Angeles Classification of Endoscopic Severity of Esophagitis**

1. *Grade A*: One or more mucosal breaks no longer than 5 mm that do not extend between the tops of two mucosal folds.

2. *Grade B*: One or more mucosal breaks more than 5 mm that do not extend between the tops of two mucosal folds.

3. *Grade C*: One or more mucosal breaks that are continuous between the tops of two or more mucosal folds, but involve less than 75% of the circumference.

4. *Grade D*: One or more mucosal breaks that involve at least 75% of the circumference.

**Classification of Barrett’s Mucosa**

1. Long-segment Barrett’s mucosa: Pink salmon colored mucosa extends 3 cm or more proximally from gastroesophageal (GE) junction with intestinal metaplasia.

2. Short-segment Barrett’s mucosa: Metaplastic epithelium projects less than 3 cm from the GE junction with intestinal metaplasia.

3. Cardia intestinal metaplasia or GE junction intestinal metaplasia (not Barrett’s mucosa):

No metaplastic tongue is evident projecting from GE junction, but histology shows specialized intestinal metaplasia distal to squamocolumnar junction.

**Endoscopic Classification of Z-line (squamo-columnar junction)**

1. *Grade 0*: Z-line is sharp and circular.

2. *Grade I:* Z-line is irregular and tongue-like projection and/or islands of columnar appearing epithelium.

3. *Grade II*: Columnar epithelial extension less than 3 cm from GE junction.

4. *Grade III*: Columnar epithelial extension more than 3 cm from GE junction.

Magnification endoscopy (using acetic acid) classification of columnar epithelium below Z-line (80 magnification) given in **Table 66.1**.

**Manometry Classification of Oesophageal Motility**

1. Inadequate LES relaxation

n Classical achalasia

n Atypical disorder of LES relaxation

**Type Endoscopic Inference**

**appearance**

I Round pits Fundic epithelium

II Tubular pits Cardiac mucosa

III Thin linear Cardiac mucosa

IV Deep linear Barrett’s mucosa

V Villous Barrett’s mucosa

VI Foveolar Barrett’s mucosa

VII Cerebroid Barrett’s mucosa

2. Uncoordinated contractions

n Diffuse oesophageal spasm

3. Hypercontraction

n Nutcracker oesophagus

n Isolated hypertensive LES

4. Hypocontraction

n Ineffective esophageal motility

**Manometry Criteria of Primary Achalasia**

***Essential***

1. Incomplete or absent LES relaxation (mean swallow induces fall in LES pressure to a nadir value more than 8 mm above gastric pressure, residual pressure).

2. Lower oesophageal aperistalsis (simultaneous oesophageal contraction with amplitude less than 30 mmHg or no apparent esophageal contraction).

***Ancillary***

1. Resting LES pressure more than 45 mmHg

2. Resting pressure in the esophagus is more than resting pressure in stomach (more pressure gradient)

3 Other motility changes that can be seen

n Abnormalities of UES

n Pyloric spasm

**Manometry Criteria of Diffuse Esophageal Spasm (DES)**

1. Simultaneous contractions associated with more than 10% wet swallow

2. Mean simultaneous contraction amplitude is more than 30 mmHg

**Manometry Criteria of Nutcracker Oesophagus**

1. Peristaltic waves with mean amplitudes > 2 SD above normal

2. Mean distal oesophageal peristaltic wave amplitude > 180 mmHg

**Three-Tier Oesophageal Defensive System to Prevent Gastric Reflux**

1. Anti-reflux barrier

n Intrinsic LES pressure

n Extrinsic compression by the crural diaphragm

n Intra-abdominal location of LES

n Integrity of phreno-esophageal ligaments

n Acute angle of His between distal oesophagus and proximal stomach acts as flap valve function

2. Luminal clearance

n Gravity

n Esophageal peristalsis

n Salivary flow

n Oesophageal glands secretion

3. Epithelial resistance

**Classical GERD Surgeries**

1. Nissen fundoplication

2. Belsey Mark IV repair

3. Hill posterior gastropexy

**Endoscopic Therapy of GERD**

1. Endoscopic suturing (endocinch device)

2. Radiofrequency ablation

3. Submucosal injection – Enteryx

4. Gate keeper therapy by placing hydrogel prosthesis

5. Full thickness device (NDO device)

**Novel Medical Therapy for GERD**

All drugs target t-LESR (transient lower esophageal sphincter relaxation)

1. CCKA antagonist – loxiglumide

2. Anti-cholinergic agents

3. Nitric oxide

4. Morphine

5. GABAB agonist – baclofen

**Ablation of Barrett’s Oesophagus**

1. Multipolar electrocoagulation

2. Argon plasma coagulation

3. Photodynamic therapy

4. Endoscopic mucosal resection (EMR)

**General Points**

1. Oesophagus is 18–26 cm in length

2. Lies in posterior mediastinum

3. Leaves thorax at T10 level through diaphragmatic hiatus

4. Length of LES is 2–4 cm.

5. Coordination of skeletal muscles of oesophagus is by nucleus ambiguus and smooth muscles by dorsal motor nucleus of vagus.

6. Most common congenital tracheo-esophageal fistula is that in which the trachea communicates with the distal segment of the atretic oesophagus.

7. Oesophageal webs, unlike oesophageal rings, incompletely encircle the oesophageal lumen.

8. Only 30–40% of symptomatic GERD (gastroesophageal reflux disease) patients have endoscopic evidence of erosive oesophagitis.

9. LES pressure less than 6 mmHg, LES length less than 2 cm and intra-abdominal length of oesophagus less than 1 cm are strongly associated with GERD.

10. Overall failure rate of PPI (proton pump inhibitor) to treat GERD is 11–33%.

11. Almost all patients would relapse following discontinuation of PPI in GERD if LES pressure is less than 10 mmHg.

**Stomach and duodenum**

**Conventional Classification of Gastritis**

1. Acute/haemorrhagic/reactive/erosive

2. Chronic/non-haemorrhagic/non-erosive

3. Specific/distinctive forms

**Revised Sydney Classification of Gastritis**

1. Erosive/haemorrhagic gastritis

n Stress

n NSAID

n Alcohol

n Radiation

2. Non-erosive/non-specific/chronic gastritis

n Diffuse antral gastritis

n Type B gastritis

n Associated with *H. pylori*

n Multifocal atrophic gastritis

n Type AB gastritis

n Associated with *H. pylori* and dietary factors

n Diffuse corporal atrophic gastritis

n Type A gastritis

n Associated with pernicious anemia

3. Specific forms

n Granulomatous

n Chemical

n Lymphocytic

n Collagenous

n Eosinophilic

n Infectious

**General Points**

1. Gastroesophageal junction is located at D10 level and gastroduodenal junction at L1.

2. Antrum of the stomach has predominant endocrine cells (G-cells; D-cells) and corpus has predominant exocrine cells (mucus neck cells: parietal cells and chief cells).

3. Gastric secretion is stimulated by

n Gastric distension

n Vagal stimulation

n Dietary amino acids

4. Junction of foregut and midgut lies at 2nd part of duodenum slightly distal to ampulla.

5. Duodenum is 20 cm long; 1st and 4th part are 5 cm and 2nd and 3rd part is 10 cm long.

6. Ratio of villi to crypt in duodenum are 4:1 or 5:1.

7. Commonest site of gastric diverticulum is posterior wall of cardia.

8. Near the ampulla in second part of duodenum is the most common site of duodenal atresia.

9. Function of proximal stomach is accommodation and storage of food. While distal stomach helps in grinding and regulation of gastric emptying.

10. Migrating motor complex (MMC) occurs in fasting state for propulsion of undigested food particles and sloughed epithelium.

11. Conditions associated with increased gastric secretion

n Duodenal ulcer

n Zollinger-Ellison syndrome

n Retained antrum syndrome

n Foregut carcinoid

n Antral G-cell hyperplasia

n Systemic mastocytosis

n Hypercalcaemia

12. Conditions associated with decreased gastric secretion

n Chronic atrophic gastritis

n AIDS

n Hypocalcaemia

n VIPoma

n Somatostatinoma

13. *H. pylori* is Gram-negative, microaerophilic, highly motile, slow growing spiral organism.

14. Culture media used for *H. pylori*

n Brain heart infusion agar

n Egg-yolk agar

n Trypticase agar

15. Histological staining for *H. pylori*

n Hematoxin eosin stain

n Warthine starry silver stain

n Geimsa

n Genta stain

n EI-Zimaity triple stain

16. Around 80% of population by second decade have *H. pylori* antibody, in developing countries like India

17. Urea breath test (UBT) is the most accurate test to diagnose *H. pylori* in bleeding peptic ulcer.

18. In presence of severe atrophic gastritis, yield of histology for *H. pylori* is very low, so cure should be documented by either UBT or stool antigen test.

19. In rapid urease test (RUT), tissue should be taken from 5 cm proximal to pylorus near angularis.

20. Drugs causing peptic ulcer:

n NSAIDs

n Cancer chemotherapy

n Potassium chloride

n Alendronate

n Hepatic arterial infusion of 5-FU

21. Six biopsy specimens are 98% sensitive to diagnose cancer in gastric ulcer.

22. Proton pump inhibitors (PPI) are metabolized by CYP-450 system.

23. Plasma half-life of PPI is < 2 hours, but due to covalent binding of H+ K+ ATPase, its duration of acid suppression is 24 hours.

24. Sucralfate contains aluminum hydroxide, which produces toxicity in renal failure.

25. Refractory ulcer is defined as failure of peptic ulcer to heal after 12 weeks of adequate anti-secretory agents in absence of concomitant NSAID use of *H. pylori* infection.

26. Gastrinoma triangle is defined, superiorly by the confluence of cystic and common bile duct; medially, by the junction of neck and body of the pancreas and inferiorly, by junction of second and third part of duodenum.

27. Site of perforation in PUD

n Anterior wall of duodenal bulb

n Lesser curvature of stomach

28. Curling’s ulcer: Acute peptic ulcer occurs in patients with severe burns.

29. Cushing’s ulcer: Acute peptic ulcer occurs in patients with head injuries.

**Biliary tract**

**Classification of Extrahepatic Biliary Atresia**

1. Type I (10%): Atresia of common bile duct (CBD) with patent proximal ducts

2. Type II (2%): Common hepatic duct (CHD) atresia with dilated bile duct at porta hepatis

3. Type III (88%): Atresia at porta hepatis

**Todani’s Classification of Choledochal Cyst**

1. Type I (82%): Saccular or fusiform dilatation of common hepatic duct or common bile duct

2. Type II (2.5%): Choledochal diverticulum

3. Type III (4%): Choledochocele/intra-duodenal bile duct dilatation

4. Type IV(A) (11%): Fusiform intrahepatic and extrahepatic duct dilatation

5. Type IV(B): Multiple extrahepatic duct dilatation

6. Type V: Caroli’s disease

**Modified Milwaukee Classification of Biliary Sphincter of Oddi Dysfunction (SOD)**

***Type I***

1. Biliary type pain

2. Serum AST or ALT > 1.1 times normal on one occasion

3. CBD diameter > 10 mm

***Type II***

1. Biliary type pain

2. One of two additional criteria

***Type III***

1. Biliary type pain only

**Classification of Pancreatic SOD**

***Type I***

1. Pancreatic type pain

2. Serum amylase or lipase level > 1.1 times normal on one occasion

3. Pancreatic duct dilatation (> 6 mm in head and 5 mm in body)

***Type II***

1. Pancreatic type pain

2. One of two additional criteria

***Type III***

1. Pancreatic pain only

**Bismuth Classification of Benign Biliary Stricture (Fig. 66.1)**

Type I: Lower CHD stricture with stump more than 2 cm long

Type II: Proximal CHD stricture with stump less than 2 cm long

Type IIIa: Hilar stricture but patent confluence

Type IIIb: Involvement of either right or left system

Type IV: Involvement of sectoral ducts

**Strasburg Classification of Laparoscopic Bile Duct**

**Injury**

A. Bile leaks from minor ducts (most common)

B. Occlusion of part of biliary tree (usually aberrant right sectoral duct)

C. Like B, transaction without ligation

D. A lateral injury to extrahepatic bile duct

E. E1–E5 like Bismuth classification

**Pronucleators and Antinucleators in Gallstone**

**Formation (Table 66.2)**

**Pronucleators Antinucleators**

Mucin glycoprotein Apolipoprotein AI, AII

IgG, IgM, IgA Apolipoprotein B

Heptoglobin UDCA

Phospholipase C Biliary glycoprotein

Fibronectin Bile acid conjugates

**Ludwig Staging System of Primary Sclerosing Cholangitis**

1. *Stage I*: Portal hepatitis with or without bile duct abnormality

2. *Stage II*: Periportal fibrosis

3. *Stage III*: Septal fibrosis or bridging necrosis

4. *Stage IV*: Cirrhosis

**Ludwig Staging System of Primary Biliary Cirrhosis**

1. *Stage I*: Inflammation within the portal tract focused on bile ducts

2. *Stage II*: Inflammation extending to hepatic parenchyma

3. *Stage III*: Fibrosis

4. *Stage IV*: Cirrhosis

**Classification of Progressive Familial Intrahepatic Cholestasis (PFIC) (Table 66.3)**

**Type Gene Transpo- GGT Effect of**

**defect rter defect UDCA**

I 18 FIC 1 Normal +

II 24 BSEP Normal -

III MDR3 Increased ±

**Types of Bile Acids**

***Primary Bile Acids***

1. Cholic acid (CA)

2. Chenodeoxycholic acid (CDCA)

***Secondary Bile Acids***

1. Deoxycholic acid (DCA)

2. Lithocholic acid (LCA)

***Tertiary Bile Acids***

1. Ursodeoxycholic acid (UDCA)

2. Sulfated LCA

Two-third of bile salts are conjugated with glycine and one-third with taurine.

**Use of Bile Salts Conjugation**

1. Prevent passive diffusion during passage through biliary ducts

2. Maintain high intraluminal bile acids

**Critical Micellization Concentration (CMC)**: Bile acid molecules that self-aggregate to form simple micelles over a narrow concentration range.

**Cholesterol Saturation Index (CSI)**: Amount of cholesterol present in the bile divided by solubility of bile and phospholipids. Normal CSI is less than 1. CSI > 1 is called supersaturated bile.

**Nucleation time**:When fresh sample of bile centrifuged, and maintained at 37oC in a dust-free environment, the time at which cholesterol microcystals appear is defined as the nucleation time. Nucleation time in stone free patients is around 10–15 days while in patients with gallstone is less than 5 days. **(Table 66.4)**

**Gallstones sequelae Frequency (%)**

Asymptomatic biliary colic 75

Intermittent biliary colic 20

Cholecystitis 8–10

Cholangitis/Pancreatitis 5

Mirizzi syndrome 0.1

Gallstone ileus < 0.1

Malignancy < 0.01

1. Around 90% of gallstones are radiolucent, while around 90% of renal stones are radi-opaque.

2. Radiopacity is due to calcium carbonate, not due to calcium bilirubinate.

**Indications of Prophylactic Cholecystectomy**

1. Porcelain gallbladder

2. Young patients with sickle cell anaemia with incidental cholelithiasis

3. A young woman of American Indian ancestry with incidental cholelithiasis.

4. Incidental cholelithiasis patients from extremely remote place.

n Normal biliary duct pressure is 10–15 cm H2O. When pressure exceeds 15 cm H2O, bile flow decreases, and at 30 cm H2O, bile flow stops.

n Normal sphincter of Oddi pressure is 20–40 mm Hg.

n Charcot’s triad (pain, jaundice and fever) present in 75% patients with cholangitis.

n Choledochal cyst triad (pain, jaundice and mass) present in 20% of patients.

n Bile acid pool is 5 mmol and it circulates 6–10 times per day.

n Duodenum is the most common site for chole-cystoenteric fistula.

n Importance of juxtapapillary duodenal diverticulum in pancreatobilary disease:

- More common in elderly

- Associated with CBD stone

- Difficult ERCP

- Postsphincterotomy bleeding

n Mortality of elective cholecystectomy is < 0.03%.

n Bile duct injury is more in laparoscopic cholecystectomy than open cholecystectomy (0–2.7% vs 0.02–0.08%).

**Advantages of Laparoscopic Cholecystectomy**

1. Less pain

2. Small incision

3. Cosmetically better

4. Shorter hospitalization

5. Early return to full activity

**General Points**

1. Post cholecystectomy syndrome – Occurrence of abdominal complaints following cholecystectomy.

2. Hemobilia – blood in the biliary tract

n Iatrogenic like post–liver biopsy, TACE, alcohol injection

n Trauma

n Malignancy

n Postsphincterotomy bleeding

3. Meltzer-Lyon test: Microscopic examination of aspirated bile for cholesterol crystals, or calcium bilirubinate crystals

4. Gallbladder polyp >10 mm requires laparoscopic cholecystectomy.

5. Saint’s triad: Hiatus hernia, gallstones and colonic diverticula.

6. Boa’s sign: Hyperesthesia on right 9th and 11th rib posteriorly in case of choledocholithiasis

7. Mucocele of gallbladder: Persistent obstruction at neck, leads to absorption of the bile and replaced by mucus secreted by gallbladder epithelium.

8. Sequelae of calculus cholecystitis

n Stone slips back to gallbladder

n Mucocele

n Pyocele

n Perforation – Fundus of the gallbladder is the commonest site

9. Diagnostic criteria for PSC

n Typical cholangiogram

n Clinical (IBD, cholestasis) and biochemical (ALP >3 times than normal for 6 months) findings

n Exclusion of secondary causes

10. Causes of secondary sclerosing cholangitis

n Congenital: Choledochal cyst

n Infective

n Biliary parasites

n HIV cholangiopathy

n Toxic

n Intraductal scolicidal

n Ischemic

n Vascular trauma

n Intra-arterial floxuridine (FUDR)

n Obstructive

n Choledocholithiasis

n Surgical stricture

n Recurrent pyogenic cholangitis

n Neoplastic

n Cholangiocarcinoma

11. More than 75% of patients with primary sclerosing cholangitis have IBD, while only 2.5–7.5% of IBD have PSC.

12. Small duct PSC (onion skin fibrosis) is seen in only 5% of total PSC.

13. Cholangiogram mimic PSC

n Sarcoidosis

n Histiocystosis

n Chronic sclerosing sialadenitis

n Inflammatory pseudo tumor

14. Frequency of cholangiocarcinoma in PSC is around 20%.

**Small intestine**

**Rome III Criteria for Irritable Bowel Syndrome (IBS)**

1. At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of the following three features:

n Relieved by defecation

n Onset associated with change in frequency of stool

n Onset associated with change in appearance of stool

2. Supportive symptoms

n Bowel movements < 3 per week

n Hard or lumpy stool

n Feeling of incomplete evacuation

n Bowel movements > 3 per week

n Urgency

n Passage of mucus

n Abdominal fullness/bloating

**Manning’s Criteria for IBS**

1. Abdominal pain that is relieved by bowel movements

2. Abdominal pain associated with more frequent stool passage

3. Sensation of incomplete evacuation

4. Passage of mucus

5. Abdominal distension

**Diagnostic Criteria for Eosinophilic Gastroenteritis**

1. Gastrointestinal symptoms

2. Tissue eosinophilia in gastrointestinal tract

3. Absence of eosinophilic infiltration outside gastrointestinal tract

4. Absence of helminths infestation

**Differential Diagnosis of Thickened Small Bowel Folds**

1. Giardiasis

2. Lymphoma

3. Amyloidosis

4. Whipple’s disease

5. Paraproteinemia

6. Intestinal lymphangiectasia

**Causes of Eosinophilic Ascites**

1. Eosinophilic gastroenteritis

2. Hypereosinophilic syndrome

3. Lymphoma

4. Vasculitis

5. Infiltrative strongyloidosis

6. Ruptured hydatid cyst

**Normal Gut Microbiological Flora**

1. Stomach: 0–103

2. Jejunum: 0–104

3. Ileum: 105–109

4. Colon: 1010–1012

**Mechanism to Prevent Small Bowel Bacterial Overgrowth**

1. Gastric acid

2. Migrating motor complex of small intestine

3. Epithelial barrier

4. Secretory IgA

5. Ileocecal valve

**ESPGHAN Criteria for Celiac Disease (CD)**

1. History and clinical presentation compatible with celiac disease

2. Serological screening compatible with celiac disease

3. Histological findings compatible with celiac disease

4. Obvious clinical and serological response to gluten-free diet

5. Subject > 2 years old

6. Excluding other conditions mimicking celiac disease

**Marsh Histological Staging of Celiac Disease**

1. Stage 0: Increase intraepithelial lymphocytes

2. Stage I: Lymphocytic infiltration in lamina propria

3. Stage II: Crypt hyperplasia

4. Stage III: Villous atrophy

5. Stage IV: Total mucosal atrophy

**Types of Mesenteric Cysts**

1. Chylolymphatic

2. Enterogenous

3. Urogenital remnants

4. Dermoid

**Causes of Total Villous Atrophy**

1. Celiac sprue

2. Tropical sprue

3. Giardiasis

4. Crohn’s disease

5. Small intestinal bacterial overgrowth

6. Eosinophilic enteritis

7. Small intestinal lymphoma

8. Severe malnutrition

**Causes of Retroperitoneal Fibrosis**

1. Benign

n Idiopathic (Ormond’s disease)

n Trauma

n Drugs

n Aortic aneurysm

n Radiation

2. Malignant

n Lymphoma

n Carcinoids

n Secondaries

**Diagnostic Criteria for Primary Gastrointestinal Lymphoma**

1. Absence of palpable peripheral lymphadenopathy

2. No mediastinal adenopathy on chest imaging

3. Normal peripheral smear

4. At laparotomy, only involvement of gastroint-estinal tract or only the regional lymph nodes

5. No involvement of liver or spleen except by direct spread of the disease from a contiguous focus

**Causes of Diarrhea in Diabetic Patients**

1. Idiopathic autonomic diabetic diarrhea

2. Bacterial overgrowth

3. Associated celiac disease

4. Pancreatic insufficiency

5. Ingestion of artificial sweetener (sorbitol)

**General Points**

1. Length of the small intestine is 6 meter and colon is 1.5 meter in adult.

2. Turnover of small intestinal epithelium is 4–6 days, while colonocyte is 3–5 days.

3. Around 90% of patients will present in first 2 months of life in case of intestinal malrotation.

4. Meckel’s diverticulum is a true diverticulum, which contains all layers of the intestinal wall.

5. Orocecal transit time is 6 hours and lactulose breath test is the most widely used method to measure orocecal transit time.

6. Intestinal secretory functions are by crypts and absorptive functions are by villi.

7. 5-HT3 and 5-HT4 stimulate intestinal motility, secretions and sensation.

8. Brainerd diarrhea: Abrupt onset of secretory diarrhea, which is self-limiting, where no organic cause found.

9. Jejunum is a leaky epithelium, which allows paracellular diffusion of the solutes.

10. “Tightness” of the epithelium increases from proximal to distal intestine.

11. Caloric value of short chain fatty acid (C2–4; acetate, propionate and butyrate) is 3.4–5.9 kcal/g.

12. Short bowel is defined as length of small bowel less than 200 cm.

13. At least 100 cm of jejunum is required to maintain nutritional balance.

14. Prolamins and glutinins of wheat are called gluten, and prolamins of wheat alone is called glidin.

15. Small intestinal neoplasms comprise around 1–2% of gastrointestinal malignancy.

16. Gluten challenge should be continued in doubtful case of celiac disease for at least 6 weeks or until symptoms develop.

17. Enteropathy associated lymphoma of small intestine is T-cell lymphoma and rest of the small intestinal lymphomas are B-cell lymphoma.

18. Colllagenous sprue is defined as subepithelial collagen band thicker than 12 m in the small intestine.

19. Tropical sprue is defined as malabsorption of two or more substances in people in the tropics when other known causes have been excluded.

20. Greatest sensitivity of radiation is during G2 -M phases of cell cycle.

21. Post laparotomy, small intestinal motility comes within 24 hours, stomach within 48 hours and colon within 3–5 days.

**Large intestine**

**Rome III Criteria for Constipation**

Two or more of the following symptoms for at least 12 weeks, not necessarily consecutive, in preceding 12 months:

1. < 3 defecation per week

2. Straining > 25% of defecation

3. Hard, lumpy stool

4. Sense of incomplete evacuation

5. Sensation of anorectal obstruction and blockage

6. Manual removal to facilitate defecation

**Criteria for PFD (Pelvic Floor Dysynergia)**

1. Criteria for constipation

2. Manometric, EMG or radiological evidence of pelvic floor dysfunction

3. Evidence of adequate straining during defecation

4. Evidence of incomplete evacuation

**Hinchey’s Grading of Diverticulitis**

I. Confined pericolic abscess

II. Distant abscess

III.Generalized peritonitis, non-communicating with bowel lumen

IV. Fecal peritonitis (communicating)

**Types of Diverticulitis**

1. Uncomplicated – Peridiverticulitis

2. Complicated – obstruction, abscess, fistula, perforation

**Aetiology of Large Bowel Obstruction**

1. Neoplasm

2. Post diverticulitis

3. Crohn’s disease

4. Ischemic

5. Radiation

6. Volvulus

**Types of Hirschsprung’s Disease**

1. *Classic type*: Aganglionic segment extending from internal anal sphincter proximally into rectum and sigmoid colon

2. *Short segment*: Only involvement of rectum

3. *Ultra short segment*: Only in the internal anal sphincter

**Classification of Carcinoid Tumors**

1. Foregut

2. Midgut

3. Hindgut

**Types of Carcinoid Syndrome**

***Typical carcinoid syndrome*** – Characterized by flushing, diarrhea, bronchospasm, right sided heart failure and pellagra-like skin reaction.

***Atypical carcinoid syndrome*** – Due to deficiency of dopa decarboxylase enzyme, serotonin will not form and increases 5-hydroxytryptophan.

**Classification of Colorectal Polyps**

1. **Neoplastic polyps**

n *Benign*

Tubular adenoma (80%)

- Tubulovillous adenoma (8–16%)

- Villous adenoma (3–16%)

n *Malignant*

- Non-invasive carcinoma

- Carcinoma in situ

- Intramucosal carcinoma

- Invasive carcinoma

2. **Non-neoplastic polyps**

n Hyperplastic polyp

n Juvenile polyp

n Peutz-Jegher polyp

n Inflammatory polyp

3. **Submucosal lesions**

n Colitis cystic profunda

n Pneumatosis cystoid intestinalis

n Lymphoid polyps

n Lipomas

n Carcinoids

**Risk Factors for Adverse Outcomes in Patients with Malignant Polyp Following Polypectomy**

1. Poor degree of differentiation

2. Invasion of veins and lymphatics

3. Polypectomy margin is involved

4. Presence of invasion of submucosa

If none of the above factors is found, patient is cured by endoscopic polypectomy.

**Factors Determining Adenoma Recurrence after Colonoscopic Polypectomy**

***High Risk for Recurrence***

1. First degree relative with colorectal cancer

2. Large adenoma (>1 cm)

3. Multiple (3) adenomas

4. Villous adenoma

5. Adenoma with high-grade dysplasia

***Low Risk for Recurrence***

1. Small (<1 cm) tubular adenoma

2. No family history of colorectal cancer

**Classification of Gastrointestinal Polyposis**

1. **Inherited polyposis syndromes**

n Adenomatous polyposis syndromes

n Familial adenomatous polyposis (APC gene)

n Variants of FAP

n Gardner’s syndrome (APC gene)

n Turcot’s syndrome (APC, MMR gene)

n Attenuated APC (APC gene)

n Hamartomatous polyposis syndromes

n Peutz-Jeghers syndrome (STK 11 gene)

n Juvenile polyposis (PTEN, DPC4 gene)

n Syndrome related to juvenile polyposis

n Cowden’s disease (PTEN gene)

n Bannayan–Ruvalcaba–Riley syndrome (PTEN gene)

n Rare hamartomatous polyposis syndrome

n Hereditary mixed polyposis syndrome

2. **Non-inherited polyposis syndromes**

n Cronkhite-Canada syndrome

n Hyperplastic polyposis syndrome

n Lymphomatous polyposis

n Nodular lymphoid hyperplasia

**Classification of Internal Haemorrhoids**

I. Hemorrhoids bleeding with defecation

II. Hemorrhoids prolapse with defecation, but return naturally

III.Prolapse through anal canal and can be replaced manually

IV. Prolapse permanently

**Classification of Fistula in Ano**

1. Low level fistula: When internal opening of fistula lies below anorectal ring

2. High level fistula: When internal opening of fistula lies above anorectal ring

**Types of Fistula According to Location of Fistula**

1. Submucus

2. Intersphincteric

3. Transphincteric

4. Suprasphincteric

5. Extrasphincteric

**Classification of Mesenteric Ischaemia**

1. Acute mesenteric ischaemia (25%)

n SMA embolus (50%)

n SMA thrombus (10%)

n Non-occlusive mesenteric ischaemia (25%)

n SMV thrombosis (10%)

n Focal segmental ischaemia (5%)

2. Chronic mesenteric ischaemia (5%)

3. Colonic ischaemia (75%)

**Clinical Grading of Continence**

1. Grade I: Continent to solid & liquid stool & gas

2. Grade II: Incontinent to gas only

3. Grade III: Incontinent to liquid stool and gas

4. Grade IV: Incontinent to solid & liquid stool &gas

**Adenoma with Advanced Pathology (AAP)**

Characterized by adenoma larger than 1 cm, villous histology or high-grade dysplasia.

**Causes of Angiodysplasia in Renal Failure**

1. Fluid overload leads to failure of precapillary sphincter.

2. Reactive hyperemia following dialysis.

3. Hyperkalemia and hypergastrinemia mediated reduction in precapillary arterial tone.

4. Dieulafoy’s lesion (exulceratio simplex) is a large “caliber-persistent” vessel within the submucosa.

**Important Definitions**

1. *Megacolon* is defined as when the radiographic diameter of the rectosigmoid region is greater than 6.5 cm or the cecal diameter greater than 12 cm.

2. *Gastrointestinal polyp* is defined as a discrete mass of tissue that protrudes into the lumen of the bowel.

3. *Juvenile polyps* are hamartomas characterized by excess proliferation of lamina propria and dilated cystic glands.

4. *Peutz-Jegher polyps* are characterized by glandular epithelium that is supported by an arborizing framework of well-developed smooth muscle contiguous with the muscularis mucosa (lamina propria is normal).

5. *Synchronous lesion* – diagnosed at the same time as an index colorectal neoplasm.

6. *Metachronous lesion* – diagnosed at least 6 months later than index colorectal neoplasm.

7. *Proctitis* is defined as inflammation of the rectal lining (12–15 cm).

8. *Proctocolitis* is defined as inflammation extending beyond 15 cm in the rectum.

9. *Anal fissure* – Longitudinal cut in the anoderm, starting from anal verge and can extending to the dentate line.

10. *Fistula in ano* – Tunnel that connects an internal opening with an external opening, usually on perianal skin

11. *Goodsall’s law* – Used to identify internal opening of the fistula. Once an imaginary line drawn transversely

through the centre of the anus; external openings anterior to this line, follows straight path towards the anal canal; while curved path towards the anal canal if external opening lies posterior to this line.

12. *Anoderm* lies distal to the dentate line, characterized by non-keratinized squamous epithelium.

13. *Levator ani syndrome* – Affects young women, characterized by vague sensation, high in the rectum, worsens after defecation and improved by lying down position due to spasm of levator muscles.

14. *Proctalgia fugax* – Affects young male, characterized by sharp cramping pain, awakening the patient from sleep, aggravated by stress and occurs due to anal smooth muscles dysfunction.

15. *Rectal prolapse* is defined as protrusion of concentric radial folds through the anal canal.

16. *Solitary rectal ulcer syndrome* (SRUS) is poorly defined terminology characterized by fibromuscular proliferation in lamina propria.

17. *Stercoral ulcer* – Colonic ulcers resulting from pressure necrosis of the mucosa by the direct effect of stool. Sigmoid colon and rectum is the most common site.

18. *Lymphocytic colitis* – Characterized by increase in intraepithelial lymphocytes more than 25 per 100 surface epithelia.

19. *Collagenous colitis* – Characterized by increase in subepithelial collagen band more than 10 m.

20. *Intussusceptions* – Invagination of proximal part of the gut into the distal part.

21. *Volvulus* – Axial rotation of part of the alimentary tract.

22. *Hepatic/splenic flexure syndrome* – Entrapment of gas in the hepatic or splenic flexure, usually associated with constipation and emotional stress.

23. *Urgency* – Uncontrollable desire to have a bowel movement.

24. *Tenesmus* – Ineffectual and painful straining to defecate.

25. *Dyschezia* – Painful defecation.

26. *Pilonidal sinus* – Skin-lined cysts localized over the sacrum, which are connected with the overlying skin by a narrow epithelialized canal with an opening in the posterior mid line.

27. *Diversion colitis* – Inflammation process that occurs in the segments of colon following surgical diversion of the fecal stream.

28. *Cathartic colon* – Diagnosis based on barium enema, characterized by loss of haustration, pseudostrictures, dilated colon and terminal ileum and gaping of ileocecal valve.

29. *Richter’s hernia* – Protrusion of only one side of the bowel (usually anti-mesenteric) through the hernial orifices.

30. *Pseudomelanosis coli* – Brownish discoloration of the colonic mucosa caused by accumulation of pigment, lipofuscin, in macrophages of lamina propria.

31. *Pneumatosis coli* – Multiple gas-filled cysts located in the submucosa and subserosa of the intestine.

32. *Colitis cystica profunda* – Mucin-filled cysts located in the submucosa of the large intestine.

33. *SMA syndrome* – Impingement of SMA on 3rd part of duodenum leading to intestinal obstruction is called SMA syndrome.

34. *Celiac axis compression syndrome (Dunbar syndrome) –* Compression of celiac axis by both the median arcuate ligament of the diaphragm and the celiac ganglion.

35. *Pseudomyxoma peritonei* – This is a rare metastatic peritoneal tumor characterized by gelatinous implants on the peritoneum.

**General Points**

1. Cecum is the widest and sigmoid colon is the narrowest portion of colon.

2. Functional anal canal is 3–4 cm long and rectum is 12–16 cm long.

3. Colonic epithelium lacks villi and crypts are lined by goblet cells.

4. Colonic longitudinal muscle fibers coalesce to form teniae, present throughout the colon except in the appendix and rectum, thus diverticula do not occur in the appendix and rectum.

5. Internal anal sphincter is a continuation of circular smooth muscle of rectum.

6. Sigmoid colon diverticula are more common in Western world while right-sided diverticula are more common in Asian countries.

7. Right colon is the most common site of diverticular bleeding; while left colon is the most common site for diverticulitis.

8. Absence of recto-anal inhibitory reflex on anorectal manometry is the diagnostic test for Hirschsprung’s disease.

9. Most alimentary carcinoids are non functional. Once they metastasize to the liver, they have a high propensity for functionality.

10.Symptoms of carcinoid syndrome develop in 5% of carcinoid tumours.

11. Urinary HIAA (hydroxy indol acetic acid) more than 25 mg/day is diagnostic for carcinoid syndrome.

12. Human papilloma virus (HPV) is the most common cause of condyloma accuminata.

13. Malignant potential of adenomatous polyps depends on size of polyps (more the size, more the chance of malignancy), histology type (villous > tubulovillous > tubular adenoma) and degree of dysplasia (high grade > low grade dysplasia).

14. Serrated adenomas have features of both hyperplastic and adenomatous polyps.

15. Polyp less than 5 mm in diameter is called diminutive polyp.

16. In FAP, tumour initiation is accelerated (due to APC gene mutation), whereas in HNPCC tumour promotion is accelerated (due to p53, ras, MMR gene mutation).

17. Around 30% of elderly patients with one adenoma have one synchronous lesion.

18. Patients with distal, small tubular adenoma have 20% chance of having proximal lesion and majority are small adenomas.

19. Adenoma recurrence is 5 years (20%).

20. Patients with advanced age, male gender and family history of colorectal cancer require full length colonoscopy if sigmoidoscopy shows distal small adenoma.

21. HNPCC is the most common hereditary colorectal cancer.

22. 30% of patients with colorectal cancer have metastasis at the time of presentation and another 30% will develop metastasis within 2 years following resection.

23. Around 10–25% of liver metastasis due to colorectal cancer is resectable.

24. Single juvenile polyp has no malignant potential, but juvenile polyposis syndrome is premalignant condition.

25. Juvenile polyps produce symptoms in childhood, while adenomatous syndrome is usually evident during early adult life.

26. Majority (90%) of anal fissure located in mid posterior position of the anus, because posterior area is less well perfused and tone of the internal sphincter is high posteriorly.

27. Arteriovenous malformations are developmental anomalies, while vascular ectasia are acquired lesions.

**Chapter 67.**

**Quickies**

EOSINOPHILIC oESOPHAGITIS

1. Eosinophilic oesophagitis (EoE) is chronic, local immune mediated oesophageal disease characterized, by symptoms related to oesophageal dysfunction (food impaction and dysphagia) and, histologically by eosinophils- predominant inflammation.

2. The genetic variation of thymic stromal lymphopoietin (TSLP) and calpain 14 (CAPN14) contributes to the development of EOE.

3. Healthy esophageal mucosa is devoid of eosinophils. Food (allergen) acts as an environmental trigger for adaptive immune response (Th2 type); leading to recruitment of eosinophils. Eosinophil degranulates lead to various cytokines release (inflammatory response). Release of extracellular matrix in response of chronic inflammation leads fibrosis. Fibrosis is responsible for oesophageal narrowing (oesophageal rings).

4. Various causes of oesophageal eosinophilia: Celiac disease, eosinophilic gastroenteritis, chronic disease, achalasia cardia, connective tissue diseases.

5. Dysphagia and chocking are the most common symptoms. Severity of inflammation does not correlate with the density of the eosinophilic inflammation.

6. **Diagnostic criteria**: (a) symptoms of oesophageal dysfunction; (b) eosinophilic esophageal inflammation, with >15 eosinophils per high-power filed; (c) excluding other causes of oesophageal eosinophilia.

7. Endoscopic findings: (a) inflammation: Longitudinal furrows/ridges; white exudates; oedematous mucosa; fragile: feline oesophagus: fixed oesophageal rings; esophageal stenosis.

8. Current recommendation to take at least 6 biopsies from two different sites (distal & proximal oesophagus). Biopsy from antrum & duodenum are also mandatory to exclude eosinophilic gastroenteritis. Around 50% of patients with EoE have peripheral eosinophilia and elevated IgE level. Six most common food groups (Milk, wheat, soybean/legumes, eggs, nutes, and fish/shell fish) are described to cause EOE. It is not a premalignant condition.

9. Three basic treatment modalities: Drugs; diet elimination and endoscopic dilatation.

10. Proton pump inhibitors (PPIs) are first step in the treatment (50% histologic remission). Topical corticosteroids like fluticasone propionate and budesonide given more than 80% histological remissions, but with high relapse rate following discontinue.

11. Topical corticosteroids various formula like metered dose inhaler, viscous solution and effervescent tablets.

12. The multistage step-up elimination diet management approach of EoE is one of the most important solutions.

13. Endoscopic dilatation improves subepithelial fibrosis efficacy is 75% and risk of oesophageal perforation is around 1%.

14. Drugs at experimental stages: Anti-IL5 (Reslizumb); Anti-TNF (Infliximab); Anti-IgE (omalizumb); Anti-TGF-.

CELIAC DISEASE

1. Celiac disease (CeD) is a chronic immune-mediated enteropathy precipitated by dietary gluten in genetically susceptible individuals. Current diagnosis is based on atrophy of intestinal villi in small intestinal biopsies, crypt hyperplasia and intraepithelial lymphocytosis (IEL), and the presence of circulating CeD-specific antibodies to tissue transglutaminase (tTG), deamidated gliadin peptides (DGP) and endomysium (EMA)

2. It is a strong interplay between genetic and environmental factors. Ninety percent of Caucasian CeD patients possess the HLADQ2.5 haplotype and the remaining carry HLA-DQ8, HLA-DQ2.2 alone or HLA-DQ7 alone.

3. HLA-DQ2.5 homozygosity has been associated with a more severe CeD phenotype with earlier disease onset, greater villous atrophy, diarrhoea and lower haemoglobin at presentation, and a slower rate of villous healing on a gluten-free diet (GFD). The contribution of non-HLA genes to CeD risk susceptibility is much less strong.

4. Inappropriate adaptive immune response to gluten-derived peptides is the primary mechanism in patients with CeD. Activated CD4+ T-lymphocytes plays important role in immune response. Tissue transglutaminase is abundantly present in extracellular and intracellular compartments of various organs like heart, liver and the small intestine. Gluten peptides containing T-cell epitopes resist gastrointestinal degradation. tTG catalyses the deamidation of gluten peptides, which can then bind more efficiently to the disease-relevant HLA-DQ molecules on antigen-presenting cells (APCs). Activated gluten-specific CD4+

T cells secrete a variety of pro-inflammatory cytokines such as IFN- and IL-21 that contribute to the intestinal lesion and promote activation of IELs and stimulate B-cell responses. Pathogenic bacteria, viruses, and non-gluten components of wheat, such as amylase-trypsin inhibitors (ATIs), may also induce DC maturation and proinflammatory cytokine production, modulating the induction of CD4+ T-cell responses.

5. The clinical presentation is broad and includes gastrointestinal upset, chronic fatigue, nutrient deficiencies, poor growth and failure to thrive. Extra-intestinal manifestations (atypical CeD) include short stature, anemia, delayed puberty, dental enamel hypoplasia, reduced bone density, oral ulcers, liver and biliary disease and dermatitis herpetiformis. Silent CeD means serological and histological abnormalities without evidence of clinical symptoms. Refractory disease is defined by the presence of malabsorptive symptoms and villous atrophy that persist 1 year after a strict GFD.

6. Conditions associated with CeD: Type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune hepatitis.

7. Complications of CeD: Osteoporosis; Enteropathy-associated intestinal T cells lymphoma; Collagenous sprue; Refractory sprue; Ulcerative jejunoileitis and Small bowel adenocarcinoma.

8. Serological diagnosis: IgA anti-tissue transglutaminase antibodies (tTGA, >95% specificity and sensitivity) by enzyme-linked immunosorbent assay (ELISA). IgA anti-endomysial (IgA EMA, 100% specificity) detected by indirect subjective immunofluorescence. Patients with IgA deficiency (2–10% individual with CeD) should undergo IgG tTG test.

9. Histology (gold standard): Villous atrophy, crypt hyperplasia, decreased enterocytes height, inflammatory infiltrates in small-bowel. Marsh classification of histological grading of the CeD is very useful tool **(Table 67.1)**.

10. Management: Life-long gluten-free diet (GFD) is the mainstay of the treatment. Clinical improvement occurs within a few weeks and the mucosal damage recovers in 1–2 yrs.

11. Novel treatment under clinical trials: Enzyme supplement therapy with bacterial prolyl-endopeptidasis expressed by various microorganism has been proposed to accelerate gluten digestion in the gastrointestinal tract and thus to destroy T cell epitopes. Blocking gluten entry across the intestinal epithelium using Zonulin inhibitor larazotide may play promising role is certain subgroup of patients. Improvement of intestinal permeability by Rho/Rho kinase inhibitor is under clinical trial. Various immunotherapy (anti-IL15, anti-IFN-, anti-integrin 4 antibody) are under different stages of clinical trials.

PORTOPULMONARY HYPERTENSION

1. Pulmonary arterial hypertension (PAH) that is associated with portal hypertension (2–16% of patients) is known as Portopulmonary hypertension (PPHTN).

2. Pathogenesis: Various hypothesis have been proposed. (a) Imbalance of vasoconstrictive and vasodilatory mediators is the most accepted hypothesis. Various humoral substances (like serotonin, interleukin-1, endothelin-1, glucagon, secretin, thromboxane B2 and vasoactive intestinal peptide) reach to pulmonary circulation via portosystemic collaterals. (b) thrombi from the portal circulation pass through portosystemic shunts

and reach the pulmonary circulation, resulting in PPHTN, (c) hyperdynamic circulation, (d) inflammation.

3. The pulmonary histopathology of PPHTN is indistinguishable from pulmonary hypertension of other causes.

4. Clinical features: Dyspnea on exertion, atypical chest pain, elevated jugular venous pressure, leg oedema.

5. Transthoracic echocardiography (TTE) is one of the most important initial modality. Right heart catheterization (RHC) gives definitive diagnosis, but which patients should be subjected is a matter of debate.

6. Features of pulmonary hypertension in RHC: (a) elevated mean pulmonary artery pressure (mPAP) >20 mmHg at rest; (b) normal or low pulmonary capillary wedge pressure (PCWP) 15 mmHg at rest; (c) an elevated pulmonary vascular resistance (PVR;  240 dynes/sec/cm-5]). Elevated PVR differentiates patients with precapillary disease from those in whom elevated mPAP is due to hyperdynamic circulatory states secondary to cirrhosis liver.

7. Treatment for PPHTN has been extrapolated from studies performed in patients with idiopathic PAH (IPAH). The use of beta-blockers (worsen right heart failure) and/or transjugular intrahepatic portosystemic shunts (TIPS, worsen right heart preload) may be harmful to patients with PPHTN. Diuretics improve symptoms in patients with PPHTN.

8. Patients with a mean pulmonary artery pressure (mPAP) >60 mmHg cannot undergo liver transplantation. In the United States, PPHTN in those with chronic liver disease is a MELD exception; patients with PPHTN have their MELD score upgraded 10% every 3 months while they are on the liver transplantation waiting list; otherwise, the MELD score will underestimate their mortality risk. Risk of liver transplantation is high in patients with PPHTN. Intraoperative hemodynamic monitoring with right heart catheter is therefore generally advised, for better monitor as large volume shifts occur during liver transplantation that can stress right heart function. Severe PAH (systolic PAP >60 mmHg) is associated with high perioperative risk and poor clinical outcome, while mild (30–44 mmHg) to moderate (45–59 mmHg) PAH has very little influence on mortality after liver transplantation.

9. PAH-specific pharmacotherapy:

n Endothelin receptor antagonists (ERAs) - bosentan, ambrisentan and macitentan. Bosentan has hepatotoxicity, while ambrisentan has less hepatotoxicity but more fluid retention.

n Phosphodiesterase-5 inhibitors (PDE5Is) - sildenafil and tadalafil. They worsen portal hypertension by worsening splanchanic vasodilatation. No significant hepatotoxicity observed.

n Prostacyclin pathway agonists - selexipag, treprostinil and epoprostenol.

n Guanylate cyclase stimulant – riociguat.

HEPATOPULMONARY SYNDROME

1. Hepatopulmonary syndrome (HPS) is one of the pulmonary complications (2–46% of patients) of end-stage liver disease, characterized by impaired arterial oxygenation induced by intrapulmonary vascular dilatation. Hepatic hydrothorax (6–10% of patients) is the result of ascetic fluid passage to the pleural space through diaphragmatic defects.

2. HPS was associated with worse quality of life, and higher risk of death compared to non-HPS matched for age, sex and MELD score cirrhotic subjects.

3. Pathogenesis: Cardinal anatomic disturbance of HPS is intrapulmonary capillary vasodilatations leads to ventilation-perfusion mismatch. Normal diameter of intrapulmonary capillary is between 8–15 m, which increase in the range from 15–100 m in patients of HPS. This dilatation leads to passage of excessive amount of blood through the pulmonary circulation without completing gas exchange, leading to increased alveolar arterial gradient and arterial hypoxemia. Another mechanism causing hypoxia in HPS is intrapulmonary arteriovenous shunting; which leads to passage of blood directly into the central circulation, without coming in touch with the alveoli. Thus, severity of arterial hypoxemia is related to the extent of ventilation-perfusion mismatch, intrapulmonary shunting and diffusion impairment.

4. Pulmonary vasodilatation: Imbalance between vasodilators and vasoconstrictors leads is the main reason. Liver cirrhosis lead to endothelin-1 (ET-1) secretion, which activates pulmonary endothelial nitric oxide synthase (eNOS), leading to excessive production of nitric oxide (NO), a natural vasodilator. Bacterial translocation and the subsequent pulmonary macrophage accumulation result in the production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-), which contribute in NO-mediated vasodilatation. Increase carbon monoxide, another pulmonary vasodilator produced by macrophage.

5. Angiogenesis: Pulmonary macrophage accumulation and TNF--increased circulation trigger vascular endothelial growth factor (VEGF) pathways, concluding in VEGF-mediated pulmonary angiogenesis.

6. Platypnea (worsening dyspnea when patient moves from a supine to an upright position), is considered to be pathognomonic for HPS. It is due to decrease in PaO2 in the arterial blood of 5% from supine to upright position

due to increased perfusion of the basis of the lungs and elevated intrapulmonary shunting, a phenomenon called orthodeoxia. Orthopnea, the worsening of dyspnea in lying position, has also been observed frequently in patients with HPS. Cyanosis, fatigue, spider naevi and digital clubbing are other clinical findings of HPS.

7. Diagnostic criteria:

n Presence of liver disease and/or portal hypertension

n Partial pressure of oxygen <80 mmHg or alveolar–arterial oxygen gradient [P(A-a)O2 gradient] 15 mmHg (or >20 mmHg for patients >65-years-old) while breathing ambient air

n Documented intrapulmonary vascular dilatation by contrast-enhanced echocardiography or lung perfusion scanning with radioactive albumin.

8. Hepatopulmonary syndrome – severity criteria

n Mild P(A-a)O2 gradient 15 mmHg, PaO2  80 mmHg

n Moderate P(A-a)O2 gradient 15 mmHg, PaO2 60 mmHg to < 80 mmHg

n Severe P(A-a)O2 gradient 15 mmHg, PaO2 50 mmHg to < 60 mmHg

n Very severe P(A-a)O2 gradient 15 mmHg, PaO2 < 50 mmHg

9. Contrast-echo: Contrast-echo is the most important diagnostic tool. Normal saline is shaken to produce microbubbles >10 m in diameter and is administered to a peripheral vein in the arm while a four-chamber transthoracic echocardiography is performed. Micro-bubbles cannot pass through normal capillaries and are normally trapped in the pulmonary circulation. In the presence of a dilated vascular bed and/or arteriovenous shunting, microbubbles reach the left cardiac chambers between the fourth and sixth cardiac cycle indicative of intrapulmonary vasodilatation. The appearance of microbubbles in the left cardiac chambers less than three cardiac cycles indicates intracardiac shunting.

10. Technetium-99m-labeled macroaggregated albumin lung perfusion test: Brain uptake of the radionuclide higher or equal to 6% implies intrapulmonary or intracardiac shunting.

11. Pulmonary angiography: Type 1 is characterized by minimally dilated vessels, and type 2 delineated by well defined arteriovenous communications and resistance to 100% oxygen administration.

12. Pulse oximetry as a screening test for the presence of HPS.

13. DLCO: A reduced diffusing capacity for carbon monoxide (DLCO) is the single most common defect among pulmonary function tests that has been correlated to the presence of HPS.

14. Liver transplant is the only successful treatment of HPS with 88% 5-year post transplantation survival. No significant difference in overall survival between HPS and non-HPS transplantation candidates was demonstrated in the literature. Various pharmaceutical agents tried with poor success rate, they are: octreotide, sorafinib, norfloxacin, garlic, mycophenolate mofetil, methylene blue, pentoxifylline, etc.

NEUROENDOCRINE TUMOuRS

1. Neuroendocrine tumours (NETs) are heterogenous neoplasms of varied histology, comprising about 2% of all malignancies, arising from secretory cells of the diffuse neuroendocrine system. Gastroenteropancreatic NETs (GEP-NETs) include carcinoid tumours of the gastrointestinal tract (stomach and small bowel 30%, rectum 26%, colon 17% and appendix 5.7%) and pancreatic NETs (pNETs, 12%).

2 Carcinoid tumour of gastrointestinal tract is originated from enterochromaffin cells of the gut, pNETs are from the islets of Langarhans. Midgut NETs have high malignant potential, whereas gastric and rectal NETs often have a low tendency to metastasize but can progress rapidly once they become metastatic. pNETs produce variety of peptide hormones like insulin (insulinoma), gastrin (gastrinoma) and glucagon (glucagonoma). NETs should be described as functional only when signs and symptoms consistent with excess hormone secretion.

3. NETs are subdivided according to tumour grade (the mitotic rate and/or the Ki-67 index) and differentiation (well-differentiated and poorly differentiated tumours). According to WHO classification **(Table 67.2)**, well-differentiated NETs were subdivided as either G1 or G2 tumors, while poorly differentiated neuroendocrine carcinomas (NECs) were considered as G3 tumours (for GI tract). WHO in 2017 classified pNETs into well-differentiated (low-grade, intermediate-grade, or high-grade) and poorly differentiated (high-grade, NECs).

**Grade Mitotic Count Ki-67 Index, %**

**(per 10 HPFs)**

G1 (low grade) <2 <2

G2 (intermediate grade) 2–20 >2–20

G3 (high grade) >20 >20

4. Synaptophysin, chromogranin A (CgA), neuron-specific enolase (NSE), and cluster of differentiation 56 (CD56,

neural cell adhesion molecule) are immunohistochemical markers. Both synaptophysin and CgA are diffusely

expressed in well-differentiated NETs, whereas poorly differentiated tumours show synaptophysin positivity losing CgA expression and acquiring NSE expression. Early NETs are associated with a very favourable long-term prognosis, whereas outcome of metastatic disease depends on tumour grade and primary site.

5. The majority of NETs are sporadic, but hereditary syndromes that predispose to it include multiple endocrine neoplasia type 1 (MEN-1), MEN-2, von Hippel–Lindau (VHL) syndrome, neurofibromatosis and tuberous sclerosis.

6. *Gastric NETs* - Classified into three types: Type I is associated with chronic atrophic gastritis type, with or without pernicious anaemia. Type II is associated with Zollinger-Ellison syndrome and MEN-1 syndrome. Type III tumours are sporadic, large, solitary and invasive tumours that occasionally produce an atypical carcinoid syndrome mediated by histamine and serotonin.

7. *Appendiceal NETs* - Benign lesion usually identifies post operatively. Carcinoid syndrome is rare. *Colorectal NETs*- rare but very aggressive tumour. Two types of tumour pathological types: small-cell carcinomas (like lung) and moderately differentiated (like adenocarcinoma of colon) NECs. *Pancreatic NETs -* Insulinoma, gastrinomas, glucagonomas, pancreatic polypeptide-secreting tumours (Ppomas), VIPomas, somatostatino-mas. The clinical presentation of insulinoma is characterized by the classic “Whipple triad,” consisting of symptomatic hypoglycaemia, low blood glucose levels, and relief of symptoms after glucose administration. *Small bowel NETs* - distal ileum is the most common site. Multifocal tumour is seen in 25% of cases. Regional lymph node metastasis leads to dense desmoplastic reaction in the mesentery. Liver metastasis leads to carcinoid syndrome.

8. The classical carcinoid syndrome: Watery diarrhoea, flushing, bronchospasm, hypotension and right-sided heart disease. It is due to serotonin hypersecretion leads to vasodilatation, bronchoconstriction and smooth muscle contraction. Serotonin is usually metabolized in the liver. Carcinoid syndrome occurs in case of liver metastasis when serotonin bypasses the liver. Measurement of urinary 5-hydroxyindole acetic acid (5-HIAA, a serotonin metabolite) and plasma CgA (a glycoprotein secreted with serotonin) for diagnosis of NETs.

9. GI endoscopy is the procedure of choice to diagnose rectal, duodenal, colonic and gastric NETs. Contrast CT is useful for small bowel NETs as well as liver metastasis.

Somatostatin receptor scintigraphy (gallium-68-DOTATATE PET/CT) is a sensitive method for the detection of the primary tumour and its metastases.

10. Management of localized lesions - Surgery is the main treatment modality. Functional pNETs with intermediate-to-high grade, >2 cm should undergo curative resection, while tumour <2 cm may need only enucleation. Wait and watch policy is usually implicated in patients with non-functional pNETs <2 cm size. Small bowel resection is for small bowel NETs. Entire small bowel should be palpated during the surgery as multifocal tumour is common. Small rectal and gastroduodenal NETs should be removed endoscopically. Larger lesions should be managed by oncological resection. Appendectomy is sufficient for tumour less than 1 cm size, whereas right hemicolectomy is required for tumour >1 cm size.

11. Management of advanced tumours **(Table 67.3)** - Lanreotide or octreotide long-acting repeatable (LAR) at doses of 10, 20 or 30 mg monthly helps to control disease progression. Peptide Receptor Radionuclide Therapy (PRRT) is a form of systemic radiotherapy that allows targeted delivery of radionuclides to tumour cells expressing high levels of Somatostatin Receptor Subtypes (SSTRs). High-level evidence for the antitumor activity of PRRT with lutetium has been observed in clinical trials. 177Lu-DOTATATE every 8 weeks for 4 cycles plus octreotide 30 mg every 4 weeks is standard of care in many countries with advanced NETs. Everolimus, an oral inhibitor of mTOR, has been investigated extensively in patients with NETs. Sunitinib, a small molecule that inhibits 3 receptors of VEGF, has been tested in NETs.

**Type of NETs Modalities**

**G1 NETs** Somatostatin analogue, Interferon, Sunitinib, everolimus, bevacizumab

PRRT

**G2 NETs** Chemotherapy PRRT Somatostatin

analogue + PRRT

**G3 NETs** Somatostatin analogue for symptoms

control, chemotherapy, ablative therapy for hepatic metastasis

Bevacizumab, monoclonal antibody against VEGF needs to prove its efficacy. Interferon-alpha has some role is selected populations. Chemotherapy is the cornerstone of therapy for patients with poorly differentiated NETs (NECs). Platinum-containing regimens are most important, while FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) and FOLFIRINOX (FOLFIRI plus oxaliplatin) used in patients

who progress on platinum-based chemotherapy. Ablative therapy like chemoembolization, selective internal radiation therapy, etc is used in selective patients.

GASTROINTESTINAL STROMAL TUMOuRS

1. Gastrointestinal stromal tumours (GISTs) are rare neoplasms of the gastrointestinal tract (1–2% of gastrointestinal neoplasm), usually asymptomatic, associated with high rates of malignant transformation. Stomach (56%) is the most common site, followed by small bowel (32%) and colon (6%). Around 10–30% of the GISTs progress to malignancy. More than 70% of GISTs has exophytic growth. Common locations for GIST metastasis are to the liver (28%), and the mesentery and omentum (30%).

2. Usually GISTs are asymptomatic, identify during imaging or endoscopy. Majority of the symptoms are non-specific. Gastrointestinal bleeding and obstruction due to exophytic GISTs are some specific symptoms.

3. CT scan is the most important investigations. Tumours are classified as small (<5 cm), intermediate (5–10 cm), or large (>10 cm) on CT imaging. Histology and immunohistochemistry are the most important to diagnose GISTs. Three different histologic findings, including spindle (70%), epithelioid (20%) or mixed type (10%). Around 80% of GISTs stain positive for both CD117 and DOG-1.

4. According to NIH classification, tumour size and mitotic index determines outcome and recurrence of GISTs. They are categorizing into very low, low, intermediate and high-risk groups. Tumours >5 cm in diameter plus a mitotic count higher than 5/50 high power fields (HPF) and tumours >10 cm with any mitotic rate have a higher risk of recurrence.

5. Surgical treatment is the gold standard for GISTs. There four agents approved for the treatment of GISTs are imatinib (400 mg), sunitinib, regorafenib and ponatinib. GISTs that are CD117 and PDGFRA positive are thought to benefit from this therapy. Many GISTs with CD117 mutations in exons 9, 11, 13, 14 and 17 have imatinib resistance. Sunitinib treatment is the preferred therapy for exon 9 mutations and wild-type GISTs (no CD117 or PDGFRA mutations). Nivolumab (Opdivo) and ipilimumab (Yervoy) are immunotherapy under the evaluation in patients with advanced GISTs. Surgery plus adjuvant

therapy with tyrosine kinase inhibitors improve overall survival in patients with exophytic metastatic tumour.

MEDICAL THERAPY FOR OBESITY

1. Obesity is a chronic condition, which is becoming major health problem around the world contributing to significant morbidity and mortality.

World Health Organization (WHO) defines obesity by body mass index (BMI), which is calculated by dividing weight in kilograms by height in Meter Square. If BMI is 18.5 to <25, it falls within the normal weight, If your BMI is 25.0 to <30, it falls within the overweight range and If your BMI is 30.0 or higher, it falls within the obese range. There is increasing evidence that obesity needs to be defined with lower BMI cutoff among Asian population, making the cutoff to be 27.5 kg/m2.

2. Waist circumference 31 in (80 cm) in Asian females and 35 in (90 cm) in Asian males is also considered abnormal. Obesity and abdominal obesity could contribute to serious medical complications that can impair quality of life and increased morbidity and premature death **(Table 67.4)**.

Stroke Idiopathic intracranial Cataracts

hypertension

Pulmonary Coronary heart disease Cancer

diseases Diabetes

Hypertension

Dyslipidemia

Gallbladder Lives disease Gynecological

disease abnormalities

Osteoarthritis Urinary stress Phlebitis

and Gout Incontinence

3. Body size depends on complex interaction between environmental and genetic factors. Genetic and environmental interplay is very important. With increase consumption of calorie dense food, portion size, and more meals eaten outside along with snacking habits and sedentary lifestyle, environmental factor has become a major modifier in this modern world. Current Obesity epidemic is an outcome of an excessive intake of calories as oppose to energy expenditure over long period of time.

4. Arcuate nucleus of hypothalamus plays a key role, activation of neuron secreting neuropeptide Y (NPY) and agouti-related protein (AgRP) promotes food intake, whereas activation of neurons secreting pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) has an anorexigenic effect. NYP/ArRPneurons also inhibits POMC/CRT neurons through gamma-aminobutyric acid. This system in very complex and sends signals to various parts of brain.

5. Melanin concentrating hormone, growth hormone, orexin A and B are other central hormones, which promotes food intake. Peripheral organs also play important role

and participate in this interaction, via anorexigenic hormones, insulin, cholecystokinin and pancreatic polypeptide produced by pancreas, Peptide YY by gastrointestinal tract, glucagon-like peptide 1 by proximal gastrointestinal tract, leptin by fat cells, there secretion increases after food consumption vs ghrelin produced by stomach and duodenum (orexigenic) before food consumption. This hormones work both centrally and peripherally. The other major satiety signals are transmitted via vagal afferents from gut in response to food from sites like oral taste stimuli, GI tract stretch stimuli, etc to hind brain.

6. Once then anorexigenic pathways are activated, the major mediator is peripheral sympathetic system. Other factors, which also regulate the weight, are adrenal glucocorticoids, gonadal steroid hormones and gut microbe.

7. This complex pathophysiology has been exploited to make pharmacological treatment for obesity. Medical therapy has been increasingly available to manage this chronic condition. It is a useful tool and used as an aid to lifestyle changes to create negative energy balance and promote weight loss. Most of the weight loss medication work by suppressing appetite by activating anorexigenic neurons.

8. Endocrine Society/American Association of Clinical Endocrinology recommends to consider weight loss medication if patient fails to loss weight with lifestyle changes for 6 months and if BMI is above 30 or if BMI is above 27 with one obesity-related complication.

9. **Orlistat -** Alters the fat digestion by inhibiting pancreatic lipase enzyme thereby increasing fecal fat excretion and reducing 25–30% of calories ingested as fat. Patient losses on an average 5–10 kilograms over a period of 12 months (8% from baseline), which is maintained for 2–3 yrs. Reduction of blood pressure as well as total cholesterol is other additional effects. Side effects include cramps, oily spotting and flatus. Fat soluble vitamin deficiency and calcium oxalate stones are some other side effects. Dose is 120 or 60 mg 3 times a day before meals. Pregnancy, chronic malabsorption, cholestasis or a history of calcium oxalate stones are contraindications of orlistat.

10.**Phenteramine/Benzphetamine/Phendimetrazine/Diethylpropion -** All are sympathomimetics promoting stimulation of satiety neurons by promoting release or preventing uptake of norepinephrine peripherally. Around 7.4 kg weight loss was observed in clinical trials. It is recommended for short term or intermittent use only, which is 12 weeks at a time because of risk of side effects. Tachycardia, hypertension, insomnia, dry mouth, constipation and nervousness are the common side effects. Sibutramine is another sympathomimetic weight

loss drug which was discontinued in 2010 because of increased risk of non-fatal myocardial infarction and

stroke.

11. **Qsymia (phenteramine+Topiramate) -** Sympatho-mimetics effect of phenteramine combined with possible effects topiramate on neuropeptide Y. This medication resulted in 8–10 kg of weight loss. Dry mouth, paresthesia, constipation are the common side effects. Abrupt withdrawal of topiramate can cause seizure. Recommended dose is 3.75/23 mg for 14 days, followed by 7.5/46 mg. Pregnancy, glaucoma and hyperthyroidism are contra-indications.

12. **Lorcaserin -** It is a selective serotonin 2C receptor agonist and it reduces the appetite (10 mg BID). Fenfluramine and dexfenfluramine, non-selective serotonin receptor agonist, caused weight loss but where associated with cardiac valve diseases, hence taken off market. Around 3–4 kg weight loss was observed in clinical trials. Other beneficial effects include glucose, kidney function, blood pressure and low-density lipoprotein (LDL) cholesterol. Headache, upper respiratory infections, nasopharyngitis, dizziness and nausea are the common side effects. Pregnancy, chronic kidney are contraindications.

13. **Bupropion-naltrexone -** Bupropion is dopamine and norepinephrine reuptake inhibitor, whereas naltrexone is opioid receptor antagonist, and this lead to suppress appetite. Around 4–5% of weight loss observed with this medication. Nausea, headache and constipation are the most common side effects. Dose is naltrexone 8 mg/bupropion 90 mg once a day. After 1 week, the dose is increased to one tablet twice daily followed by two tablets twice daily after 4 weeks. Uncontrolled hypertensions, seizure disorder, eating disorder are the contra-indications.

14. **Liraglutide -** Chemically modified version of human GLP-1, promotes glucose dependent insulin release, inhibits glucagon secretion and gastric emptying. GLP1 also have positive effect on satiety centre promoting the weight loss. Around 8 kg weight loss was observed over 1 yr in various studies. Diarrhoea, low blood sugar, anorexia are side effects. Dose is3 mg daily subcutaneous injection.

15. Goal of therapies in obese individual is to achieve long-term weight reduction and prevent weight-related complication along with improvement in their health status. Studies have shown that even 5–10% of weight reduction can reduce the risk of development of diabetes, hypertension at risk patients. Short-term weight loss is achievable with lifestyle changes alone or combination

of anti-obesity medication with lifestyle changes. But

maintenance of weight loss is a challenge because of many factors like weight loss induced changes in energy expenditure, hormonal mediators of appetite, which favour weight gain. Hence if weight loss medication is used as an aid, to treat this chronic condition, it could be planned to be used as a long-term medication if well tolerated. The potential benefits of weight loss must be considered in light of the potential risks of drug therapy at every step.

16. *How to choose a drug therapy* - Detailed history and assessment of weight-related comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, heart disease, sleep apnea and symptomatic osteoarthritis is important. Review current medication list, to make sure it’s not one of the contributing factor in patient’s failure. Thorough counseling around healthy eating, physical activity and health-seeking behaviour is essential. Weight centric approach is suggested, which means to choose a drug, which will not only treat obesity but also underlying co-morbid condition.Patient preferences, cost, relative contraindication and potential adverse effects should also be considered.

17. *Recommendation* - Once patient is started on drug therapy; they should assessed every month for first 3 months to assess the amount of weight loss and side effects at each visit. If patient has not lost 3–5% of weight from its baseline either increases the dosage of medication or switches the medication. Although more and more medical therapy for obesity is available, it requires knowledge, commitment and patient centered approach for it to be successful. Cost of this medication may be biggest hindrance currently. Hence weigh the risks and benefits of all treatment options lifestyle, pharmacologic, device, surgical) while treating the obesity in your clinic.

Further Reading

1. Elisa Torrijos, Rosario Gonzalez-Mendiola, Manuela Alvarad, et al. Eosinophilic Esophagitis: Review and update. *Frontiers in Medicine* 2018;5:247.

2. Clayton F, Peterson K. Eosinophilic esophagitis: pathophysiology and definition. *Gastrointest Endosc Clin N Am* 2018;28:1–14.

3. Ilaria Parzanese, Dorina Qehajaj, Federica Patrinicola, et al. Celiac disease: From pathophysiology to treatment. *World J Gastrointest Pathophysiol* 2017;8:27–38.

4. Jason A. Tye-Din, Heather J. Galipeau Agardh, et al. Celiac disease: a review of current concepts in pathogenesis, prevention, and novel therapies*. Front Pediatr* 2018;6:350.

5. Stergios Soulaidopoulos, Evangelos Cholongitas, George Giannakoulas, et al. Review article: Update on current and emergent data on hepatopulmonary syndrome. *World J Gastroenterol* 2018;24:1285–98.

6. Fussner LA, Krowka MJ. Current approach to the diagnosis and management of portopulmonary hypertension. *Curr Gastroenterol Rep* 2016;18:29.

7. Rodríguez-Roisin R, Krowka MJ, Hervé P, et al. ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J* 2004;24:861–80.

8. Bryan Oronsky, Patrick C, Daniel Morgensztern, et al. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia* 2017;19:991–1002.

9. Mauro Cives, Jonathan Strosberg. Gastroenteropancreatic neuroendocrine tumors. *Ca Cancer J Clin* 2018;68:471–87.

10. Trisha Parab, Michael DeRogatis, Alexander Boaz, et al. Gastrointestinal stromal tumors: a comprehensive review. *J Gastrointest Oncol* 2019;10:144–54.

11. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014;129:S102–38.