

Okay
bit by bit

Third edition

Notes & Notes

For MRCP part 1 & 11

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Gastroenterology

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The 10 Golden Tips for MRCP written exams you will ever need

1. **For MRCP, do not read hard; read smart.**
2. **Three to six months is usually enough for preparation.**
3. **Practice the best of the five questions as much as possible.**
4. **The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.**
5. **Remember, you are getting ideas and concepts from the questions.**
6. **Time factor in the exam room is the leading killer after poor preparation.**
7. **Manage your time wisely.**
8. **Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)**
9. **Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)**
10. **Practice, practice and practice.**



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Oesophageal diseases

Achalasia

Definition

- Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, oesophagus above dilated.

Pathophysiology

- Atrophy of inhibitory neurons in the Auerbach plexus → lack of inhibitory neurotransmitters (e.g., NO, VIP) → inability to relax and increased resting pressure of the LES, as well as dysfunctional peristalsis → esophageal dilation proximal to LES

Epidemiology

- prevalence of around 10 /100,000 persons.
- typically presents in middle-age
- equally common in men and women.

Causes

- Primary achalasia (most common): cause is unknown
- Secondary achalasia (pseudoachalasia):
 - ⇒ mechanical obstruction (e.g., a malignancy)
 - ⇒ Chagas disease

Features

- Symptoms usually develop years before the patient presents
- Dysphagia of **BOTH** liquids and solids.
- Regurgitation of food → heartburn, cough, aspiration pneumonia etc
- Oesophageal spasm → vague chest discomfort (common)
- Weight loss

Complications

- Increased risk of esophageal cancer.

Investigations

- Barium swallow
 - ⇒ **initial investigation**
 - ⇒ will show: dilated oesophagus, fluid level, 'bird's beak' appearance
- Manometry:
 - ⇒ The **confirmatory test of choice**
 - ⇒ Will show:
 - excessive LOS tone which doesn't relax on swallowing
 - Lack of peristalsis in the lower two-thirds of the esophagus
- Upper endoscopy
 - ⇒ to rule out pseudoachalasia
 - ⇒ Usually normal, May show retained food in esophagus or increased resistance of LES during passage with endoscope
- CXR: Will show:
 - ⇒ wide mediastinum, (**>6 cm** on an upright **PA** chest X-ray or **> 8 cm** on supine **AP** chest film).
 - ⇒ fluid level

Treatment

- **Heller cardiomyotomy** (Laparoscopic myotomy)
 - ⇒ **The best initial treatment** for most patients with achalasia.
- **Balloon dilation** (Pneumatic dilatation)
 - ⇒ the preferred option for older unfit patients or patients who choose a nonsurgical treatment.
 - ⇒ Current guidelines recommend obtaining **gastrograffin study followed by barium esophagram in all patients after pneumatic dilation to exclude esophageal perforation**
 - ⇒ long-term efficacy is less than that of surgical myotomy. 25% of patients treated with pneumatic dilation required re-dilation.
- **Intra-sphincteric injection of botulinum toxin**
 - ⇒ Reserved for the elderly and who cannot tolerate dilatation or surgery.
 - ⇒ Reduces the LOS pressure and **provides symptomatic relief**. However, the effects are temporary, and patients need to undergo repeat injections every six to twelve months.
- **Drug therapy** has a role but is limited by side-effects
 - ⇒ Short-term improvement in clinical symptoms may occur with isosorbide mononitrate, a long-acting nitrate or with nifedipine, a calcium-channel blocker.
- **Contraindications**
 - ⇒ **Promotility agents like metoclopramide** increase the lower oesophageal sphincter pressure and so are contraindicated in achalasia.

Images



This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film



Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

TOP TIPS

Dysphagia affecting both solids and liquids from the start - think achalasia

The gold standard test for achalasia is oesophageal manometry

The most appropriate initial investigation of a high dysphagia is a barium swallow, which identifies the site of pathology and forewarns of pitfalls such as a pharyngeal pouch, which if unidentified can increase the risk of perforation at endoscopy.

Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia:

Diagnosis	Characteristic features
Oesophageal cancer	<ul style="list-style-type: none"> Dysphagia may be associated with weight loss, anorexia or vomiting during eating Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use
Oesophagitis	<ul style="list-style-type: none"> May be history of heartburn Odynophagia (Painful swallowing) but no weight loss and systemically well
Oesophageal candidiasis	<ul style="list-style-type: none"> There may be a history of HIV or other risk factors such as steroid inhaler use Treatment → oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).
Achalasia	<ul style="list-style-type: none"> Dysphagia of both liquids and solids from the start Heartburn Regurgitation of food - may lead to cough, aspiration pneumonia etc
Pharyngeal pouch	<ul style="list-style-type: none"> More common in older men Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles Usually not seen but if large then a midline lump in the neck that gurgles on palpation Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen
Systemic sclerosis	<ul style="list-style-type: none"> Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oesophageal dysmotility, Sclerodactyly, Telangiectasia As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. This contrasts to achalasia where the LES pressure is increased
Myasthenia gravis	<ul style="list-style-type: none"> Other symptoms may include extraocular muscle weakness or ptosis Dysphagia with liquids as well as solids
Globus hystericus	<ul style="list-style-type: none"> May be history of anxiety Symptoms are often intermittent and relieved by swallowing Usually painless - the presence of pain should warrant further investigation for organic causes

Causes of dysphagia - by classification

Classification	Examples
Extrinsic	<ul style="list-style-type: none"> Mediastinal masses Cervical spondylosis
Oesophageal wall	<ul style="list-style-type: none"> Achalasia Diffuse oesophageal spasm Hypertensive lower oesophageal sphincter
Intrinsic	<ul style="list-style-type: none"> Tumours Strictures Oesophageal web Schatzki rings
Neurological	<ul style="list-style-type: none"> CVA Parkinson's disease Multiple Sclerosis Brainstem pathology Myasthenia Gravis

Dysphagia

- Dysphagia to both solids and liquids → **Achalasia** (motility disorder)
- Dysphagia to solids only → **Oesophageal obstruction** (structural disorder, e.g. malignancy)

Investigations

- Barium contrast oesophagram is the **initial test** (prior to upper endoscopy)

Oesophageal disorders

The table below lists a small group of oesophageal disorders that are not covered elsewhere in the notes.

Disorder	Notes
Plummer-Vinson syndrome	<p>Triad of:</p> <ul style="list-style-type: none"> dysphagia (secondary to oesophageal webs) glossitis iron-deficiency anaemia <p>Treatment includes iron supplementation and dilation of the webs</p>
Mallory-Weiss syndrome	Severe vomiting → painful mucosal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics
Boerhaave syndrome	Severe vomiting → oesophageal rupture

Oesophageal web

Oesophageal web	
What is it?	a thin mucosal membrane projecting into the lumen → oesophageal constriction
Common age and gender?	middle-aged females
Common symptoms?	dysphagia and regurgitation of food
Common location?	<ul style="list-style-type: none"> ▪ In the cervical oesophagus near cricopharyngeus muscle. ▪ Typically arise from the anterior wall and never from the posterior wall.
Associations?	<ol style="list-style-type: none"> 1. Plummer-Vinson syndrome 2. graft-versus-host disease 3. gastroesophageal reflux disease 4. external beam radiation
Investigation of choice?	Barium swallow
Consequences?	<ul style="list-style-type: none"> ▪ Dysphagia ▪ Squamous cell carcinoma

Diffuse oesophageal spasm

- Features
 - ⇒ Dysphagia
 - ⇒ Chest pain
- Diagnosis
 - ⇒ barium swallow demonstrates a 'corkscrew appearance'
 - ⇒ Manometry reveals:
 - prolonged, repetitive and **high amplitude contractions**.
 - The lower oesophageal sphincter pressure is increased and there is incomplete relaxation of the sphincter.

Differential diagnosis manometry findings:

- **Absence** of peristalsis in the body of the oesophagus + high lower oesophageal sphincter → **Achalasia**
- **Normal** contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **Hypertensive lower oesophageal sphincter**
- **High** amplitude contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **Diffuse oesophageal spasm**

Gastro-oesophageal reflux disease (GORD)

Definition: regurgitation of stomach contents into the esophagus

Pathophysiology

- Decreased tone of the lower esophageal sphincter.
- **The most important physiological mechanism that prevents reflux** → **Parasympathetic stimulation of the lower circular smooth-muscle fibres of the oesophagus**

Cause

- Transient lower esophageal sphincter relaxation is **the most common cause**
- Pregnancy → decreased motility secondary to progesterone
- gastric acidity
- gastric outlet obstruction
- decreased esophageal motility
- hiatal hernia: ≥ 90% of patients with **severe GORD**
- Obesity → Transient relaxations of the lower esophageal sphincter (TRLES). The main stimulus for TRLES is **gastric distension**, particularly in the fundus.
- Lifestyle habits such as **smoking, caffeine and alcohol consumption**
- Scleroderma
- Angle of His enlargement (> 60°)

Features

- Heartburn and regurgitation when lying down.
- GORD is the most common non-cardiac cause of **chest pain**.
- Extraesophageal symptoms (eg, chronic cough, hoarseness, wheezing)
 - ⇒ The three most common causes of a persistent cough are postnasal drip, asthma, and **GORD**.
- Acid reflux in chronic GORD can lead to damage of the enamel layer of teeth.
- **May present with over-the-counter antacids side effects** which may include magnesium hydroxide.
 - ⇒ **Magnesium hydroxide** can act as an **osmotic laxative**, resulting in the adverse effect of **diarrhea**.

Investigations

- **Endoscopy: Indications for upper GI endoscopy:**
 - ⇒ **No symptomatic improvement after PPI trial**
 - ⇒ **Alarm features**
 - New onset dyspepsia in patient ≥60 years
 - Dysphagia
 - Odynophagia
 - Early satiety
 - Persisting vomiting
 - Unintentional weight loss
 - Aspiration pneumonia
 - Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
 - Iron deficiency anemia
 - Anorexia
 - Gastrointestinal cancer in a first-degree relative
 - ⇒ The most common endoscopic finding is reflux esophagitis.
 - ⇒ **Symptoms do not correlate with mucosal status at endoscopy appearance**
- **24-hr oesophageal pH monitoring:** If endoscopy is negative (**the gold standard test for diagnosis**)
 - ⇒ To confirm the diagnosis of GORD in patients with persistent symptoms of GORD despite a trial of PPI therapy.
 - ⇒ Evaluation before surgical or endoscopic antireflux procedure
- **Oesophageal manometry**
 - ⇒ in patients with suspected GORD and a normal upper endoscopy to exclude an esophageal motility disorder.
 - ⇒ To evaluate esophageal peristaltic function prior to antireflux surgery.

Treatment

- **Lifestyle changes**
 - ⇒ Small portions;
 - ⇒ avoid eating (< 3 hours) before bedtime.
 - ⇒ Avoid foods with high fat content
 - ⇒ **Avoid:** nicotine, alcohol, coffee, and certain drugs (e.g., calcium channel blockers, diazepam)
- **Pharmacological: if lifestyle changes are ineffective**
 - ⇒ **Proton pump inhibition (PPI):**
 - full-dose PPI (e.g. 20 mg omeprazole OD) for 4 or 8 weeks.
 - **In those failing to respond to two months of full dose therapy doubling the dose of proton pump inhibitor for one month increases response rate.**
 - If no response, increase the dose to (twice daily therapy)
 - If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms.
 - ⇒ **H2 receptor antagonist**
 - The 2nd line if there is an inadequate response to a PPI
 - In those failing to respond to a double dose of proton pump inhibition an **H2 receptor antagonist** may be added or substituted in treatment or a prokinetic agent added to treatment.
- **Laparoscopic Nissen fundoplication**
 - ⇒ **the treatment of choice for patients with GORD refractory to or intolerant of proton pump inhibitor therapy.**
 - ⇒ The patient should have had an endoscopy within the six months prior to surgery to exclude any unsuspected pathology such as Barrett's oesophagus or adenocarcinoma.
 - ⇒ **the most useful in assessing the role of surgery → Oesophageal motility and pH study**
- **Severe oesophagitis**
 - ⇒ **1st line:** full-dose PPI (e.g. omeprazole 20 mg OD) for 8 weeks
 - ⇒ **2nd line:** high dose PPI (double standard dose e.g. 40 mg omeprazole OD) of the initial PPI, switching to another full-dose PPI or switching to another high-dose PPI
 - ⇒ Maintenance treatment → long-term full-dose PPI.
 - ⇒ If fail to respond to maintenance treatment, → switch to another PPI at full dose or high dose.
- **Management of GORD in pregnancy includes**
 - ⇒ 1st line: lifestyle and dietary modification
 - ⇒ 2nd line: antacids and sucralfate. Antacids containing sodium bicarbonate and magnesium trisilicate should be avoided in pregnancy.
 - ⇒ 3rd line: similar to nonpregnant patients, H2RAs and then PPIs.

Complications

- **Barrett esophagus:** Metaplasia of the lower esophagus
- **Esophageal strictures** occur in 10%
 - ⇒ Two types of rings (**Schatzki rings**): muscular ring, or A ring: located approximately 2 cm above the gastroesophageal junction. Rare
 - ⇒ mucosal ring, or B ring: **most common.** located at the squamo-columnar junction.
 - ⇒ mechanical cause of dysphagia
 - ⇒ most patients respond well to dilatation therapy.
 - ⇒ People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy
- **Adenocarcinoma** of the lower esophagus.

GORD management

- 1st line → lifestyle changes
 - ⇒ don't lie down after eating
 - ⇒ avoid spicy foods
 - ⇒ eat small servings
- 2nd line → proton pump inhibitors (omeprazole, lansoprazole) for at least 8 weeks (once daily therapy)
 - ⇒ No response: → further diagnostic evaluation
 - ⇒ Partial response: → increase the dose to (twice daily therapy)
 - ⇒ Good response: → discontinue PPI after 8 weeks
 - ⇒ If symptoms recur after discontinuation of PPIs → Maintenance therapy
 - ⇒ After 8 weeks of initial treatment, reduce PPI to lowest effective dose
- 3rd line → H2 receptor antagonists(cimetidine, ranitidine)
- 4th line → Surgical Nissen fundoplication or hiatal hernia repair

Barrett's oesophagus**Overview**

- Metaplasia of the lower oesophageal mucosa 1 cm or more proximal to the gastroesophageal junction. (the normal squamous epithelium of the oesophagus replaced by a columnar epithelium) (ie, intestinal metaplasia)
- The physiological transformation zone ("Z-line") between squamous and columnar epithelium is shifted upwards
- Metaplasia is defined as the replacement of one type of cells with another type whereas dysplasia is the disordered growth of the cells.
- Barrett esophagus is a premalignant condition of the lower esophagus caused by chronic esophageal reflux
- the columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, brush border)

Risk factors

- Age > 50 years
- Male gender
- **Ethnicity:** more common in white populations than Hispanic, Black, or Asian.
- Long duration or frequency of **Gastro-oesophageal reflux disease (GORD)** symptoms
- Previous oesophagitis
- Hiatus hernia
- Central obesity

Diagnosis

- Endoscopic evaluation, with:
 - ⇒ Visualization of columnar epithelium 1 cm or more above the gastroesophageal junction
 - ⇒ Biopsy sampling of esophageal epithelium with histologic confirmation of intestinal metaplasia (American guidelines) or histologic confirmation of columnar epithelium (British guidelines).

Management (based on presence or absence of dysplasia)

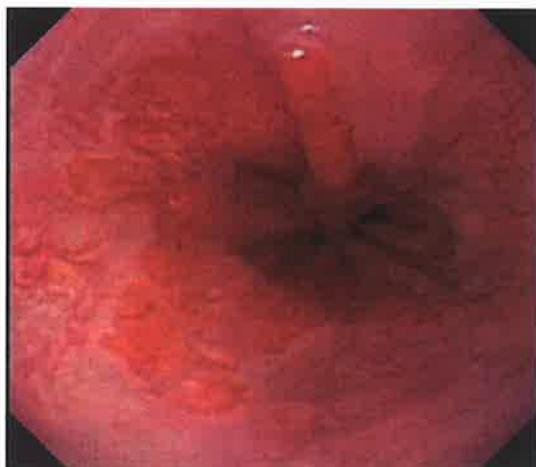
- **Nondysplastic:** proton pump inhibitors + surveillance endoscopy with repeated biopsy every 3 to 5 years

- ⇒ NO dysplasia and <3 cm segment of Barrett's → **endoscopy every three to five years with biopsies**
- ⇒ NO dysplasia and segment Barrett's >3 cm → Endoscopy every **two to three** years
- **Low-grade dysplasia (LGD)**
 - ⇒ **Repeat endoscopic biopsy in 6 months.** If LGD is found → Radiofrequency ablation
 - ⇒ If ablation is not undertaken, 6-monthly surveillance is recommended
- **Moderate to high grade dysplasia or recurrent disease**
 - ⇒ 1st line: Endoscopic ablation therapy (endoscopic resection of any visible mucosal irregularities, followed by **Radiofrequency Ablation (RFA)** to ablate the remaining metaplastic epithelium.)
 - ⇒ 2nd line: Oesophagectomy
- **High-dose proton pump inhibitor:**
 - ⇒ The best next line of management
 - ⇒ whilst this is commonly used in patients with Barrett's the evidence base that this reduces the chance of progression to dysplasia or induces regression of the lesion is limited

Histology at biopsy	Endoscopy frequency	Actions
No dysplasia	Every 2 - 5 years	
Low-grade dysplasia	Every 6 months	Repeat endoscopy with quadrantic biopsies every 1cm.
High-grade dysplasia	Every 3 months	If a visible lesion is present, consider endoscopic ablation with mucosal resection (EMR) or radiofrequency ablation.

Prognosis

- ↑↑ risk of oesophageal adenocarcinoma (50-100 fold), although the absolute risk is low (< 1%).



Barrett's oesophagus

Oesophagitis in immunosuppressive patients

Causes

- **Candidal** esophagitis is the most common cause of symptomatic disease.
- Ulcerative esophagitis resulting from **cytomegalovirus** is the next most important etiologies.
 - ⇒ Cytomegalovirus (CMV) most commonly causes multiple ulcers at the lower esophageal sphincter
- **Herpes simplex** virus esophagitis appears to be relatively uncommon.

Features

- The hallmark of oesophagitis is odynophagia or pain on swallowing.

Diagnosis

- Endoscopy with a biopsy

Treatment

- *Candida spp.*
 - ⇒ Nonpregnant patients, we suggest initial therapy with fluconazole
 - ⇒ Pregnant patients → amphotericin B is the treatment of choice during the first trimester since oral azoles are teratogenic.
- Herpes simplex virus (HSV) → oral or iv acyclovir
- Cytomegalovirus → ganciclovir or valganciclovir

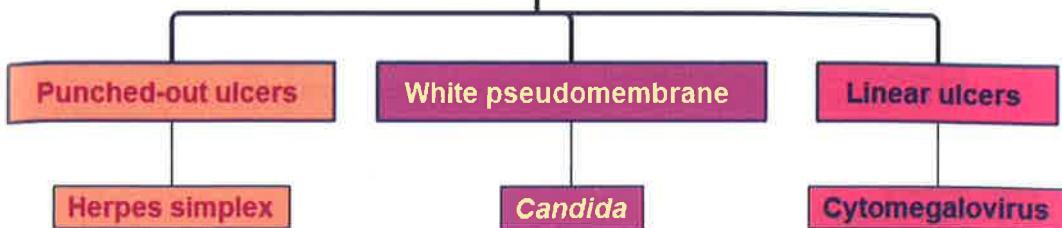
- Oesophagitis in the immunocompromised that presents with **punched-out ulcers** → Herpes simplex virus-1
- Oesophagitis in the immunocompromised that presents with a **white pseudomembrane** → *Candida spp.*
- Oesophagitis in the immunocompromised that presents with **linear ulcers** → Cytomegalovirus

Candida oesophagitis

Although oropharyngeal candidiasis may be treated with topical antifungal agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges) ***Candida oesophagitis requires oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).***

HIV patient presented with painfull swallowing difficulty, an upper GI endoscopy shows ulcerative oesophagitis, what is the most likely diagnosis?

Endoscopic diagnosis of Oesophagitis in immunocompromised patients



Eosinophilic oesophagitis

Overview

- Chronic immune-mediated eosinophil-predominant inflammation of the esophageal mucosa
Should be considered in adults with:
 - ⇒ History of food impaction, with persistent dysphagia, or
 - ⇒ Gastroesophageal reflux disease that fails to respond to medical therapy.
- Associated with Allergies** : (e.g., asthma, rhinitis, atopic dermatitis, alimentary allergies)

Features

- Episodic oesophageal spasm and intermittent dysphagia

Diagnosis

- Upper endoscopy with esophageal **biopsy** → presence of **epithelial infiltrate of ≥ 15 eosinophils per high-power microscopy field**

Treatment

- Diet modification. **Refer for allergy testing** (Eosinophilic esophagitis commonly associated with allergies). Once an antigen is identified, avoidance can improve symptoms
- Proton pump inhibitors**. If the patient does not respond to a low-dose proton pump inhibitor, it is appropriate to increase the dose to a maximal dose before trying other treatment strategies.
- Topical “swallowed” corticosteroids for 8 weeks

Patients who present with food impaction, dysphagia, and history of atopy should undergo an upper endoscopy evaluation with esophageal biopsy to diagnose eosinophilic esophagitis.

Oesophageal cancer

Oesophageal adenocarcinoma is associated with GORD or Barrett's

Epidemiology

- Sex:** ♂ > ♀ (3:1)
- Squamous cell carcinoma (SCC) is the most common type of esophageal cancer worldwide.
- Adenocarcinoma: most common type of esophageal cancer in the UK and US

Types

- **Adenocarcinoma**
 - ⇒ The most common form of esophageal cancer in the UK and US.
 - ⇒ Affects primarily white men.
 - ⇒ begins in the cells of mucus-secreting glands (**glandular cells of the submucosa**) in the esophagus.
 - ⇒ Occurs most often in the **lower** portion of the esophagus.
- **Squamous cell carcinoma (SCC)**
 - ⇒ The most prevalent esophageal cancer worldwide.
 - ⇒ Develops in the **thin, flat cells** of the **mucosa**, which line the oesophagus.
 - ⇒ Occurs most often in the upper two-thirds of the esophagus.

Risk factors

- **Risk factors for SCC**
 - ⇒ Smoking
 - ⇒ Alcohol (Unlike adenocarcinoma).
 - ⇒ Diet
 - Red meat consumption
 - Low selenium levels. selenium supplementation reduces the risk
 - Zinc deficiency
 - Low dietary folate intake
 - low intake of fruits and vegetables
 - Hot liquids
 - ⇒ **Tylosis** (rare, autosomal dominant disorder characterized by hyperkeratosis of the palms and soles, with thickening and fissuring of the skin.)
 - ⇒ **Achalasia cardia**
 - ⇒ **Plummer-Vinson syndrome**
 - ⇒ Oral bisphosphonates
 - ⇒ Poor oral hygiene
 - ⇒ Infection with the human papillomavirus (HPV)
- **Risk factors for adenocarcinoma**
 - ⇒ Gastroesophageal reflux (GORD) → the most common predisposing factor
 - ⇒ Barrett esophagus
 - ⇒ Smoking (twofold risk)
 - ⇒ Obesity
 - ⇒ Male sex
 - ⇒ Older age (50–60 years)

Oesophageal cancer risk factors

- Alcohol is NOT a risk factor for Adenocarcinoma
- *H. pylori* infection associated with DECREASE incidence of oesophageal cancer.
Helicobacter pylori may actually be protective against oesophageal cancer

The most important risk factors for esophageal adenocarcinoma are gastroesophageal reflux and associated Barrett esophagus.

The primary risk factors for squamous cell esophageal cancer are alcohol consumption, smoking, and dietary factors (e.g., diet low in fruits and vegetables).

Dermatological conditions associated with oesophageal carcinoma →Tylosis (95% will get squamous oesophageal cancer)

Localization

- **Squamous cell esophageal cancer:** mostly in the **upper two-thirds** of the esophagus
- **Adenocarcinoma:** mostly in the **lower third** of the esophagus

Features

- Early stages: Often asymptomatic
- Late stage: **progressive dysphagia, initially worse on solids and then later to include liquids**
- Sudden onset of hiccups is common when tumor spreads to diaphragm
- **General signs: Weight loss, dyspepsia, anaemia**

Diagnosis

- **Upper GI endoscopy is the first line test**
- **Staging:**
 - ⇒ For local tumor extent (mural invasion or tumour depth): Endoscopic ultrasound.
 - ⇒ For distant metastases:
 - CT of the Chest, abdomen and pelvis.
 - PET/CT scan is more sensitive than CT for detecting metastatic disease and are now widely used for detecting occult metastases if metastases are not seen on the initial staging CT scans.

Treatment

- **Superficial intramucosal oesophageal cancer** is best managed by endoscopic resection and surveillance.
- **Early-stage cancers** in surgical candidates are best treated by oesophagectomy.
- **For locally advanced disease**, combined modality therapy is considered the current standard. This involves **chemotherapy or chemoradiotherapy followed by surgery**.
- **High-risk patients** should be treated with a combination of chemotherapy and radiotherapy for best results, but local recurrence rates remain high.
- **Palliative**
 - ⇒ Opioid for pain relief
 - ⇒ Nifedipine helps relieve painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve his odynophagia.

Oesophageal cancer

- **Most oesophageal cancers are not resectable at presentation**
- **Chemo-radiotherapy then surgery is preferred to surgery alone.**

What is the most common type of **Oesophageal cancer?**

- Squamous cell carcinoma is the most prevalent esophageal cancer worldwide.
- Adenocarcinoma is the most common form of esophageal cancer in the UK and United States

	Squamous cell carcinoma (SCC)	Adenocarcinoma
Prevalence	More common worldwide	More common in UK/US
Major risk factors	Smoking, alcohol Achalasia, Plummer Vinson	Barrett's oesophagus, GORD, smoking, and obesity.

Part of oesophagus affected	Upper 2/3	Lower 1/3
Prognosis	Poor long -term prognosis after resection	Better long-term prognosis after resection than that of SCC
Treatment	More sensitive to chemo-radio therapy than adenocarcinoma	

Prognosis

- Poor prognosis due to advanced disease at presentation.
- Most patients present with stage 3 disease (late stage) and survival at 5 years is only 9%.

Pharyngeal pouch**Definition**

- A pharyngeal pouch is a **posterior medial** diverticulum through **Killian's dehiscence**.
⇒ Killian's dehiscence is a triangular area in the wall of the pharynx **between the thyropharyngeus and cricopharyngeus muscles**.
- Upper esophageal diverticulum (Common site)
- Zenker's diverticulum is the most common type of esophageal diverticula defined as a posterior "false" diverticulum that has a neck proximal to the cricopharyngeal muscle.

Epidemiology

- more common in **older** patients
- 5 times more common in **men**

Associations

- **Achalasia** → Inadequate relaxation of the esophageal sphincter ↑intraluminal pressure → outpouching of the esophageal wall → pulsion diverticulum (e.g., Zenker diverticulum)
- Inflammation of the mediastinum with scarring and retraction (e.g., secondary to tuberculosis or fungal infection) → traction diverticulum (Common site: the middle esophagus)
- Gastro-oesophageal reflux disease

Features

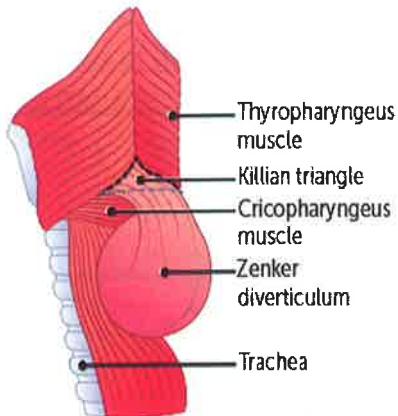
- Dysphagia (most common)
- Regurgitation of undigested food
- Aspiration
- Coughing after food intake
- Retrosternal pressure sensation and pain
- **Halitosis** (a bad breath)
- Neck swelling which gurgles on palpation (Boyce's sign)
- Weight loss

Diagnosis

- Barium studies (best confirmatory test)
 - ⇒ detected best by using **lateral X-ray** shows a contrast-filled pouch **protruding dorsally from the hypopharynx at the level of C5/C6**
 - ⇒ Upper gastrointestinal endoscopy is risky, since the pouches are thin-walled and easy to perforate; this is the reason why a **barium swallow may be the preferable first-line investigation in elderly patients with dysphagia**.
- Upper endoscopy **under direct vision** should be performed to exclude malignancy.

Treatment

- Diverticula of the **upper** esophagus :Surgical, with either an open or endoscopic approach.
- Diverticula of the **middle and distal** esophagus (traction diverticula and epiphrenic diverticula) usually do not require treatment (most of them are asymptomatic).



Acute upper gastrointestinal bleeding (UGIB) (NICE 2012)

Definition

- bleeding derived from a source proximal to the ligament of Treitz.

Causes: Most commonly due to either:

- peptic ulcer disease or
- oesophageal varices.

Risk assessment

- use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

Blatchford score

- The **Blatchford score** is based on clinical parameters alone:
 - ⇒ Elevated blood urea nitrogen
 - ⇒ Reduced haemoglobin
 - ⇒ A drop in systolic blood pressure
 - ⇒ Raised pulse rate
 - ⇒ The presence of melaena or syncope, and
 - ⇒ Evidence of hepatic or cardiac disease.

Admission risk marker	Score
Urea (mmol/l)	$6.5 - 8 = 2$ $8 - 10 = 3$ $10 - 25 = 4$ $> 25 = 6$
Haemoglobin (g/l)	<p>Men</p> <ul style="list-style-type: none"> $12 - 13 = 1$ $10 - 12 = 3$ $< 10 = 6$ <p>Women</p>

Admission risk marker	Score
	<ul style="list-style-type: none"> • $10 - 12 = 1$ • $< 10 = 6$
Systolic blood pressure (mmHg)	$100 - 109 = 1$ $90 - 99 = 2$ $< 90 = 3$
Other markers	<p>Pulse $\geq 100/\text{min} = 1$ Presentation with melaena = 1 Presentation with syncope = 2 Hepatic disease = 2 Cardiac failure = 2</p>

Patients with a Blatchford score of 0 may be considered for early discharge

Rockall score

- Used to:
 - determine the prognosis of upper GIT bleeds.
 - assess severity of GIT bleeds and / or to triage patients for emergency endoscopy.
- Consists of 5 categories:
 1. age
 2. shock
 3. **co-morbidity e.g. ischaemic heart disease (IHD)**
 4. diagnosis and
 5. evidence of bleeding (the latter two can only be categorised after endoscopy).
- ⇒ Each category is scored between 0 and 2 points, with the exception of **co-morbidities which has a maximum score of 3**.
- ⇒ **Renal failure, liver failure and metastatic cancer carry the highest points, and thus confer the highest risk of death**, of any of the other parameters included in the scoring system.
- The full Rockall scoring system is shown in the table below:

	Score 0	Score 1	Score 2	Score 3
Age	<60	60-79	>80	-
Shock	No shock	Pulse >100	Systolic blood pressure $<100\text{ mmHg}$	-
Co-morbidity	Nil major		CCF, IHD, major morbidity	Renal or liver failure, metastatic cancer
Diagnosis	Mallory-Weiss tear	All other diagnoses	GI malignancy	-
Evidence of bleeding	None	-	Blood, adherent clot, spurting vessel	-

- **Interpretation:**

- Increasing scores are strongly correlated with **increasing risk of mortality**,
- The total score predicts mortality as follows:

- ❖ Score 0, → 0.2%;
- ❖ score 2, → 5%;
- ❖ score 4, → 24%;
- ❖ score 6, → 49%.

➤ correlation with **risk of re-bleeding** is also present but not as strong.

Grades of hypovolaemic shock

The table below outlines the signs and symptoms of the different **grades** of hypovolaemic shock:

Grade 1	<ul style="list-style-type: none"> • Up to about 15% loss of effective blood volume (~750ml in an average adult who is assumed to have a blood volume of 5 litres). • This leads to a mild resting tachycardia and can be well tolerated in otherwise healthy individuals. • In the elderly or those with underlying conditions such as ischaemic heart disease the additional myocardial oxygen demands may not be tolerated so well.
Grade 2	<ul style="list-style-type: none"> • Between 15-30% loss of blood volume (750-1500ml) • will provoke a moderate tachycardia and begin to narrow the pulse pressure. • The capillary refill time will be extended.
Grade 3	<ul style="list-style-type: none"> • At 30 - 40% loss of effective blood volume (1500 - 2000 ml) • the compensatory mechanisms begin to fail and hypotension, tachycardia and low urine output (<0.5ml/kg/hr in adults) are seen.
Grade 4	<ul style="list-style-type: none"> • At 40-50% loss of blood volume (2000-2500 ml) • profound hypotension will develop and if prolonged will cause end-organ damage and death.

Classification of haemorrhage:

Parameter	I	II	III	IV
Blood loss (ml)	<750	750-1500	1500-2000	>2000
Blood loss (%)	<15%	15-30%	30-40%	>40%
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	>35
Urine output (ml/hour)	>30	20-30	5-15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

Blood test evidence of upper gastrointestinal haemorrhage

- **Reactive thrombocytosis**
- Urea elevated in excess of creatinine

Treatment

- **Resuscitation**
 - ABC, wide-bore intravenous access
 - platelet transfusion if actively bleeding platelet count of **less than $50 \times 10^9/\text{litre}$**
 - fresh frozen plasma to patients who have either a fibrinogen level of **less than 1 g/litre**, or a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal
 - prothrombin complex concentrate to patients who are taking warfarin and actively bleeding
- **Endoscopy**
 - should be offered immediately after resuscitation in patients with a severe bleed
 - all patients should have endoscopy within 24 hours
 - Recent NICE guidelines do not recommend proton pump inhibition (PPIs) before endoscopy.
 - **He may have alcohol dependency and therefore should be prescribed Pabrinex whilst waiting for endoscopy.**
- **Management of non-variceal bleeding**
 - NICE do not recommend the use of proton pump inhibitors (PPIs) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding although PPIs should be given to patients with **non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy**
 - The best evidence for pharmacological intervention post-stabilisation of bleeding peptic ulcer disease is for proton pump inhibitors.
 - **the most appropriate intervention to prevent further bleeding → IV omeprazole**
 - ❖ reduction in risk of recurrent bleeding of over 50%,
 - ❖ reduction in need for surgical intervention of approximately 40%.
 - if further bleeding then options include repeat endoscopy, interventional radiology and surgery
- **Management of variceal bleeding**
 - ⇒ **terlipressin** and prophylactic antibiotics should be given to patients at presentation (i.e. before endoscopy)
 - ⇒ band ligation should be used for oesophageal varices and injections of N-butyl-2-cyanoacrylate for patients with gastric varices
 - ⇒ transjugular intrahepatic portosystemic shunts (TIPS) should be offered if bleeding from varices is not controlled with the above measures

Oesophageal varices

Antibiotic prophylaxis reduces mortality in cirrhotic patients with gastrointestinal bleeding

Overview

- **Oesophageal varices** are tributaries of the left gastric vein , found in lower 1/3 of esophagus
 - ⇒ **lower 1/3 of oesophagus** is drained into the superficial veins lining the esophageal mucosa, → **left gastric vein** → portal vein.
 - ⇒ upper 2/3 of oesophagus are drained via esophageal veins → azygos vein → superior vena cava. (These veins have no part in the development of esophageal varices)
- Esophageal varices are the most common cause of death in cirrhosis.

Acute treatment of variceal haemorrhage

Terlipressin - method of action = constriction of the splanchnic vessels

- ABC: patients should ideally be resuscitated prior to endoscopy
- correct clotting: FFP, vitamin K
- vasoactive agents:
 - ⇒ **terlipressin is currently the only licensed vasoactive agent** and is supported by NICE guidelines.
 - powerful splanchnic vasoconstrictor
 - It has been shown to be of benefit in **initial haemostasis** and preventing rebleeding.
 - **the most appropriate treatment whilst awaiting urgent endoscopy**
 - As a vasoconstrictor its administration is **contraindicated in those with a history of ischaemic heart disease** as it may precipitate myocardial ischaemia.
 - ⇒ Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality
- prophylactic antibiotics
 - ⇒ have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis.
 - ⇒ Quinolones are typically used.
- endoscopy:
 - ⇒ endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation
- Sengstaken-Blakemore tube if uncontrolled haemorrhage
 - ⇒ Balloon tamponade (for example, using a Sengstaken-Blakemore tube) may be used as a holding measure **in situations where, for whatever reason, a definitive procedure cannot be performed to control bleeding** (for example, endoscopy or transjugular intrahepatic portosystemic shunting).
 - ⇒ It is generally very effective in achieving control of variceal bleeding.
- Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail

Prophylaxis of variceal haemorrhage

- propranolol:
 - ⇒ reduced rebleeding and mortality compared to placebo
- endoscopic variceal band ligation (EVL)
 - ⇒ is superior to endoscopic sclerotherapy.
 - ⇒ It should be performed at two-weekly intervals until all varices have been eradicated.
 - ⇒ Proton pump inhibitor cover is given to prevent EVL-induced ulceration

Prognosis

- **Overall mortality from bleeding varices is around 30%**

Esophageal Rupture

- **Causes**
 - ⇒ Iatrogenic esophageal perforation:
 - most common cause of esophageal perforation
 - Generally injury during upper endoscopy
 - ❖ Symptoms usually within 24 hours of endoscopy
 - ⇒ Foreign body ingestion
 - ⇒ Trauma
 - ⇒ Malignancy
 - ⇒ Boerhaave syndrome

- Severe vomiting/increased intrathoracic pressure → rupture of all layers of the esophageal wall
 - In > 90% of cases, the rupture occurs in the **distal third** of the esophagus on the **left dorsolateral** wall surface.
 - Sex: ♂ > ♀ (3:1)
 - Associations
 - ❖ Excessive intake of alcohol or food in the recent past
 - ❖ Repeated episodes of vomiting
 - ❖ Childbirth
 - ❖ Seizures
 - ❖ Prolonged coughing
 - ❖ Weightlifting
- **Feature:**
- Mackler's triad (vomiting, chest pain and surgical emphysema) is classical but absent in almost half the cases.
 - surgical emphysema
 - ❖ Subcutaneous emphysema → crepitus in the suprasternal notch
 - ❖ mediastinal emphysema → "crunching" or "crackling" sound on chest auscultation (**Hamman's sign**)
 - ⇒ **The most relevant finding on examination is the crepitus over the chest**
 - Dyspnea, cyanosis
- **investigations:**
- **Gastrograffin swallow** will confirm the site of perforation in approximately 65-75% of cases, and is the **recommended first line investigation**.
 - **chest x ray**
 - useful in the initial diagnosis
 - The most common finding is a **unilateral effusion**, usually on the left.
 - ❖ Because the most perforations occur in the left posterior aspect of the esophagus.
 - Other findings may include
 - ❖ pneumothorax, hydropneumothorax, pneumomediastinum,
 - ❖ surgical emphysema.
 - ❖ mediastinal widening.
 - **Lateral neck x rays**
 - may be useful in the early stages where the diagnosis is uncertain and surgical emphysema is not seen on a plain CXR.
 - **CT scan:**
 - indicated in unstable/uncooperative patients, pneumoperitoneum on x-ray, or ifx-rays and contrast esophagram are inconclusive
 - Barium swallow
 - more sensitive at 90% for detecting small perforations but carries the risk of a severe inflammatory response (**mediastinitis**).
- **Prognosis**
- A reported mortality estimate is approximately 35%, making it the most lethal perforation of the GI tract.
 - If intervention is delayed longer than 24 hours, the mortality rate (even with surgical intervention) rises to higher than 50% and to nearly 90% after 48 hours. Left untreated, the mortality rate is close to 100%.

Hiccup

- caused by frequent or rhythmic clonic contraction of the diaphragm.
- When prolonged, other causes should be considered including:
 - CNS disease - posterior fossa tumour, brain injury, encephalitis
 - Phrenic nerve or diaphragm irritation - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis
 - Systemic causes include alcohol intoxication and uraemia.
 - Other causes include foreign body or insect in the ear.
 - In infants it may be associated with apnoea or hyperventilation.
- Treatment
 - ⇒ Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.
 - ⇒ Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

Gastric conditions

Helicobacter pylori

H. pylori eradication:

- PPI + amoxicillin + clarithromycin, or
- PPI + metronidazole + clarithromycin

Overview

- *Helicobacter pylori* is a **Gram negative bacteria** associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations

- Peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- gastric cancer (≈ 5%)
 - ⇒ The most common location is the **lesser curvature**.
 - ⇒ appears as an **ulcer with heaped-up margins**.
- B cell lymphoma of MALT tissue (eradication of *H pylori* results causes regression in 80% of patients)
- Atrophic gastritis

***Helicobacter pylori* is NOT associated with GORD**

- There is no apparent role of *H pylori* in Gastro-oesophageal reflux disease (GORD)
- there is currently no role in GORD for the eradication of *H pylori*

Diagnosis

Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks

Noninvasive methods

Urea breath test

- The preferred method for initial diagnosis or confirmation of eradication
- sensitivity 95-98%, specificity 97-98%
- should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)

Serum antibody

- sensitivity 85%, specificity 80%
- remains positive after eradication (cannot distinguish between a past and current infection.)

Stool antigen test

- Sensitivity 90%, specificity 95%
- Can be used for initial diagnosis BUT NICE guidelines do not recommend its use to confirm eradication due to a lack of evidence.

Invasive methods

Rapid urease test (e.g. CLO test)

- Performed on biopsy tissue obtained during endoscopy
- Detects the amount of ammonia produced by *H. pylori* during urea hydrolysis
- Sensitivity 93-97%, specificity 95-98%
- the false negative rate increases significantly in:
 - ⇒ recent gastrointestinal haemorrhage,
 - ⇒ acid suppression therapy and
 - ⇒ recent antibiotic treatment.

Culture of gastric biopsy (Gold standard)

- sensitivity 70%, specificity 100%
- Staining and direct microscopic identification (silver stain)
- Curved, gram-negative rods with multiple flagella is the typical appearance of *H. pylori*.

Gastric biopsy

- Histological evaluation alone, no culture
- Sensitivity 95-99%, specificity 95-99%

Test to confirm eradication :

- When to test for complete eradication?
 - ⇒ Re-testing for *Helicobacter pylori* is indicated only in the setting of peptic ulcer disease to confirm eradication where an initial test is positive.
- Which test?
 - ⇒ Carbon-13 urea breath testing is the only well validated method for confirming the successful eradication of *Helicobacter pylori*.

PPIs should be discontinued at least 2 weeks prior to most *H. pylori* testing modalities to minimize rates of false-negative results. However, some testing modalities, e.g., histology, are not affected by recent PPI treatment.

Management

First-line treatment

- ⇒ Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole.
- ⇒ Allergic to penicillin → PPI + metronidazole + clarithromycin
- ⇒ Allergic to penicillin + previous exposure to clarithromycin → PPI + bismuth + metronidazole + tetracycline

- **Re-testing for *H. pylori***
 - ⇒ **Re-testing for *H. pylori* before second-line treatment** is considered to confirm eradication as there are serious side effects associated with antibiotics, e.g. *Clostridium difficile* infection, and antibiotic resistance is increasing.
 - ⇒ Eradication therapy is effective in 80-85% of cases and should not be repeated without evidence of treatment failure.
 - ⇒ **the carbon-13 urea breath test is the most accurate method of re-testing for *H. pylori*.**
 - ⇒ NICE guidelines 2019 state: Perform re-testing for *H pylori* using a **carbon- 13 urea breath test**. (**There is currently insufficient evidence to recommend the stool antigen test as a test of eradication**)
- **Second-line treatment** (If still symptomatic after first-line + **positive re-testing for *H. pylori***)
 - ⇒ **Not allergic to penicillin** → PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line)
 - ⇒ **If there is a previous exposure to clarithromycin and metronidazole** → PPI + amoxicillin + quinolone or tetracycline (whichever has the lowest acquisition cost).
 - ⇒ **Allergic to penicillin + NO previous exposure to a quinolone** → PPI + metronidazole + levofloxacin
 - ⇒ **Allergic to penicillin + previous exposure to a quinolone** → PPI + bismuth + metronidazole + tetracycline.

Peptic ulcer

Basic

Bleeding from Posterior duodenal ulcers are due to erosion of the gastroduodenal artery

- **The right and left gastroepiploic arteries (gastro-omental arteries) supply the greater curvature of the stomach.**
 - **The source of ulcer bleeding in the greater curvature of the stomach** → Left gastroepiploic artery
- The **right gastric artery** arises from the hepatic artery or the left hepatic artery, supplies the pylorus and travels along the **lesser curvature of the stomach**, supplying it, and anastomosing with the left gastric artery.
 - **the cause of ulcer bleeding in the lesser curvature of the stomach** → right gastric artery
- The **pancreaticoduodenal artery** (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum and the head of the pancreas.
- The **right hepatic artery** supplies the right lobe of the liver and part of the caudate lobe.

The golden notes

Sources of bleeding in peptic ulcers:

- greater curvature of the stomach → Left gastroepiploic artery
- lesser curvature of the stomach → right gastric artery
- Posterior duodenal ulcers → gastroduodenal artery
 - pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum.

The golden notes**Sites of peptic ulcers:**

- 80% are duodenal.
- The most common site → near the pylorus, on the duodenal side
- The less frequent site → lesser curvature of stomach or at the point at which the esophagus enters the stomach.

Risk factors for peptic ulceration include

- *Helicobacter pylori* (*H. pylori*) infection,
- non-steroidal anti-inflammatory drug (NSAID) use,
- cigarette smoking and
- genetic factors - Lewis blood group antigens facilitate *H. pylori* attachment to the mucosa.

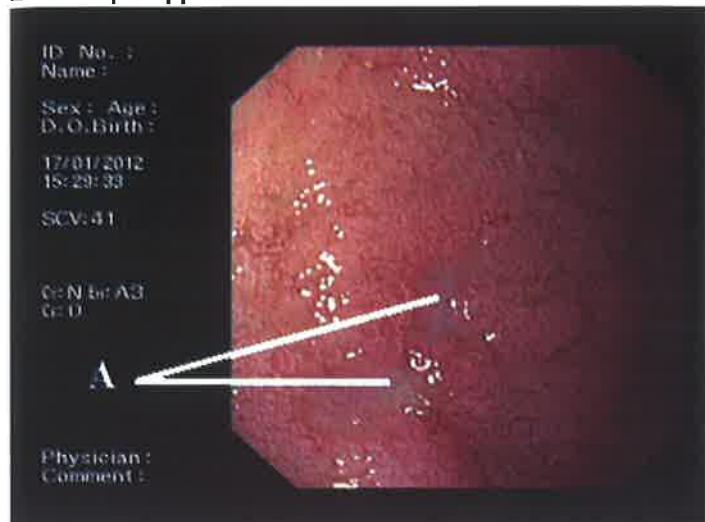
Interventions for peptic ulcer disease (NICE 2012)

- peptic ulcer + *H pylori* → *H pylori* eradication therapy
- peptic ulcer + *H pylori* → retesting for *H pylori* 6 to 8 weeks after beginning treatment,
- gastric ulcer + *H pylori* → repeat endoscopy 6 to 8 weeks after beginning treatment
- In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a COX-2 selective NSAID instead of a standard NSAID with a PPI.
 - ⇒ The Two highly selective or specific in their ability to inhibit COX-2 while having little or no COX-1 affinity are **rofecoxib** and **celecoxib**.
- Offer H₂RA therapy if there is an inadequate response to a PPI.

The effect of *Helicobacter* eradication on healing and recurrence of peptic ulcer:

- The effects is dependent upon whether ulceration is gastric or duodenal and whether the patient is taking non-steroidal anti-inflammatory drugs or not.
 - **For duodenal ulcers** eradication slightly **increases healing** (additional 5.4% over acid suppression alone) but dramatically **decreases recurrence** (increases the number of patients ulcer free at 12 months by 52%).
 - **For gastric ulcers** eradication therapy **has no effect on healing but does decrease recurrence** (an additional 32% of patients are ulcer free at 12 months compared to acid suppression alone).
 - **In patients taking non-steroidal anti-inflammatory drugs** eradication therapy has **no effect on peptic ulcer healing** (gastric or duodenal), **but will decrease ulcer recurrence**
 - continued non-steroidal anti-inflammatory drug use markedly reduces the size of effect that eradication therapy has on reducing ulcer recurrence.

Endoscopic appearance of ulcers:



- The endoscopic appearances are of two small duodenal ulcers (**A**) without evidence of recent haemorrhage. There is some co-existent duodenitis.
- The presence of villi identifies this as the duodenum.**
- The mucosal appearances are not consistent with that of the stomach (absence of rugae, paler squamous epithelium rather than redder columnar epithelium) or the oesophagus (pale pink non-villous squamous epithelium).

Following endoscopic intervention

- immediately post-endoscopy, patients should be commenced on a high dose oral or intravenous proton pump inhibitor,** this reduces the risk of rebleeding.
- Amoxicillin and clarithromycin may be indicated if there is evidence of Helicobacter pylori infection. This need not be started immediately post-endoscopy but treatment should not be unnecessarily delayed.

Zollinger-Ellison syndrome

Zollinger-Ellison syndrome: epigastric pain and diarrhoea

Definition

- gastrinoma (Zollinger-Ellison syndrome)** is a gastrin-secreting neuroendocrine tumor that is most often localized to the duodenum and pancreas.
 - Gastrin is released by G cells in the antrum under normal physiological conditions.

Tumor location

- Duodenum (~ 70% of cases)
 - Most ulcers are located in the first part of the duodenum.
- Pancreas (~ 25% of cases): typically, the head
- Ectopic locations (5–15% of cases)

Causes

- Most gastrinomas occur sporadically.
- **Around 30% occur as part of MEN type I syndrome**

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age of onset: 30–50 years

Pathophysiology

- Hypergastrinemia → stimulation of parietal cells → gastric acid hypersecretion, which leads to:
 - Peptic ulcer disease
 - Inactivation of pancreatic enzymes → diarrhea, steatorrhea → malabsorption

Features

- multiple gastroduodenal ulcers
- diarrhoea
 - diarrhea in Zollinger-Ellison syndrome (gastrinoma) is due to malabsorption.
- malabsorption

Diagnosis

- Best initial test: **esophagogastroduodenoscopy**
 - Important to rule out *H. pylori* infection and malignant ulcers
 - Typically reveals multiple ulcers and thick gastric folds
 - ↓ Gastric pH
- **Fasting gastrin levels: the single best screen test**
 - ⇒ fasting gastrin test > 1000 with low PH < 2 is **diagnostic**
 - ⇒ if level < 1000 and the diagnosis is suspected, then **secretin stimulation testing** or **calcium stimulation testing**
 - secretin stimulation test
 - ❖ rise > 200 after 15 minute of dosing is considered positive
 - calcium stimulation test
 - ❖ rise > 395 is considered positive
- **Secretin stimulation test** (if fasting serum gastrin test is inconclusive)
 - ⇒ gastrin levels remaining elevated after administration of secretin.

The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the **jejunum**) should raise suspicion of gastrinoma.

Treatment

- Reduce acid production
 - **PPIs** (e.g., omeprazole), H2 antagonists (e.g., ranitidine)
 - Octreotide (a somatostatin analog) may be used in refractory cases.
- Non-metastatic disease:
 - ⇒ **surgical resection of the gastrinoma is the treatment of choice**
 - possibility of cure is up to 25% of patients.
- Metastatic disease:
 - ⇒ chemotherapy
 - ⇒ In approximately 50% of cases, the tumor has already metastasized at the time of diagnosis

Somatostatin

Source	Action	Regulation	Notes
<ul style="list-style-type: none"> D cells (pyloric antrum, and duodenum mucosa) delta cells (pancreas) ventromedial nucleus of the hypothalamus. 	<ul style="list-style-type: none"> ↓ gastric H⁺ and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release ↓ GH release 	<ul style="list-style-type: none"> ↑ by H⁺ ↓ by vagal stimulation 	<ul style="list-style-type: none"> Inhibitory hormone Antigrowth hormone effects (digestion and absorption of substances needed for growth) Produce vasoconstriction of the splanchnic system. Somatostatin is treatment for VIPoma and carcinoid tumors

- Inhibit TSH secretion.**
- Mechanism of action**

➤ Somatostatin receptor is linked to adenylyl cyclase by Gi protein, which inhibits cAMP production and reduces secretion of hormones.

Somatostatinoma

- Annual incidence → 1 in 40 million.
- Associations:**
 - ⇒ Impaired glucose tolerance (IGT) or diabetes mellitus (95%)
 - ⇒ Gallstones (68%)
 - ⇒ Weight loss (25%)
 - ⇒ Anaemia (14%)
 - ⇒ Multiple endocrine neoplasia type 1 (7%)
 - ⇒ Diarrhoea
- Diagnosis:**
 - ⇒ The tumours are often multisecretory → ↑↑ **Somatostatin, adrenocorticotrophic hormone (ACTH) and calcitonin**
 - ⇒ Contrast spiral computed tomography scanning is effective for detecting the primary tumour in only 50% of cases;
 - ⇒ Radiolabeled octreotide or endoscopic ultrasound scanning are often required.
- Treatment:**
 - ⇒ surgery is rarely possible due to presence of metastases,
 - ⇒ hepatic embolisation can be helpful for symptom control.

Gastric MALT lymphoma

Gastric MALT lymphoma - eradicate H. pylori

Overview

- lymphoma of **Mucosa-Associated Lymphoid Tissue (MALT)**
- (MALT) is typically a low-grade, B-cell neoplasia originating from mucosa-associated lymphoid tissue
- associated with *H. pylori* infection in 95% of cases
- good prognosis
- Within the stomach **the antrum is most commonly involved**

Epidemiology

- MALT lymphoma**

- ⇒ 7% to 8% of all B-cell lymphomas
- ⇒ the third most common type of non-Hodgkin's lymphoma
- ⇒ the most common type of primary **extra-nodal** lymphoma and represents up to 50% of primary gastric lymphomas.

- **Gastric MALT lymphomas**

- ⇒ account for about 30% of all MALT lymphomas,
- ⇒ median age of 57 years
- ⇒ no sex predilection.

Features

- **paraproteinaemia may be present**
- infiltrate of small-size lymphocytes that destroy gastric glands, configuring the so-called '**lymphoepithelial lesion**' which is **pathognomonic of lymphoma**
- The common cytogenetic abnormalities demonstrated in MALT lymphomas is **t(11;18)**,
 - ⇒ seen in 30% to 40% of gastric and lung MALT lymphomas
 - ⇒ This is clinically important, as **t(11;18)-positive cases are less likely to respond to *H pylori*-eradication therapy**
 - ⇒ there is a high incidence of t(11;18) in ***H pylori*-negative gastric MALT lymphoma**,
 - ⇒ t(11;18)-positive cases are **more likely to present with advanced-stage disease** associated with aberrant expression of nuclear BCL10
 - ⇒ t(11;18)-positive cases are **less likely to transform to aggressive lymphomas**, as they are unlikely to develop secondary chromosomal abnormalities.

Treatment

- if low grade then 80% respond to *H. pylori* eradication
- low grade localised gastric helicobacter pylori positive :
 - ⇒ first line → antibiotics plus a proton-pump inhibitor (PPI)
 - ⇒ second line → radiotherapy
 - Patients are considered to have failed *H pylori* eradication when:
 - ❖ there is no regression at repeat endoscopy 2 months after treatment,
 - ❖ or when there is lack of complete regression at approximately 18 months after treatment.
- low grade localised gastric helicobacter pylori negative:
 - ⇒ first line → radiotherapy
- low grade advance gastric (Disease not confined to the stomach)
 - ⇒ first line → chemotherapy
 - If *H pylori* -positive, → add eradication therapy.
- High grade histological transformation:
 - ⇒ First line → chemotherapy
 - ⇒ MALT lymphoma is defined as a low-grade neoplasm. However, gastric MALT lymphoma can show a component of high-grade transformation.
 - ⇒ This is characterised by an **increase in the number of transformed blasts**, which can eventually lead to **complete effacement of the original MALT lymphoma**.

Ref: bestpractice.bmjjournals.com.2017

Gastroparesis

Definition

- Delayed gastric emptying in the absence of a mechanical obstruction

Causes

- Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery
- Occurs in 10–20% of diabetics after 10 years.

Mechanism

- The major stimulant for gastric motility is "stretch."

- In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.

Symptoms

- erratic blood glucose control
- chronic nausea, vomiting, epigastric pain, bloating
- early satiety, abdominal fullness, constipation.

Diagnosis

- **Gastric-emptying scan**
 - ⇒ Gastric emptying scintigraphy demonstrating >10% retention of the radionuclide meal at the end of 4 hours is diagnostic.

Management

- **Metoclopramide: the first drug of choice**
 - **Action:** both a dopamine receptor antagonist and a serotonin receptor agonist.
 - **Indication:** It is better for short-term treatment. Its use in the long-term treatment of gastroparesis is no longer recommended.
 - **Side effects:** extrapyramidal
- **Domperidone**
 - ⇒ **Action:** dopamine antagonist with an affinity for the D2 receptor in the brain and peripheral gastrointestinal system.
 - ⇒ **Indications:** only used for nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort.
 - ⇒ **Side effects:** associated with a small increased risk of life-threatening cardiac effects.
 - ⇒ **Advantages:** It does not cross the blood-brain barrier, so does not cause the neurological adverse effects associated with metoclopramide.
 - ⇒ **Contraindications**
 - Contraindicated in patients with hepatic or cardiac disease.
 - Should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4
- **Erythromycin**
 - ⇒ **Action:** ↑ release of "motilin," a pro-motility GI hormone.
 - ⇒ used in the acute care setting if the patient is admitted to hospital.
- Dietary modification (small, frequent meals that are low in fat and contain only soluble fiber), glycemic control and hydration

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting → Think about a diagnosis of gastroparesis.

Gastric cancer

Gastric adenocarcinoma - signet ring cells

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Peak incidence: 70 years
- Geographical distribution:
 - ⇒ strong regional differences
 - ⇒ High incidence in South Korea, China and Japan

- ⇒ Declining incidence in the United States and Europe
- overall incidence is decreasing, but **incidence of tumours arising from the cardia is increasing**
- Adenocarcinoma** is the most common gastric cancer (90% of cases). Arises from glandular cells in the stomach. Most commonly located on the lesser curvature

Risk factors

- Exogenous risk factors**
 - ⇒ Diet: salty, spicy, nitrates, dietary nitrosamines (smoked foods).
 - ⇒ H. pylori infection: **the most common risk factor** (> 60%)
 - ⇒ Smoking
 - ⇒ Epstein-Barr virus
 - ⇒ Low socioeconomic status
 - ⇒ Obesity
- Gastric conditions**
 - ⇒ Pernicious anaemia → Chronic atrophic gastritis → gastric adenocarcinoma.
 - ⇒ Achlorhydria: decrease in gastric acid production (e.g., due to Ménétrier disease)
 - ⇒ Gastric ulcers
 - ⇒ Partial gastrectomy
 - ⇒ Adenomatous gastric polyps
 - ⇒ Gastroesophageal reflux disease
- Hereditary factors**
 - ⇒ Positive family history
 - ⇒ **Blood type A: gAstric cAancer**
 - ⇒ Gastric adenomatous polyps: Hereditary nonpolyposis colorectal cancer
- Factors associated with decreased risk of gastric tumours** (negative association)
 - ⇒ Duodenal ulcer
 - ⇒ NSAID use

Features

- Early stages: Often asymptomatic
- About half of patients with gastric cancer present with advanced disease at the time of diagnosis.**
- General signs: Weight loss, chronic iron deficiency anemia
- Signs of gastric outlet obstruction: Dysphagia, Abdominal pain, Early satiety, Vomiting
- Signs of upper gastrointestinal bleeding: Hematemesis, Melena
- Signs of metastatic disease
 - ⇒ Hepatomegaly, Ascites: liver is the most common site of metastasis.
 - ⇒ Left supraclavicular adenopathy (Virchow node)
 - ⇒ Palpable umbilical nodule (**Sister Mary Joseph node**)
 - ⇒ Mucin-secreting "signet-ring" cells in the ovaries are diagnostic of **Krukenberg tumors**, which are indicative of stomach adenocarcinoma metastasis.
- Paraneoplastic syndromes
 - ⇒ Leser-Trélat sign (: (multiple seborrheic keratoses, often with an inflammatory base.)
 - ⇒ Malignant acanthosis nigricans

Always rule out malignancy in patients with acanthosis nigricans.

Types of gastric adenocarcinoma

- **Intestinal type of gastric adenocarcinoma**
 - ⇒ the **most common** type of gastric adenocarcinoma.
 - ⇒ presents as a large, **irregular ulcer with heaped up margins**, typically at the lesser curvature of the antrum.
 - ⇒ associated with *Helicobacter pylori*, chronic gastritis, atrophy, and intestinal metaplasia
- **Diffuse gastric adenocarcinoma**
 - ⇒ characterized by **thickening and rigidity of the gastric wall**.
 - ⇒ Infiltrate the **submucosa**, (**Scirrhous infiltration of the submucosa**) so that mucosal sampling may not show neoplastic cells.
 - ⇒ associated with a poor prognosis compared with the intestinal type
 - ⇒ Unlike the intestinal type of gastric adenocarcinoma, it is more common in women and individuals less than 50 years old.
 - ⇒ associated with H. pylori infection, **but NOT with atrophy and intestinal metaplasia**
 - ⇒ associated with signet ring cells and linitis plastica.
 - ⇒ **Linitis plastica** is a particularly aggressive form of diffuse adenocarcinoma. It is also known as "leather bottle stomach" because the stomach is diffusely thickened, with a small lumen that cannot expand, leading to the symptom of early satiety. This thickening can be seen on the CT image.

Histology

- **Signet ring cells** may be seen in gastric cancer.
 - ⇒ They contain a large vacuole of mucus which displaces the nucleus to one side.
 - ⇒ **Higher numbers of signet ring cells are associated with a worse prognosis**

Diagnosis

- Endoscopy with biopsy: (best initial and confirmatory test)
- Staging: CT or endoscopic ultrasound - **endoscopic ultrasound has recently been shown to be superior to CT**

Treatment

- Early-stage disease → surgery alone (**Total or sub-total Gastrectomy**)
- Locally advanced disease → surgery followed by postoperative chemoradiation, or chemotherapy before and after surgery.
- Metastatic disease → chemotherapy, immunotherapy, or chemoradiation and supportive care measures.
- Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

(TRUSTuzumab; HER2; Gastric cancer; Breast cancer)

Post gastrectomy complications

- **Malabsorption:** Lack of chyme stimulation → ↓ pancreatic enzyme levels → protein and carbohydrate maldigestion → fat-soluble vitamin deficiency
- Loss of parietal cells → ↓/absent intrinsic factor production → vitamin B12 deficiency → **pernicious anemia**

- Loss of parietal cells → ↓ gastric acid → ↓ iron absorption → **iron deficiency anemia** (low pH environment is necessary for the reduction of Fe^{3+} (ferric iron) to Fe^{2+} (ferrous iron) the absorbable form of iron).
- Small intestinal bacterial overgrowth**
- Dumping syndrome**
 - ⇒ **Early dumping** (Occur hours after meal ingestion): rapid emptying of undiluted hyperosmolar chyme into the small intestine → fluid shift to the intestinal lumen → small bowel distension → vagal stimulation → increased intestinal motility (nausea, vomiting, diarrhoea, and cramps) + Vasomotor symptoms such as sweating, flushing, and palpitations.
 - ⇒ **Late dumping** (occur hours after meal ingestion): rapid emptying of glucose-containing chyme into the small intestine → quick reabsorption of glucose → hyperglycaemia → excessive release of insulin → hypoglycaemia and release of catecholamines → signs of hypoglycaemia (e.g., hunger, tremor, light-headedness)

Prognosis

- At diagnosis, 60% of cancers have already reached an advanced stage that does not allow for curative treatment.
- 5-year survival**
 - ⇒ confined to the mucosa and submucosa ($> 90\%$)
 - ⇒ extended beyond the submucosa ($< 10\%$).

Gastrointestinal stromal tumour (GIST)

- common type of sarcoma; it develops in the gastrointestinal (GI) tract
- occur most often in adults over the age of 50 years
- Location of GISTs:**
 - ⇒ **most commonly involve the stomach (60%),**
 - ⇒ jejunum and ileum (30%),
 - ⇒ duodenum (4%–5%), and
 - ⇒ colorectal (< 5%).
- Tumours in the small bowel and rectum appear to be more aggressive than those occurring in the stomach.
- the cell of origin of gastric GISTs → Interstitial cells of Cajal** within Auerbach's plexus
 - ⇒ the interstitial cells of Cajal act as pacemaker cells of the GIT, with regulation of peristalsis in the adult intestine
- Approximately 80%–95% of GISTs harbor an activating mutation in the **KIT gene**
 - ⇒ about 80% of KIT-negative GISTs have an activating mutation in the **PDGFRA** gene.
 - a mutation in PDGFRA may make the tumour resistant to the standard drugs to treat GIST.
 - tumours with a PDGFRA mutation are usually less aggressive than the more common ones with KIT mutation.
- 50% are present with metastatic disease, (commonly liver metastases),
- Features**
 - Mostly asymptomatic.
 - Tumor induce GI bleed and anemia
 - Other symptoms secondary to mass effects:
 - Abdominal discomfort, early satiety, palpable abdominal mass
 - Bowel obstruction or perforation
 - Dysphagia
- Diagnosis:**
 - Gold standard test is endoscopy with biopsy
 - Histopathology: **Spindle cell** in 70 to 80%, epithelioid cells in 20 to 30

- CT and endoscopic ultrasound allow tumour staging to plan further management.
- Immunohistochemical Staining
 - Up to 95% of GISTs are positive for KIT expression (CD117)
 - 60%-70% are positive for CD34 expression.
- Management
 - all GISTs \geq 2 cm → surgery
 - Surgery is usually the first treatment method used for GIST.
 - If the tumour is too large to be removed at the time of diagnosis, it may be treated initially with imatinib. If sufficient shrinkage has occurred after 6-12 months, it may be operated.
 - incidentally encountered GISTs < 2 cm → watchful waiting and surveillance for such very small GISTs might be reasonable.
 - for patients with KIT-positive unresectable and/or metastatic GIST → **Medical Management:**
 - **first line** → **Imatinib** mesylate is an oral adenosine triphosphate (ATP)-competitive TKI that selectively inhibits the activity of KIT, PDGFRA.
 - ❖ It is effective in 80% of patients and on average will control the disease for about two years.
 - ❖ imatinib may be used as an adjuvant therapy after surgery to reduce the risk of the cancer returning
 - **second-line** → **In case of imatinib resistance:** patients can be switched directly from low-dose imatinib (400 mg/day) to another TKI, such as the only approved **second-line** therapy, **sunitinib**.
 - **3rd line** → **Regorafenib** (if imatinib and sunitinib are not effective or not tolerated)

Menetrier's disease

- A rare condition associated with **giant gastric folds**, predominantly in the fundus and body of the stomach.
- **Histologically there is hyperplasia of the gastric pits, gland atrophy and an increase in overall mucosal thickness.**
- Hypochlorhydria is usually present.
- Patients often complain of epigastric pain
- protein loss from the gastric mucosa can result in mild hypoalbuminaemia.
- some patients improve spontaneously, whereas in others this can be a premalignant state.
- Antisecretory drugs such as proton-pump inhibitors can be tried for symptom relief.

Bowel conditions

Dyspepsia

Causes of dyspepsia

- Gastro-oesophageal reflux disease (GORD) (15 - 25%)
- Gastric and duodenal ulcers (15 - 25%) and
- Stomach cancer (2%).
- The remaining 60% are classified as non-ulcer dyspepsia (NUD).
- **Drugs causing dyspepsia**
 - NSAIDs (**ibuprofen is associated with the lowest risk of peptic ulcer disease**)
 - bisphosphonates
 - steroids

- The following **drugs may cause reflux by reducing lower oesophageal sphincter (LOS) pressure**
 - calcium channel blockers*
 - nitrates*
 - ❖ *calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.
 - **theophyllines**

Indications of **Urgent** referral for an endoscopy (i.e. within 2 weeks). (NICE 2015)

- **dysphagia**
- **upper abdominal mass** consistent with stomach cancer
- Any sign of chronic gastrointestinal bleeding
- Persistent vomiting
- Iron deficiency anaemia,
- Suspicious barium meal.
- Progressive unintentional weight loss
- **Patients aged ≥ 55 years who've got weight loss**, AND any of the following:
 - upper abdominal pain
 - reflux
 - **dyspepsia**

Non-urgent

- Patients with **haematemesis**
- Patients aged ≥ 55 years who've got:
 - **treatment-resistant dyspepsia** or
 - upper abdominal pain with low haemoglobin levels or
 - **raised platelet count** with any of the following: nausea, vomiting, weight loss, reflux, dyspepsia, upper abdominal pain
 - nausea or vomiting with any of the following: weight loss, reflux, dyspepsia, upper abdominal pain

Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

- This can be summarised at a step-wise approach
 1. Review medications for possible causes of dyspepsia
 2. Lifestyle advice
 3. Trial of full-dose proton pump inhibitor for one month OR a 'test and treat' approach for *H. pylori*
- lifestyle advice
 - ⇒ avoid known precipitants: eg: smoking, alcohol, coffee, chocolate, fatty foods and being overweight
 - ⇒ Raising the head of the bed and having a main meal well before going to bed may help some people.
- Testing for *H. pylori* infection
 - initial diagnosis: NICE recommend using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology 'where its performance has been locally validated'
 - test of cure: carbon-13 urea breath test
- cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people.
- If *H pylori* has been excluded and symptoms persist, offer either a **low-dose PPI** or an **H₂RA** for 4 weeks.

Malabsorption

Features

- Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss.
- **The presence of anaemia with low albumin raises the possibility of malabsorption**

Causes may be broadly divided into:

1. **intestinal causes** (e.g. villous atrophy),
 - coeliac disease
 - Crohn's disease
 - tropical sprue
 - Whipple's disease
 - Giardiasis
 - brush border enzyme deficiencies (e.g. lactase insufficiency)
2. **pancreatic causes** (deficiency of pancreatic enzyme production or secretion)
 - chronic pancreatitis
 - cystic fibrosis
 - pancreatic cancer
3. **biliary causes** (deficiency of bile-salts needed for emulsification of fats)
 - biliary obstruction
 - primary biliary cirrhosis
4. **Other causes**
 - bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
 - lymphoma
 - **short bowel syndrome**
 - Does not develop unless more than **two thirds of the small intestine** have been removed.
 - features include:
 - ❖ Abdominal pain
 - ❖ Diarrhea and steatorrhoea
 - ❖ Fluid depletion
 - ❖ Weight loss and malnutrition
 - ❖ Fatigue
 - ❖ complications caused by malabsorption of vitamins and minerals
 - ❖ **Hyperoxaluria** occurs both in patients with an ileal resection and in patients with a short bowel who have had a distal small bowel resection (for example, Crohn's disease, infarcted bowel).
 - ⇒ **What is the most effective advice in preventing further renal calculi? → Dietary exclusion of chocolate, tea, rhubarb and spinach**

D-xylose test

- D-xylose is a monosaccharide which is absorbed through the small intestines and excreted through the kidneys.
- **D-xylose test** is helpful in differentiating between structural and functional causes of malabsorption.
 - structural (e.g. Celiac disease, Crohn disease) or functional (e.g. pancreatic insufficiency)
- An abnormally low excretion of D-xylose is indicative of a structural pathology.
- This test distinguishes between malabsorption due to small-intestinal diseases and malabsorption due to pancreatic exocrine insufficiency.
- A 5-hour urinary excretion of 5 g or greater is normal following the oral administration of 25 g of D-xylose to a well-hydrated subject.
- Decreased xylose absorption and excretion are found:
 - In patients with damage to the proximal small intestine

- When there is bacterial overgrowth in the small intestine (the bacteria catabolise the xylose)
- Patients with **pancreatic steatorrhoea (chronic pancreatitis) usually have normal xylose absorption.**
- Abnormal results might be encountered in renal failure, in the elderly and in patients with ascites due to an excretion defect rather than malabsorption.

Diarrhoea (NICE 2012)

- Diarrhoea is defined as the abnormal passage of loose or liquid stools **more than 3 times daily or a volume of stool greater than 200 g/day.**
- Diarrhoea is considered to be chronic if it persists for **more than 4 weeks.**

Jejunal villous atrophy

Causes of villous atrophy (other than coeliacs): tropical sprue, Whipple's, lymphoma, hypogammaglobulinaemia

Causes

- coeliac disease
- tropical sprue
- hypogammaglobulinaemia
- gastrointestinal lymphoma
- Whipple's disease
- cow's milk intolerance

Coeliac disease

Coeliac disease - tissue transglutaminase antibodies first-line test

- Caused by sensitivity to the protein gluten.
- **due to T cell mediated hypersensitivity reaction**
- Mechanism: repeated protein gluten exposure → villous atrophy → malabsorption.
- Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis).
- It is strongly associated with HLA-DQ2 (95% of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7
- **The prevalence of coeliac disease in Europe between 1:100 and 1:300.**
- It presents at any age but in adults the commonest age of presentation is 20s and 30s.
- Women are slightly more commonly affected.
- The action of tissue transglutaminase on alpha-gliadin generates epitopes to CD4+ T-lymphocytes, which provoke an inflammatory response in the intestinal wall.

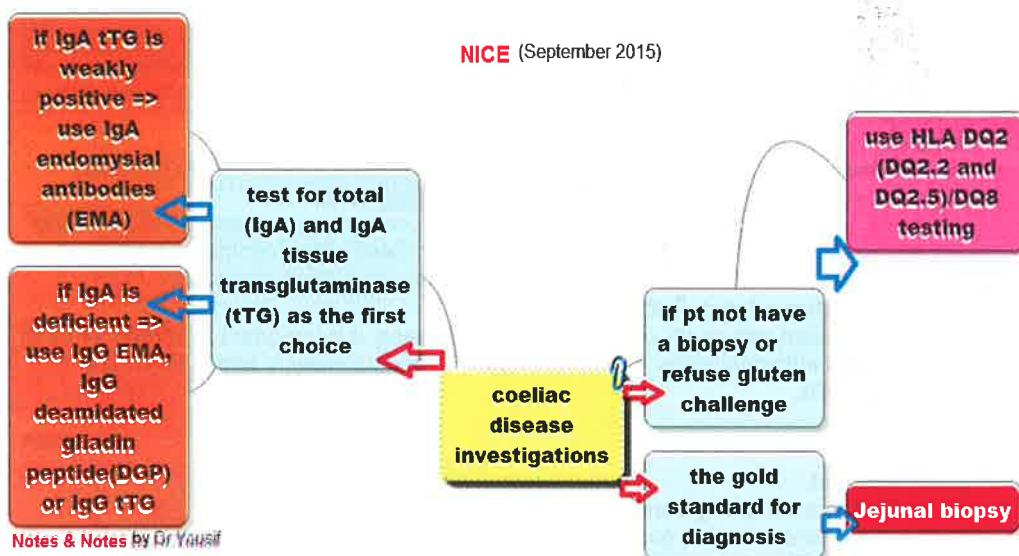
In 2009 NICE suggest that the following patients should be screened for coeliac disease:

Signs and symptoms	Conditions
<ul style="list-style-type: none"> Chronic or intermittent diarrhoea Failure to thrive or faltering growth (in children) Persistent or unexplained gastrointestinal symptoms including nausea and vomiting Prolonged fatigue ('tired all the time') Recurrent abdominal pain, cramping or distension Sudden or unexpected weight loss Unexplained iron-deficiency anaemia, or other unspecified anaemia 	<ul style="list-style-type: none"> Autoimmune thyroid disease Dermatitis herpetiformis Irritable bowel syndrome Type 1 diabetes First-degree relatives (parents, siblings or children) with coeliac disease

Associated conditions:

- Insulin-dependent diabetes mellitus,
- hypothyroidism,
- chronic liver disease and
- fibrosing alveolitis

Investigations



Diagnosis

- Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet.
- If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing.

Immunology

- tissue transglutaminase (TTG) antibodies (IgA) are the **first-choice**
 - Selective IgA deficiency is more common in patients with coeliac disease.

- For this reason, IgA levels should be checked when serological tests are ordered.
- If the patient has **selective IgA deficiency** → tissue transglutaminase IgG can be measured.
- Patients normally need to be following a gluten-free diet for **at least 6 months before the serology becomes negatives.**
- endomyseal antibody (IgA) → 90% sensitive and almost 100% specific.
 - **Anti-endomysial antibodies are sensitive and specific, but miss the disease in about 5% of the population who are IgA deficient.**
- anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE
- anti-casein antibodies are also found in some patients

Jejunal biopsy

- **duodenal biopsies are the gold standard for diagnosis:**
 - villous atrophy
 - **crypt hyperplasia**
 - increase in intraepithelial lymphocytes
 - lamina propria infiltration with lymphocytes
 - **Appearances may resemble severe tropical sprue**

Rectal gluten challenge has been described but is not widely used

Subtotal villous atrophy is seen in a number of conditions other than coeliac disease such as:

- Severe tropical sprue
- Cow's milk/soya sensitivity in children
- Gastroenteritis
- **Whipple's disease**
- Hypogammaglobulinaemia
- Neomycin therapy
- Laxative abuse
- Norwalk agent.

Other investigations

- **Imaging**
 - Which would most likely seen on abdominal radiograph with barium contrast?
 - **Decreased jejunal folds, increased ileal folds**
 - ❖ imaging and biopsy of the GI mucosa show a characteristic blunting of jejunal villi. This is often associated with a compensatory "jejunization" of the ileum to enhance nutrient absorption.
- **Screen for other related autoimmunities**
 - In a patient with newly diagnosed **celiac disease**, it is important to screen for other related autoimmunities as well, e.g. type 1 diabetes mellitus and autoimmune thyroiditis.

Management

- gluten-free diet.
 - **Gluten containing cereals include:**
 - wheat: bread, pasta, pastry
 - barley: beer
 - ❖ whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
 - rye
 - oats (some patients with coeliac disease appear able to tolerate oats)
 - **Some notable foods which are gluten-free include:**
 - Rice
 - Potatoes
 - corn (maize)

follow-up

- Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet.

Associations and Complications

If the patient still symptomatic despite being compliant with a gluten free diet → think of T Cell lymphoma

- Enteropathy associated **T Cell lymphoma** (EATL)
 - is a form of Non-Hodgkin's lymphoma
 - coeliac disease increase the risk of developing EATL within the 1st year of diagnosis, however with a strict gluten free diet, the risk returns to that of the general population after this point.
- Recurrent mouth ulcers**
- Hyposplenism** (Splenic atrophy): seen in 50% of cases and responds poorly to gluten withdrawal.
- selective Ig A deficiency
- Small-bowel ulceration is associated with ulcerating jejunitis, but not colonic or gastric ulcers.

MRCPUK-part-1-January 2016 exam: Why do patients with coeliac disease require regular immunisations?

→ Functional hyposplenism

Whipple's disease

Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

- Whipple's disease is a rare **multi-system** disorder
- Caused by *Tropheryma whipplei*, a **Gram positive** bacterium

Epidemiology

- more common in those who are HLA-B27 positive
- most common in white males aged 40-50 years
- rarely described in women (M:F ratio 9:1).

Pathophysiology

- Malabsorption in Whipple disease is caused by **macrophages** in the small bowel lamina propria compressing the lacteals.

Features

- malabsorption: diarrhoea, weight loss
- large-joint arthralgia
- lymphadenopathy
- skin: hyperpigmentation and photosensitivity
- pleurisy, pericarditis
- neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus, **characteristic oculo-masticatory movements**

Investigation

- jejunal biopsy** shows deposition of macrophages containing **Periodic acid-Schiff (PAS)** granules
- presence of *T. whipplei* DNA in tissue by PCR.

Management

- oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin
- other option:
 - ⇒ **initial two week course of parenteral penicillin** and streptomycin; followed by a prolonged course (one year) of tetracycline.

Tropical Sprue

- most common in the Caribbean and the Far-East.
 - ⇒ occurs in tropical regions, predominantly central America and South-Eastern Asia.
- characterized by a picture of small intestinal malabsorption and the cause is thought to be infectious in origin.
 - ⇒ It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as coliforms, and then a degree of villous atrophy leading to malabsorption and B12, folate deficiency.
 - deficiency in folate contributes to greater **mucosal injury**.

Features

- Patients classically have a history of recent travel to a tropical area
- present with indigestion, cramps within 2 or 3 weeks after an acute enteric infection.
- Megaloblastic anemia due to folate or B12 deficiency is a common finding.

Diagnosis:

- Jejunal biopsy reveals:
 - Mild villous atrophy
 - ↑ villous crypts
 - Mononuclear cellular infiltrates
 - Enlarged epithelial cells
 - Large nuclei caused by folate and/or vitamin B12 deficiency.
- barium swallow may show thickening of mucosal folds

Treatment:

- The main treatment for tropical sprue is broad-spectrum antibiotics (i.e., tetracycline) and vitamin supplementation (i.e., folic acid, vitamin B12).
 - Tetracyclines 250mg qds up to 6 months
 - Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines.
 - Folate and B12 deficiencies should also be corrected
- Complete recovery is possible with appropriate therapy.

Irritable bowel syndrome (IBS)

Insoluble sources of fibre such as bran and wholemeal should be avoided in IBS

Pathophysiology

- Studies looking at dietary restriction followed by reintroduction suggest **food intolerance** in 30-60% of patients with IBS.
- increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation.
- Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms.

Feature

- **features supporting a diagnosis of IBS** include:
 - A long history with a relapsing and remitting course
 - Exacerbations triggered by life events
 - Symptoms aggravated by eating, and
 - Coexistence of anxiety and depression.
- **features which suggest organic disease rather than IBS** include:
 - Fever
 - Onset of symptoms in old age
 - Progressive deterioration
 - Weight loss
 - Rectal bleeding (not due to fissures or haemorrhoids)
 - Steatorrhoea, and
 - Dehydration.

Diagnosis (NICE 2008)

- The diagnosis of IBS should be **considered** if the patient has had the following for at least 6 months:
 1. abdominal pain, and/or
 2. bloating, and/or
 3. change in bowel habit
- **A positive diagnosis of IBS should be made** if the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:
 1. altered stool passage (straining, urgency, incomplete evacuation)
 2. abdominal bloating (more common in women than men), distension, tension or hardness
 3. symptoms made worse by eating
 4. passage of mucus
- Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis
- **Red flag features** should be enquired about:
 1. rectal bleeding
 2. unexplained/unintentional weight loss
 3. family history of bowel or ovarian cancer
 4. onset after 60 years of age
- Also on clinical examination the other **'red flag'** indicators are:
 - Anaemia
 - Abdominal mass
 - Rectal mass, and
 - Inflammatory markers for inflammatory bowel disease.
- Suggested primary care **investigations** are:
 - full blood count
 - ESR/CRP
 - coeliac disease screen (tissue transglutaminase antibodies)

Management (NICE 2015).

NICE recommend avoiding lactulose in the management of IBS

First-line pharmacological treatment - according to predominant symptom

- pain: antispasmodic agents
 - Pinaverium is used to reduce the pain duration associated with (IBS).

- diarrhoea: loperamide is first-line
- constipation: laxatives but avoid lactulose
- For patients with constipation who are not responding to conventional laxatives linaclotide may be considered, if:
 - optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
 - they have had constipation for at least 12 months

Second-line pharmacological treatment

- low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

Other management options

- psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

General dietary advice

- have regular meals and take time to eat
- avoid missing meals or leaving long gaps between eating
- drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- restrict tea and coffee to 3 cups per day
- reduce intake of alcohol and fizzy drinks
- consider limiting intake of high-fibre food (for example, whole meal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
- reduce intake of 'resistant starch' often found in processed foods
- limit fresh fruit to 3 portions per day
- for diarrhoea, avoid sorbitol
- for wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

Fibre

- There are two main types of fibre - soluble fibre (which dissolves in water) and insoluble fibre.
- It is **soluble fibre** rather than insoluble fibre that seems to help ease symptoms in some cases.
 - **A diet high in soluble fibre is often prescribed for the treatment of IBS**
 - Dietary sources of soluble fibre include **oats**, ispaghula (psyllium), nuts and seeds, some fruit and vegetables and pectins.
 - A fibre supplement called ispaghula powder is also available from pharmacies and health food shops. This seems to be the most beneficial type of supplement.
- **Insoluble fibre** is chiefly found in corn (maize) bran, wheat bran and some fruit and vegetables. In particular, avoid bran as a fibre supplement.

Malnutrition

- **Pathophysiology**
 - **Food intolerance** (in 30-60% of patients with (IBS).)
 - increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation.
 - Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms.
- **definition:** NICE define malnutrition as the following:
 1. a Body Mass Index (BMI) of less than 18.5; or

- 2. unintentional weight loss greater than 10% within the last 3-6 months; or
- 3. a BMI of less than 20 and unintentional weight loss greater than 5% within the last 3-6 months
- Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.
- **Screening for malnutrition if mostly done using MUST (Malnutrition Universal Screen Tool).**
 - it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores (**The Waterlow score** is used to estimate the risk of a patient developing a pressure sore)
 - it takes into account BMI, recent weight change and the presence of acute disease
 - categorises patients into low, medium and high risk
- **Management** of malnutrition is difficult. NICE recommend the following points:
 - dietitian support if the patient is high-risk
 - a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
 - if ONS are used they should be taken between meals, rather than instead of meals

Waterlow score is used to estimate the **risk of a patient developing a pressure sore**, this includes an assessment of malnutrition as one of its components

Lactose intolerance

- Lactase acts on lactose to generate glucose and galactose.
- **more common in Asian, and East Asian races.**
 - **South-east Asian** people, like the Vietnamese, Thais, and Chinese, have a very high prevalence of lactase deficiency.
- **Any GI infection may precipitate the diagnosis of lactose intolerance**, as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection.
- A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance.
- Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance
- many medications use lactose as a binding and stabilising agent.
- **Diagnosed with** a DNA assay of the lactase gene along with a hydrogen breath test.
- **Treatment** of lactose intolerance is with careful replacement of lactase.

Functional constipation

- The Rome III criteria for functional constipation is as follows (it must include two or more of the following):
 - straining during at least 25% of defecations
 - lumpy or hard stools in at least 25% of defecations
 - sensation of incomplete evacuation for at least 25% of defecations
 - sensation of anorectal obstruction/blockage for at least 25% of defecations
 - manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
 - fewer than three defecations per week
 - loose stools are rarely present without the use of laxatives, and
 - insufficient criteria for irritable bowel syndrome.
- These criteria must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

Energy from food

- The amount of energy that may be derived from 1 gram of food is as follows:
 - carbohydrates: 4 kcal
 - protein: 4 kcal
 - **fat: 9 kcal**
- The amount of energy a food product contains is expressed in calories (kcal). In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

Protein losing enteropathy

Definition

- excessive leakage of plasma proteins into the lumen of the GIT
- refers to any condition of the GIT that results in a net loss of protein from the body.

Causes

- lymphatic obstruction, (lymphatic leakage secondary to obstruction.): e.g:
 - primary intestinal lymphangiectasia,
 - conditions associated with venous stasis such as right-sided heart failure.
- mucosal disease:
 - inflammatory exudation through mucosal damage:
 - inflammatory bowel diseases,
 - NSAID enteropathy,
 - GI malignancy.
 - increased permeability from non-erosive mucosal disease
 - amyloidosis,
 - GI infections,
 - rheumatic diseases,

Features

- The most common presenting symptom is **swelling of the legs** due to decreased plasma oncotic pressure.
 - bilateral oedema from hypoproteinaemia is generalised and may be seen in the peri-orbital region as well as in the extremities
- diarrhoea

Investigations

- **Measurement of α_1 -Antitrypsin in a sample of faeces**
 - **the most appropriate to confirm the diagnosis**
 - Albumin is degraded by proteases in the gut; however, α_1 -antitrypsin is a plasma protein that is resistant to degradation by proteases (it is a protease inhibitor) and its measurement can indicate leakage of plasma proteins into the gut.
- Serum albumin
 - albumin level <20 g/L (<2 g/dL) is usually required to cause peripheral oedema
 - Finding of low serum albumin prompts investigation to determine whether the aetiology is due to loss in the urine, hepatic synthetic dysfunction, or gastrointestinal losses. History of significant diarrhoea in conjunction with ruling out alternative causes makes the diagnosis.

Treatment

- Treat the underlying disease.

Enteral feeding

Definition

- Enteral feeding = any route of feeding that utilizes the patient's GI tract to deliver appropriate nutrition (differs from parenteral nutrition, which delivers nutrition intravenously, completely bypassing the GI tract)

Enteral nutrition VS parenteral nutrition

- Enteral nutrition is preferred to parenteral nutrition whenever feasible - if the GI tract is functional, use it - benefits include improved absorption, immunological benefits, and helps maintain a healthy and functional GI tract

Routes of enteral feeding:

- Short-term: nasogastric tubes
 - Consider gastric feeding unless upper GI dysfunction (then for duodenal or jejunal tube)
- Long-term (> 2–3 weeks): gastrostomy or jejunostomy tubes
 - Gastric feeding > 4 weeks consider long-term gastrostomy
 - **gastrostomy tube:**
 - mainly used in cases of proximal gastrointestinal tract obstruction to facilitate feeding.
 - **If it withdrew accidentally,** reinsertion of the tube as soon as possible would be the preferred action. However, it needs a good level of expertise to do this.
 - ❖ Therefore, in this case, **insertion of a Foley's catheter is the best practice** as it is easy to do, and this should preserve the opening of the skin and anterior abdominal wall muscles until a someone experience enough is available to re-insert the gastrostomy tube.

How to check NG placement?

- Check NG placement using aspiration and pH (check post pyloric tubes with AXR)
 - **The first line investigation to confirm correct placement of a nasogastric tube is → pH testing of gastric aspirate using indicator paper**
 - If the pH is between 1 and 5.5 then this is confirmatory evidence of correct placement.
 - If the pH reading is between 5.5 and 6 it is recommended that a second independent reading is made to confirm.
 - If aspirate pH $\geq 6 \rightarrow$ nasogastric feeding tubes feeding cannot be commenced
 - If there is any doubt, then an appropriately interpreted **chest x ray is a second line investigation.**

Key points

- Identify patients as malnourished or at risk (see below)
- Identify unsafe or inadequate oral intake with functional GI tract
- Consider bolus or continuous feeding into the stomach
- PEG can be used 4 hours after insertion but should not be removed until >2 weeks after insertion.

Indications

- pre-operative
 - Surgical patients due to have major abdominal surgery: if malnourished, unsafe swallow/inadequate oral intake and functional GI tract then consider pre-operative enteral feeding.
- **ITU patients**
 - ITU patients should have continuous feeding for 16-24h (24h if on insulin)
 - Consider motility agent in ITU or acute patients for delayed gastric emptying. If this doesn't work, then try post pyloric feeding or parenteral feeding.

Contraindications

- Mechanical ileus, bowel obstruction
- Acute abdomen (e.g., severe pancreatitis, peritonitis)
- Upper GI bleeding
- Mucositis
- Severe substrate malabsorption
- Congenital GI anomalies
- High-output fistulas
- Nonfunctional GI tract (e.g., gastroschisis, short bowel syndromes)

Patients identified as being malnourished

- BMI < 18.5 kg/m²
- unintentional weight loss of > 10% over 3-6/12
- BMI < 20 kg/m² and unintentional weight loss of > 5% over 3-6/12

AT RISK of malnutrition

- Eaten nothing or little > 5 days, who are likely to eat little for a further 5 days
- Poor absorptive capacity
- High nutrient losses
- High metabolism

Causes of diarrhoea in patients receiving enteral nutrition:

- hyperosmolar feed
- bacterial contamination
- low feed temperature
- reduced intestinal absorptive capacity
- too rapid or irregular administration
- lactose intolerance.

Causes of constipation in patients receiving enteral nutrition:

- Inadequate fluid replacement

Refeeding syndrome

Refeeding syndrome → hypophosphataemia

Give 50% of normal energy intake in starved patients (> 5 days) to avoid refeeding syndrome

Definition:

- Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation (≥ 5 days).

Pathophysiology:

- When malnourished, the body uses endogenous fuel stores for energy and maintains serum electrolytes by redistribution from intracellular spaces.
- Exogenously administered glucose results in insulin release. This results in rapid uptake of glucose, potassium, phosphate and magnesium into cells, with dramatic falls in the extracellular concentrations.

Features

- Hypophosphataemia (symptoms are due predominantly to hypophosphataemia,)
- hypokalaemia
- hypomagnesaemia
- abnormal fluid balance
- Due to understood reasons, the body retains fluid → ↑ extracellular space → ↑ cardiac work → acute heart failure.

- neurological problems resulting in:

<ul style="list-style-type: none"> ➢ Oedema ➢ Lethargy ➢ Confusion 	<ul style="list-style-type: none"> ➢ Coma ➢ Convulsions, and ➢ Death.
---	--
 - Nausea and diarrhoea is also common due to gut intolerance.
- Prevention (NICE 2006)**
- Identify patients at a high-risk of developing refeeding syndrome
 - Patients are considered **high-risk:**
 - **if one or more of the following:**
 1. BMI < 16 kg/m²
 2. unintentional weight loss >15% over 3-6 months
 3. little nutritional intake > 10 days
 4. hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)
 - **If two or more of the following:**
 1. BMI < 18.5 kg/m²
 2. unintentional weight loss > 10% over 3-6 months
 3. little nutritional intake > 5 days
 4. history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids
 - Decrease oral calorific intake to less than 50% of the recommended amount.
 - **NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.**
 - limit initial dietary intake to 1000–1500 kcal/day

Management

- Correcting electrolyte abnormalities aggressively
 - it may be preferable to provide electrolyte replenishment prior to commencing calorific intake

A patient with a history of **alcoholism** is admitted for **re-feeding**. Which component of the feed may need to be reduced to avoid **encephalopathy**?

- ➔ **Protein**
- protein content of feeds should be strictly managed in patients with alcoholism.
 - Protein rich feeds → ↑ total ammonia burden → ↑ risk of encephalopathy.

Melanosis coli

Diarrhoea - biopsy shows pigment laden macrophages = laxative abuse

- Melanosis coli is a disorder of pigmentation of the bowel wall.
- Causes
 - It is associated with laxative abuse, especially anthraquinone compounds such as senna
 - This phenomenon is seen in over 70% of persons who use anthraquinone laxatives (for example, cascara sagrada, senna, and frangula) within several months of use.
 - Also alternative "medicine" drugs contain ingredients like cascara which contain anthraquinones.
 - The modern laxatives such as liquid paraffin and polyethylene glycol do not cause these changes.
- Pathophysiology

- Chronic use of anthraquinone laxatives cause injury to the colonic epithelium, with generation of **lipofuscin pigment**. This pigment is subsequently engulfed by the macrophages to give rise to the histological picture.
- Diagnosis
 - Melanosis coli is a histological diagnosis made from rectal biopsy material which shows numerous macrophages filled with brown pigment within the lamina propria.
 - Histology demonstrates **pigment-laden macrophages**
 - The macroscopic appearance varies from deep black pigmentation to reticulated brown discolouration.
- Treatment
 - The condition is benign and reversible on stopping the laxatives.

Mesenteric ischaemia (ischaemic colitis)

The two most common symptoms of ischemic colitis are severe abdominal pain and **hematochezia** (passage of fresh blood through the anus).

- Mesenteric ischaemia is primarily caused by arterial embolism resulting in infarction of the colon.
- **More likely occur in areas such as the splenic flexure** that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.
 - especially the **superior mesenteric artery**.

Predisposing factors

- increasing age
- **atrial fibrillation**
- other causes of emboli: endocarditis
- cardiovascular disease risk factors: smoking, hypertension, diabetes

Features

- **abdominal pain**
 - abdominal pain **exacerbated by eating** is suggestive of mesenteric ischaemia.
 - Pain that is disproportionately severe compared to the abdominal findings is characteristic.
- **rectal bleeding**
- diarrhoea
- fever
- bloods typically show an elevated WBC associated with acidosis
- Acute mesenteric ischaemia is a cause of elevated amylase that is unrelated to pancreatitis.
- **Elevated serum lactate also suggests ischaemic aetiology.**

Diagnosis

- **CT scanning: the imaging modality of choice**, with a sensitivity and specificity over 90%.
 - If the presentation is clearly of acute bowel ischaemia then a CT angiography would be the best test.
 - the presentation is consistent with several other possible causes of bloody diarrhoea and abdominal pain (i.e. **acute colitis**), **Flexible sigmoidoscopy would be the best investigation** - safer than colonoscopy (relative contraindication in **active colitis**), allowing biopsies to be taken and the viewing of a possible pseudomembrane.
 - Occasionally the mucosa has a characteristic appearance.
 - Biopsies show ulceration and a polymorphonuclear infiltrate.
 - Haemosiderin-laden macrophages are characteristic but uncommon.
- Angiography: if the diagnosis is in doubt.

- Mucosal edema can be seen as the **thumbprinting sign** on plain **abdominal radiograph and barium enema**.
- **Flexible sigmoidoscopy**
 - The finding of **ulceration which spares the rectum is typical**
 - ulceration extending to the splenic flexure corresponds with the arterial supply of the inferior mesenteric artery.

Management

- supportive care
- **balloon angioplasty and stenting**
 - the preferred treatment for **hemodynamically stable** patients with acute mesenteric ischemia who do not present with signs or symptoms of advanced intestinal ischemia (peritonitis, sepsis) because this procedure is minimally invasive and studies suggest similar efficacy to open surgical treatment.
- laparotomy and bowel resection
 - laparotomy is reserved for acutely ill patients who are hemodynamically unstable or have evidence of peritonitis (rebound tenderness and involuntary guarding).

MRCPUK-part-1-jan-2018: Which part of the bowel is most prone to ischaemic colitis?

→ **Splenic flexure**

- because it receives its blood supply from terminal branches of the superior mesenteric and inferior mesenteric arteries, creating a watershed area.

Small bowel bacterial overgrowth syndrome (SBBOS)

Definition

- (SBBOS) is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms of **bloating, abdominal distension and diarrhoea**

Risk factors for SBBOS

- neonates with congenital gastrointestinal abnormalities
- scleroderma
- absent gastric acid secretion
- **small bowel diverticulae**
- fistulae between the small and large bowel
- small bowel strictures
- diabetes mellitus (diabetic neuropathy)
- adhesions.

Features: It should be noted that many of the features overlap with irritable bowel syndrome:

- chronic diarrhoea
- bloating, flatulence
- abdominal pain
- **Biochemically there is classically a low vitamin B₁₂ level and normal or elevated folate level as a result of bacterial metabolism of B₁₂ to folate.**

Steatorrhoea and flatulence are classic presenting features of small bowel bacterial overgrowth.

Investigation

- **The gold standard investigation of bacterial overgrowth is small bowel aspiration and culture**
- Other possible investigations include:
 - **hydrogen breath test**

- 14C-xylose breath test
- 14C-glycocholate breath test: used increasingly less due to low specificity
- In practice many clinicians give an empirical course of antibiotics as a trial

Management

- correction of underlying disorder
- antibiotic therapy: **rifaximin is now the treatment of choice** due to relatively low resistance.
- Co-amoxiclav or metronidazole are also effective in the majority of patients.

Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis - intravenous cefotaxime

- (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis. most commonly seen in alcoholic cirrhosis
- **typically caused by aerobic gram negative bacteria.** (usually *Escherichia coli*, *Klebsiella*)
 - **spontaneous bacterial peritonitis is almost without exception caused by a single organism.**
- **Diagnosis**
 - paracentesis: **neutrophil count > 250 cells/ul**
 - Sending some ascitic fluid in blood culture bottles increases the yield.
 - high serum ascites albumin gradient (SAAG) ($>11 \text{ g/L}$) ascitic fluid and the white cells will be **predominantly neutrophils ($>500 \text{ WBCs/mm}^3$ and $>50\%$ neutrophils)**.
- **Management:**
 - **intravenous cefotaxime** is usually given
 - other option: **IV piperacillin-tazobactam**
 - It is important to start antibiotics promptly pending the results of an ascitic analysis.
 - Antibiotic prophylaxis should be given if:
 - patients who have had an episode of SBP
 - patients with fluid protein $<15 \text{ g/l}$ and either Child-Pugh score of at least 9 or hepatorenal syndrome
 - **Norfloxacin** is recommended for short term **prophylaxis**.
- **Prognosis**
 - Alcoholic liver disease is a marker of poor prognosis in SBP.
 - Has poor prognostic significance with a one-year survival after a diagnosis of between 30-50%.
 - **An episode of spontaneous bacterial peritonitis carries a two-year mortality rate of 50%.**
- **Differential diagnosis**
 - pancreatic ascites (eg. Acute pancreatitis)
 - elevated fluid amylase helps confirm this (particularly the characteristic way in which it is in excess of the serum value).
 - The low lactate dehydrogenase ($<225 \text{ IU/L}$) helps exclude a polymicrobial ascitic fluid infection which has similar findings
 - no mention of finding any organisms on the Gram stain.
 - ❖ Bacterial growth occurs in about 80% of specimens with polymorphonuclear (PMN) count of $>250 \text{ cells/mm}^3$.
 - Ascitic fluid analysis demonstrates a low serum albumin ascites gradient (SAAG) ($<11 \text{ g/L}$).

- ❖ Cirrhosis and spontaneous bacterial peritonitis are both characterised by a high SAAG ($>11 \text{ g/L}$) and are differentiated from each other on the basis of white cell count, Gram stain and culture results.
- secondary bacterial peritonitis (ruptured viscus or loculated abscess).
 - Lactate dehydrogenase $>225 \text{ mU/L}$, glucose $<50 \text{ mg/dL}$, total protein $>1 \text{ g/dL}$ and **multiple organisms on gram stain suggest secondary bacterial peritonitis** (ruptured viscus or loculated abscess).
- Chylous ascites
 - A high level of triglycerides confirms chylous ascites.
- elevated amylase level suggest pancreatitis or gut perforation.
- elevated bilirubin level suggest biliary or gut perforation.

Abdominal tuberculosis (Tubercular peritonitis)

Features

- risk of tuberculosis
- should always be suspected in the severely malnourished patient
- Constitutional symptoms are common, including fever, anorexia and weight loss.
- extensive lymphadenopathy.

Investigations

- The cut-off for considering ascitic fluid to be exudative would be 30 g/l , but in the setting of hypoproteinaemia, this is less relevant.
- The marked increase in white cell count is strongly supportive of a diagnosis of infective ascites.

Diagnosis

- **The most sensitive test to establish the diagnosis is visually directed (laparoscopic) peritoneal biopsy with histology and culture for TB.**
- Although PCR of ascitic cells/fluid has increased non-invasive diagnosis, **the best yield remains from laparoscopy and peritoneal biopsy**, which in recent series led to a diagnosis in 95% of cases.
- An alternative in this setting might be to perform fine needle aspiration or excision biopsy of one of the palpable lymph nodes.
- The diagnostic yield of ascitic culture for mycobacteria is very low ($<10\%$) even with closed culture systems.

Which investigation is most likely to yield a diagnosis?

→ Laparoscopy and peritoneal biopsy

VIPoma

VIPoma: WDHA syndrome Watery Diarrhea, Hypokalemia, Achlorhydria.

VIP (vasoactive intestinal peptide)

- source: small intestine, pancreas
- stimulation: neural
- actions:
 - stimulates water and electrolytes secretion by pancreas and intestines,
 - inhibits gastric acid and pepsinogen secretion
 - **peripheral vasodilation**,
 - potentiates acetylcholine action on salivary glands.

VIPoma

- 90% arise from pancreas
- large volume diarrhoea, **secretory** diarrhoea ('pancreatic cholera')
 - The normal daily stool weight is 250–300 g
 - A stool volume of <700 mL/d excludes the diagnosis of VIPoma.
 - What is the most likely mechanism of diarrhoea?
 - Secretory due to enterocyte stimulation
- weight loss
- dehydration
- hypokalaemia, **hypochlorhydria. Achlorhydria**
- hypokalaemic acidosis (loss of alkaline secretions)
- mildly raised glucose.
- raised plasma pancreatic polypeptide
- abdominal colic
- cutaneous flushing
- raised plasma VIP

Volvulus

- Volvulus defined as torsion of the colon around its mesenteric axis resulting in compromised blood flow and closed loop obstruction.
- **Sigmoid volvulus (around 80% of cases)** describes large bowel obstruction caused by the sigmoid colon twisting on the sigmoid mesocolon. A similar problem may also occur at the caecum (20% of cases).
- In most people (around 80%) the caecum is a retroperitoneal structure so not at risk of twisting. In the remaining minority there is however developmental failure of peritoneal fixation of the proximal bowel putting these patients at risk of caecal volvulus.

Sigmoid volvulus associations	Caecal volvulus associations
<ul style="list-style-type: none"> • older patients • chronic constipation • Chagas disease • neurological conditions e.g. Parkinson's disease, Duchenne muscular dystrophy • psychiatric conditions e.g. schizophrenia 	<input type="checkbox"/> all ages <input type="checkbox"/> adhesions <input type="checkbox"/> pregnancy

Features

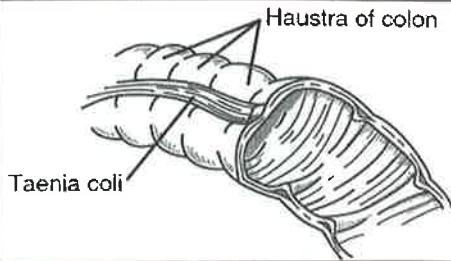
- constipation
- abdominal bloating
- abdominal pain
- nausea/vomiting

Diagnosis

- usually diagnosed on the abdominal film
 - The most helpful early diagnostic tool of intestinal obstruction is the plain abdominal X-ray.
- sigmoid volvulus:
 - large bowel obstruction (large, dilated loop of colon, often with air-fluid levels) + **coffee bean sign (omega sign)**
- caecal volvulus:
 - small bowel obstruction may be seen

Sigmoid volvulus

The most important feature of a sigmoid volvulus rather than a large redundant distended loop of sigmoid colon is the **absence of haustra**.



Coffee Bean Sign Sigmoid volvulus

Massively dilated sigmoid loop

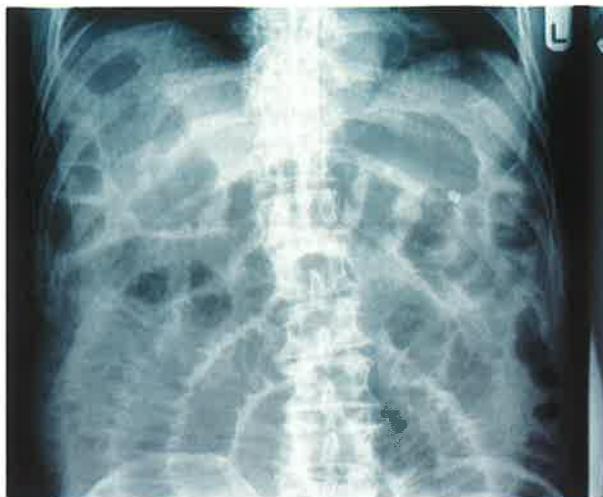
**Management**

- sigmoid volvulus:
 - rigid sigmoidoscopy with rectal tube insertion
- caecal volvulus:
 - management is usually operative. Right hemicolectomy is often needed

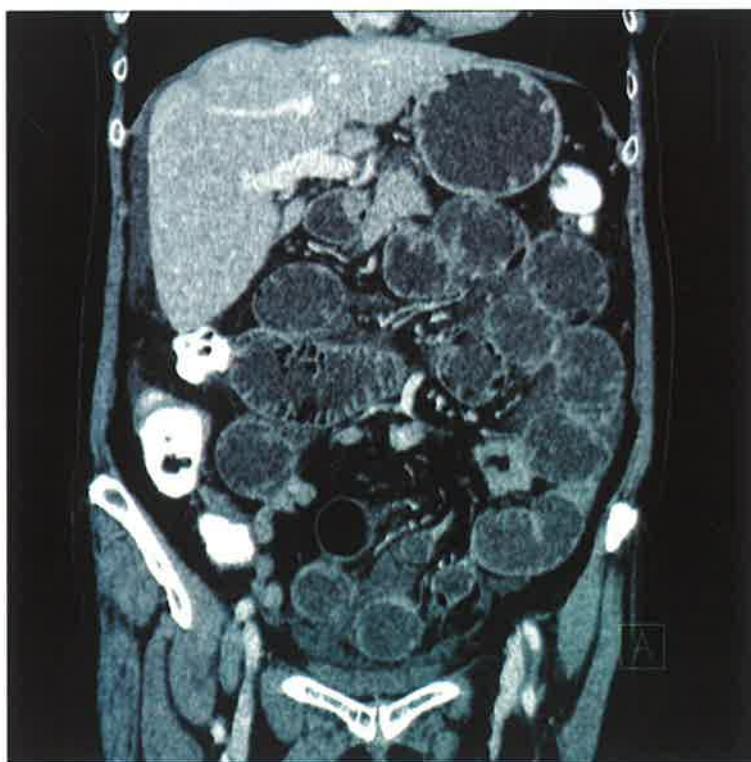
Imaging in bowel obstruction

Looking for small and large bowel obstruction is one of the key indications for performing an abdominal film.

Small bowel	Large bowel
Maximum normal diameter = 35 mm	Maximum normal diameter = 55 mm
Valvulae conniventes extend all the way across	Haustra extend about a third of the way across



Small bowel obstruction



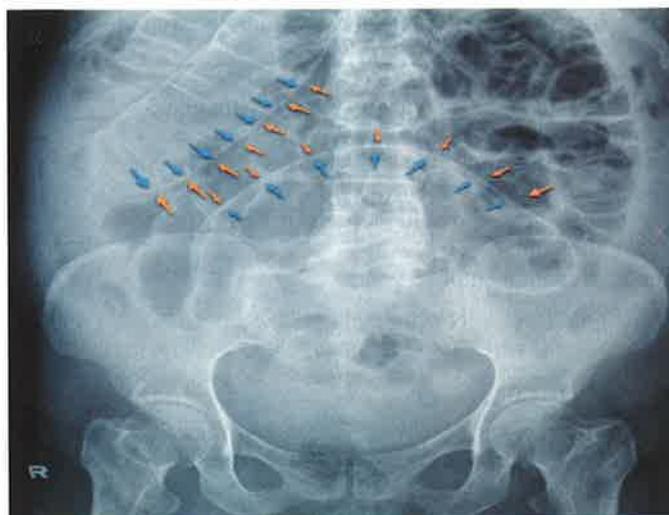
CT from a patient with small bowel obstruction secondary to adhesions. Distension of small bowel loops proximally (duodenum and jejunum) with abrupt transition to intestinal segment of normal caliber. Presence of small amount of free fluid intracavity.

Radiology: pneumoperitoneum

- An erect chest x-ray is a useful investigation in patients with an acute abdomen as it may demonstrate free air in the abdomen (pneumoperitoneum) - an abnormal finding suggestive of a perforated abdominal viscus (e.g. a perforated duodenal ulcer).
- Rigler's sign (double wall sign) may be seen on an abdominal film.
CT is now the preferred method for detecting free air in the abdomen.



Erect chest x-ray with air visible under the diaphragm on both sides.



Abdominal x-ray demonstrates numerous loops of small bowel outlined by gas both within the lumen and free within the peritoneal cavity. Ascites is also seen, with mottled gas densities over bilateral paracolic gutters. In a normal x-ray only the luminal surface (blue arrows) should be visible outlined by gas. The serosal surface (orange) should not be visible as it is normally in contact with other intra-abdominal content of similar density (other loops of bowel, omentum, fluid). In this case gas abuts the serosal surface rendering it visible. As this film has been obtained

Dumping syndrome

- occur in up to 50% of patients who have undergone gastric bypass when high levels of simple carbohydrates are ingested.
- **early dumping syndrome**
 - rapid onset , usually **within 15 minutes of eating**
 - **results from rapid emptying of food into the small bowel.**
 - Due to the hyperosmolality of the food there are rapid fluid shifts from the plasma into the bowel leading to hypotension and a sympathetic nervous system response.
 - The presenting symptoms are often colicky abdominal pain, diarrhoea, nausea, and tachycardia.
 - Treatment:
 - **usually self-limiting and resolves within 7 to 12 weeks.**
 - Patients should avoid foods high in simple sugar and replace them with high fibre, complex carbohydrates and protein-rich foods.
 - Small, frequent meals
 - leaving a 30 minute gap between solids and liquids
- **Late dumping syndrome**
 - **occurs as a result of the hyperglycaemia and subsequent insulin response leading to hypoglycaemia** which takes place **two to three hours after a meal.**
 - Symptoms include dizziness, fatigue, sweating, and weakness.
 - Management is similar to early dumping syndrome.

Small bowel lymphoma

Pain is the most common presenting feature of small bowel lymphoma

- Lymphoma comprises 15-20% of all small bowel tumours with the ileum most commonly affected.
- Primary lymphomas of the small bowel include
 - mucosa-associated lymphoid tissue (MALT) lymphoma
 - diffuse large B cell lymphoma
 - immunoproliferative small intestinal disease (IPSID), and
 - enteropathy-associated T cell lymphoma (EATL).
- Patients with coeliac disease are at higher risk of T cell lymphoma.
- There is a male predominance
- the median age at presentation of 25 years.
- Patients may present with:
 - anorexia
 - weight loss
 - nausea and vomiting
 - chronic pain
 - abdominal fullness
 - early satiety, and
 - constipation.
 - Findings on CT vary and may include multiple tumours, narrowing of the bowel lumen and mesenteric nodal masses.

Pancreatic conditions

Acute pancreatitis

Hypertriglyceridaemia (with level > 10 mmol/l) is a risk factor for acute pancreatitis

- acute inflammation of the pancreas → release of exocrine enzymes → **auto-digestion**.

Pathophysiology

- Sequence of events leading to pancreatitis:**
 - **Intrapancreatic activation of pancreatic enzymes:** secondary to pancreatic ductal outflow obstruction (e.g., gallstones, cystic fibrosis) or direct injury to pancreatic acinar cells (e.g., alcohol, drugs)
 - **Enzymatic autodigestion of pancreatic parenchyma**
 - Attraction of inflammatory cells (neutrophils, macrophages) → release of inflammatory cytokines → pancreatic inflammation (pancreatitis)
- Sequelae of pancreatitis** (depending on the severity of pancreatitis)
 - **Capillary leakage:** Release of inflammatory cytokines and vascular injury by pancreatic enzymes → vasodilation and increased vascular permeability → shift of fluid from the intravascular space into the interstitial space (third space loss) → hypotension, tachycardia → **distributive shock**
 - **Pancreatic necrosis:** Uncorrected hypotension and third space loss → decreased organ perfusion → multiorgan dysfunction (mainly renal) and pancreatic necrosis
 - **Hypocalcemia:** Lipase breaks down peripancreatic and mesenteric fat → **release of free fatty acids that bind calcium** → **hypocalcemia**

Causes

The commonest causes in UK are **gallstones** and **alcohol**

The aetiology of acute pancreatitis should be determined in at least 80% of cases and no more than 20% should be classified as idiopathic

Popular mnemonic is **GET SMASHED**

- Gallstones**
 - account for 50% of cases, with the majority of the rest being associated with alcohol.
 - For prediction of a biliary etiology, an **ALT level has the highest positive predictive value of any biochemical test.**
- Ethanol**
 - Amylase/lipase levels are **markedly** elevated in **gallstone** pancreatitis (**thousands**), whereas less increased in **alcoholic** (**hundreds**)
 - raised mean corpuscular volume (MCV) suggests chronic high alcohol use
- Trauma**
- Steroids**
- Mumps** (other viruses include Coxsackie B)
- Autoimmune** (e.g. polyarteritis nodosa), **Ascaris** infection
- Scorpion venom**
- Hypertriglyceridaemia**, **Hyperchylomicronaemia**, **Hypercalcaemia**, **Hypothermia**
- ERCP** (**acute pancreatitis following ERCP should be treated with I.V fluids + analgesia**)
- Drugs** (azathioprine, mesalazine, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)
 - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Hypertriglyceridaemia

- Definitions:
 - hypertriglyceridaemia > 1.7 mmol/L.
 - Severe hypertriglyceridaemia > 11.2-22.4 mmol/L
 - very severe as > 22.4 mmol/L.
- The third commonest cause of acute pancreatitis after alcohol and gallstones.
- **Considered a risk factor for pancreatitis when triglyceride levels are above 11.2 mmol/L.**
- **In a patient with hypertriglyceridaemia and acute abdominal pain, an amylase should be checked to exclude acute pancreatitis.**

Features

- Patients typically present with severe epigastric pain which radiates to the back, and vomiting.
- there is often a systemic inflammatory response (SIRS)
- Serum amylase is classically raised three or more times normal,
- hypocalcaemia is relatively common.
- Raised bilirubin and/or serum aminotransferase suggest underlying gallstones.
- Cirrhosis results in a small shrunken liver and raised ALT and ALP (and gamma-GT if the cause is alcohol).
- Rare features associated with pancreatitis include:
 - ischaemic (Peritscher) retinopathy - may cause temporary or permanent blindness
- Skin changes (rare)
 - Cullen's sign: periumbilical ecchymosis and discoloration (bluish-red)
 - Grey Turner's sign: flank ecchymosis with discoloration
 - Fox's sign: ecchymosis over the inguinal ligament

Marker of severity

- **CRP is now a widely used marker of severity in acute pancreatitis.**
- Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score

Prognosis

- **Criteria of poor prognosis**
 - There are a number of scoring systems which can be used to guide prognosis, but they are unreliable within the first 48 hours of the illness.
 - Ranson's scoring system reflect prognosis associated with acute pancreatitis.
- **Ranson's criteria** on admission that signify a **worse prognosis** include:
 - **Criteria present at 0 hours:**
 - Age > 55 years old - 1 point
 - WBC > 16×10^9 - 1 point
 - **Glucose > 11.1 mmol/L** - 1 point
 - LDH > 350 U/L - 1 point
 - AST > 250 U/L - 1 point
 - **Criteria present at 48 hours:**
 - Hematocrit fall of 10% or greater - 1 point
 - Urea rise of 1.8 mmol/L or more despite fluids - 1 point
 - Serum Calcium < 2 mmol/L - 1 point
 - $\text{pO}_2 < 60 \text{ mmHg}$ - 1 point (**PaO_2 of < 8.0 kPa**)
 - Base deficit > 4 meq/L - 1 point
 - Fluid sequestration > 6000 mL - 1 point
- **The mortality associated with severe acute pancreatitis → 20%**
 - often due to sepsis or multiorgan failure.
- Hematocrit (Hct)

- Should be conducted at presentation as well as 12 and 24 hours after admissions
- ↑ Hct (due to hemoconcentration) indicates third space fluid loss and inadequate fluid resuscitation
- ↓ Hct indicates the rarer acute hemorrhagic pancreatitis

- The following portend a **poor prognosis** in patients with acute pancreatitis:

WCC	>15
Urea	>16
Calcium	<2.0
Glucose	>10
CRP	>150

Complications

- ARDS (adult respiratory distress syndrome),
- acute kidney injury
- disseminated intravascular coagulation (DIC).
 - due to pancreatic enzymes entering the blood and acting on coagulation factors, thereby activating them.
- Pancreatic pseudocyst

Investigations

- **lab**
 - **Tests to confirm clinical diagnosis**
 - **Amylase is markedly raised**, often in excess of four times the normal value.
 - ❖ nonspecific
 - **Lipase**: if $\geq 3 \times$ the upper reference range → highly indicative of acute pancreatitis
 - ❖ More specific and preferred for the diagnosis
 - The enzyme levels are not directly proportional to severity or prognosis
 - **Tests to assess severity**
 - **Hematocrit (Hct)**
 - ❖ Should be conducted at presentation as well as 12 and 24 hours after admissions
 - ❖ ↑ **Hct** (due to hemoconcentration) indicates third space fluid loss and **inadequate fluid resuscitation**
 - ❖ ↓ Hct indicates the rarer acute hemorrhagic pancreatitis
 - WBC count
 - Blood urea nitrogen
 - ↑ CRP and procalcitonin levels
 - ↑ ALT
- **Images**
 - Ultrasound
 - **the most useful initial test**
 - Main purpose: detection of gallstones and/or dilatation of the biliary tract (indicating biliary origin)
 - Signs of pancreatitis
 - ❖ Indistinct pancreatic margins (edematous swelling)

- ❖ Peripancreatic build-up of fluid ; evidence of ascites in some cases
- ❖ Evidence of necrosis, abscesses, pancreatic pseudocysts
- CT with contrast
 - not routinely indicated
 - only when the diagnosis is in doubt
 - would be preferable to ultrasound in establishing the presence of inflammation (acute or chronic) of the pancreas and severity of disease
- Abdominal x ray
 - has NO role in acute pancreatitis
 - Sentinel loop sign:
 - ❖ dilatation of a loop of small intestine in the upper abdomen (duodenum/jejunum)
 - Colon cut off sign:
 - ❖ gaseous distention of the ascending and transverse colon that abruptly terminates at the splenic flexure
 - Evidence of possible complications:
 - ❖ pleural effusions,
 - ❖ pancreatic calcium stones;
 - ❖ helps rule out intestinal perforation with free air
 - may demonstrate calcification in **chronic** pancreatitis.

Follow-up:

- All patients with persistent symptoms and greater than 30% pancreatic necrosis, and those with smaller areas of necrosis and clinical suspicion of sepsis, should undergo image guided fine needle aspiration to obtain material for culture 7–14 days after the onset of pancreatitis

Treatment

- supportive, and monitoring (often in the intensive care unit).
 - Fluid resuscitation: aggressive hydration with crystalloids (e.g., normal saline)
 - Analgesia: IV opioids (e.g., fentanyl)
 - Bowel rest (NPO) and IV fluids are recommended until the pain subsides
 - Nasogastric tube insertion:
 - not routinely recommended;
 - indicated in patients with vomiting and/or significant abdominal distension
 - Nutrition
 - Begin **enteral feeding** (oral/nasogastric/naso-jejunal) **as soon as the pain subsides**
 - Total parenteral nutrition:
 - ❖ **only in patients who cannot tolerate enteral feeds** (e.g., those with persistent ileus and abdominal pain)
- if there is **gallstones**:
 - urgent **ERCP** when stable.
 - **All should have a cholecystectomy** either **during the same admission** or within four weeks depending on their clinical progress.

Systemic inflammatory response syndrome (SIRS)

Causes

- sepsis
- **pancreatitis**

Criteria

- SIRS is defined as **two or more** of the following:
 1. Temperature more than 38°C or less than 36°C
 2. Heart rate more than 90 beats/min
 3. Respiratory rate more than 20 breaths/min or PaCO₂ less than 4.3 kPa
 4. WBC count 12,000/mm³, less than 4000/mm³, or more than 10% immature (bands) form.

Management

- **resuscitation of the sick patient still follows the ABC algorithm:**
 1. Airway
 2. Breathing
 3. Circulation.

➤ **Airway control and oxygen to maintain normal saturations is the first part of that algorithm.**

➤ Subsequent fluid resuscitation and treatment of the underlying cause can then be initiated.

➤ The need for invasive monitoring and intensive care is then assessed, depending on the response to initial treatment.
- **Early goal-directed therapy (EGDT)** in cases of SIRS or septic shock is becoming increasingly recognised as potentially beneficial.

➤ **EGDT** aims to:

 - increase organ perfusion through restoration of mean arterial pressure using inotropes if necessary,
 - maintaining central venous pressure (CVP),
 - maintaining oxygenation

❖ using SjVO₂ (jugular venous oxygen saturation) as a guide to oxygen utilisation at the tissue level.

➤ If fluids are not achieving haemodynamic stability, and there is hypoperfusion (indicated by oliguria or lactataemia) → the most appropriate course of action → **central line** → vigorous resuscitation is indicated.

➤ **Insertion of a central line allows measurement of CVP, SjVO₂ and the use of inotropes.**

➤ SjVO₂ higher than 70% is indicative of organ hypoperfusion, as oxygen is not being extracted.
- **Obtain blood cultures prior to antibiotic administration**

Pancreatic pseudocysts

Definition

- encapsulated collection of pancreatic fluid which **develops 4 weeks after an acute attack of pancreatitis**; can occur in both acute and chronic pancreatitis

Pathophysiology

- pancreatic secretions leak from damaged ducts → inflammatory reaction of surrounding tissue → encapsulation of secretions by fibrous tissue

Clinical features

- Often asymptomatic
- Painless abdominal mass
- Pressure effects
- Gastric outlet obstruction (early satiety, non-bilious vomiting, abdominal pain)

- Bile duct obstruction with jaundice

Diagnostics

- abdominal ultrasound/CT/MRI → extrapancreatic fluid collection within well-defined wall/capsule, no solid cyst components detectable

Treatment

- Surgical/endoscopic; ultrasound/CT-guided **percutaneous drainage**

Chronic pancreatitis

Definition

- Chronic pancreatitis is an inflammatory condition, which can ultimately affect both the exocrine and endocrine functions of the pancreas.

Causes

- alcohol excess (80%)
 - what is the general mechanism by which alcohol induces the likely condition?
 - Alcohol increases acinar cell sensitivity to CCK (cholecystokinin), stimulating trypsinogen production in the cell**
- Unexplained (20%)
- PRSS-1 mutation** can cause a hereditary form of the disease.
 - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.
- SPINK-1 mutation** can cause a hereditary form of the disease.
 - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.

Features

- pain is typically worse 15 to 30 minutes following a meal
- steatorrhoea:
 - symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
 - Late manifestation** (after **90%** of the pancreatic parenchyma is destroyed)
- diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation

- abdominal x-ray shows pancreatic calcification in 30% of cases.
- CT is more sensitive at detecting pancreatic calcification.**
 - Sensitivity is 80%, specificity is 85%
 - More sensitive in **moderate to advanced chronic pancreatitis**
 - Malabsorption is only present in moderate to advanced chronic pancreatitis
 - abnormalities include:
 - pancreatic calcification,
 - pseudocyst formation and
 - ductal distortion.
 - CT scanning is much less effective in the diagnosis of **early chronic pancreatitis** and a normal scan does not exclude the diagnosis.
- functional tests: **faecal elastase** may be used to assess exocrine function if imaging inconclusive
- Both 72-hour faecal fat estimation and D-xylose absorption testing are used for their ability to indicate the presence, or absence, of malabsorption, neither is diagnostic of an underlying condition.
 - associated with normal urinary D-xylose test findings**

Management

- pancreatic enzyme supplements
 - Pancrelipase (Creon)**
- Analgesia

- In a patient with chronic liver disease presented with features of decompensation associated with chronic pancreatitis → **Naloxone**
 - Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution.
- antioxidants: limited evidence base - one study suggests benefit in early disease

Complications

- **Pancreatic pseudocysts**
- **Splenic vein thrombosis**
 - Occur in 10% of patients with chronic pancreatitis
 - Pathophysiology: inflammation of the splenic vein → thrombus formation → left-sided portal hypertension → **gastric varices**
 - Clinical features: can present with upper GI bleeding, ascites, and splenomegaly
 - Diagnosis: ultrasound with doppler, CT/MR angiography
 - Treatment
 - Acute: anticoagulation and/or thrombectomy
 - Chronic and symptomatic: splenectomy
- **Pancreatic ascites**
- Pancreatic diabetes
- Pancreatic cancer (especially in patients with hereditary pancreatitis)

Pancreatic cancer

- Pancreatic cancer is often diagnosed late as it tends to present in a non-specific way.
- Over 80% of pancreatic tumours are **adenocarcinomas**
- typically occur at the **head** of the pancreas.
 - most often found in the **ductal cells in the head of the pancreas**.

Associations

- increasing age
- smoking
- **diabetes**
- chronic pancreatitis (alcohol does not appear an independent risk factor though)
- hereditary non-polyposis colorectal carcinoma
- multiple endocrine neoplasia
- BRCA2 gene
- Jewish or African descent.

Features

- classically painless jaundice
- however, patients typically present in a non-specific way with anorexia, weight loss, epigastric pain
- loss of exocrine function (e.g. steatorrhoea)
- **atypical back pain is often seen**
 - **the first symptom is often pain that radiates to the back.**
 - because it is found very late when it has already impinged on other structures.
- migratory thrombophlebitis (Trousseau sign) is more common than with other cancers
 - Migratory thrombophlebitis causes recurrent tender, palpable small blood clots that come and go in various locations on the body,

Investigation

- ultrasound has a sensitivity of around 60-90%
- **high resolution CT scanning is the investigation of choice** if the diagnosis is suspected
- **Carbohydrate A Antigen 19-9 (CA-19-9)** is a tumour marker is usually **used to monitor response to treatment and possible recurrence**, rather than for diagnosis.

Management

- less than 20% are suitable for surgery at diagnosis

- a Whipple's resection (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas.
 - Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- adjuvant chemotherapy is usually given following surgery
- **ERCP with stenting is often used for palliation**
 - relief of symptoms as soon as possible is the main objective of therapy.
 - Stenting relieves symptoms of itching and reverses jaundice in about 85% of patients.
 - Stents can be inserted during an ERCP or percutaneously in those with extensive disease or in those otherwise unsuitable for surgery.

Prognosis

- It has a very high mortality rate (approximately 1 year from diagnosis), usually because it is found very late when it has already impinged on other structures.

Biliary conditions

Ascending cholangitis

- Ascending cholangitis is a bacterial infection of the biliary tree.
- The most common predisposing factor is gallstones.

Features

- **Charcot's triad** (occurs in about 20-50% of patients)
 1. right upper quadrant (RUQ) pain, (70%)
 2. fever (the most common feature, seen in 90%)
 3. jaundice (60%)
- **hypotension and confusion** are also common
 - Combining these two additional symptoms to Charcot's triad results in **Reynold's pentad**.
- elevated alkaline phosphatase and elevated direct bilirubin suggest obstruction of the biliary tree

Investigation

- The initial imaging study is ultrasonography.
- The gold standard for diagnosis is (**ERCP**) endoscopic retrograde cholangiopancreatography.

Management

- intravenous antibiotics
- endoscopic retrograde cholangiopancreatography (**ERCP**) **after 24-48 hours** to relieve any obstruction

Gallstones (Cholelithiasis)

Risk factors for biliary stones

- Cholesterol gallstones are thought to arise as a result of a triple defect:
 1. Super saturation of gallbladder bile (high in cholesterol, low in bile salts)
 2. Increased rate of cholesterol nucleation in the gallbladder
 3. Reduction in gallbladder contractility
- **Predisposing factors to gallstone formation:**
 - Older age
 - Female sex (oestrogens)
 - Oral contraceptive use
 - Cirrhosis (bile pigment stones)
 - **ileal resection** (by reducing entero-hepatic circulation and increasing bile salt loss)

- Clofibrate (by increasing biliary supersaturation)
- rapid weight loss
- Cholestyramine (by binding bile salts)
- **Crohn's disease**

Features

- most will be asymptomatic
- Classic symptoms include biliary colic, nausea, and/or vomiting
 - biliary colic: sharp, colicky pain made worse with fatty food due to ↑ release of CCK
→ contraction of gallbladder

Investigation

- liver function tests : obstructive jaundice
- Ultrasound
 - abdominal/right upper quadrant ultrasound is the test of choice for gallstone disease
 - ultrasound finding of a common bile duct dilatation is suggestive of an obstructing stone
 - Whilst ultrasound is a good preliminary investigation for common bile duct stones it lacks sensitivity.
 - The sensitivity of ultrasound for detecting stones is significantly reduced during an episode of acute pancreatitis (around 70%) so repeating an ultrasound is a reasonable suggestion as it would perform better in the current clinical context than it had done previously. However, its ability to detect CBD stones remains poor.
 - MRI is highly effective in confirming the presence of common bile duct stones,
 - ❖ endoscopic ultrasound (EUS) is a suitable alternative.
 - ❖ CT does not perform well when compared to MRI.
- Radiographs
 - cannot rule out stone with negative radiograph because cholesterol stones are radiolucent
 - pigment stones are radiopaque so may show up on radiograph
- Endoscopic retrograde cholangiopancreatography (**ERCP**), along with intra-operative cholangiography, is considered **the gold standard for diagnosis of common bile duct stones**.
 - However it is an invasive procedure associated with significant morbidity; thus it should ideally be performed as a **therapeutic rather than diagnostic** procedure.
 - The indication for ERCP is for the removal of ductal stones (predominantly CBD stones).
- Magnetic resonance cholangiopancreatography (MRCP)
 - The presence of a CBD calculus should be confirmed prior to subjecting the patient to a potentially dangerous procedure such as an ERCP - **MRCP would be the most appropriate test to do this**.
 - **the most sensitive for a diagnosis of gallstones**
 - In terms of sensitivity for determining the presence of stones anywhere within the biliary tract, MRCP and EUS would be the most sensitive investigations with little to choose between them (ERCP may well miss small stones in the gallbladder).

Management

- In patients with **severe gallstone pancreatitis** → **ERCP and endoscopic stone extraction should be performed within 72 hours of the onset of pain**.
- In patients with **mild gallstone pancreatitis**, in the absence of cholangitis, there is no evidence to support ERCP and stone extraction in the acute setting; however arrangements

must be made for definitive management of common bile duct stones on the same admission or **within two weeks of recovery**.

- **Asymptomatic gallstones** which are located in the gallbladder are common and **do not require treatment**.
- However, if stones are present in the common bile duct there is an increased risk of complications such as cholangitis or pancreatitis and surgical management should be considered.
- endoscopic retrograde cholangiopancreatography (**ERCP**) for biliary sphincterotomy and stone extraction.
 - **the most common procedure-related complication is → Pancreatitis**
 - risks of developing this complication:
 - ❖ Female sex,
 - ❖ age less than 60 and
 - ❖ a low probability of structural disease (suggested by a normal bilirubin, non-dilated ducts or suspected sphincter of Oddi dysfunction)
- Percutaneous transhepatic cholangiography is an interventional radiological procedure which is generally reserved for therapeutic decompression of an obstructed biliary system where ERCP is unsuccessful or not possible.

Complications

- Cholecystitis
- Acute pancreatitis
- Gallbladder cancer
- Choledocolithiasis
 - calculi in the common bile duct
- Fistula between gallbladder and small intestine
 - passed gallstone can obstruct the ileocecal valve

Glasgow score for Pancreatitis:

1. $\text{PaO}_2 < 7.29 \text{ kPa}$
2. Glucose $> 10 \text{ mmol/L}$
3. Age $> 55 \text{ years}$
4. WBC > 15
5. Calcium $< 2.0 \text{ mmol/L}$
6. Urea $> 16 \text{ mmol/L}$
7. LDH $> 600 \text{ IU/L}$
8. Albumin $< 32 \text{ g/L}$

Interpretation of glasgow score for pancreatitis:

- The presence of **three or more** of these criteria within the first 48 hours is indicative of **severe pancreatitis**.
- If the score ≥ 3 , severe pancreatitis is likely Referral to the HDU/ICU is suggested in this case. If the score < 3 , severe pancreatitis is unlikely.

Functional gall bladder pain

- The Rome III criteria for functional gall bladder pain are as follows:
 - episodes lasting 30 minutes or longer
 - recurrent symptoms occurring at different intervals (not daily)
 - the pain builds up to a steady level
 - the pain is moderate to severe enough to interrupt the patient's daily activities or lead to an Emergency Department visit
 - the pain is not relieved by bowel movements

- the pain is not relieved by postural change
- the pain is not relieved by antacids, and
- exclusion of other structural disease that would explain the symptoms.
- The pain may present with one or more of the following supportive criteria:
 - associated with nausea and vomiting
 - radiates to the back and/or right infra subscapular region, and
 - awakens from sleep in the middle of the night.

Choledochal cysts

- Choledochal cysts are congenital bile duct anomalies, cystic dilatations of the biliary tree
- The classic triad in adults with choledochal cysts is:
 1. abdominal pain, (Most common symptom)
 2. jaundice, and
 3. palpable right upper quadrant abdominal mass.

➤ However, this triad is found in only 10-20% of patients.
- Adults may present with complications (eg, hepatic abscesses, cirrhosis, portal hypertension, recurrent pancreatitis, cholelithiasis)
- Abdominal ultrasonography is the investigation of choice
- Choledochal cysts are usually diagnosed in the neonatal period but a few are delayed until adulthood. The Todani classification is used to define these:
 - **Type 1 - a fusiform dilation of the common hepatic duct (CHD) - the most common**
 - Type 2 - a diverticulum of the CHD
 - Type 3 - a choledochcele
 - Type 4 - describes extension into the intrahepatic ducts (the second most common)
 - Type 5 - intrahepatic cystic disease only.
- Treatment
 - Resection and reconstruction is advised to prevent recurrent cholangitis, pancreatitis, and malignant change.

Sphincter of Oddi dysfunction

- Type 1 Sphincter of Oddi dysfunction (SOD) is characterised by:
 - abdominal pain,
 - deranged liver function tests,
 - a dilated biliary tree without strictures, and
 - delayed emptying of contrast at ERCP.
 - Delayed excretion of contrast is definitive and Sphincter of Oddi manometry need not be carried out with this finding.
- Type 2 SOD
 - pain with only one or two other criteria from the type 1 definition
- type 3 SOD
 - biliary type pain only.
 - Diagnosis in type 3 is supported by abnormal manometry although this will only be present in 12-28% of these patients so the diagnosis is most often one of exclusion.

Post-cholecystectomy syndrome

- Post-cholecystectomy syndrome is a recognised complication of cholecystectomies.
- Typically, symptoms of dyspepsia, vomiting, pain, flatulence and diarrhoea occur in up to 40% patients post-surgery.
- The pathology behind the syndrome isn't completely clear, however there is some association with remnant stones and biliary injury.
- Pain is often due to sphincter of Oddi dysfunction and the development of surgical adhesions.
- Management:
 - low-fat diet
 - bile acid sequestrants, such as Cholestyramine, to bind the excess bile acids and thus preventing lower gastrointestinal signs.
 - Proton-pump inhibitors like Lansoprazole do play a role, if the patient is complaining of dyspeptic like symptoms.

Bile-acid malabsorption

SeHCAT is the investigation of choice for bile acid malabsorption

- Although a small proportion of bile acids (3%) are excreted in the faeces, about 97% of bile acids are recycled.
- Bile-acid malabsorption is a cause of chronic diarrhoea.
 - the bile, with no gall bladder to store it, is excreted directly into the gut → diarrhoea
- In people with bile acid malabsorption, excess bile in the colon stimulates electrolyte and water secretion, which results in chronic watery diarrhoea.
- **May affect 10% of patients following cholecystectomy.**
- **Typically it is post-prandial**
- There is evidence suggesting that up to **one-third** of people with a diagnosis of IBS with diarrhoea (IBS-D) have bile acid malabsorption

mechanisms

- Bile acid malabsorption causes diarrhoea by 1 of the following mechanisms:
 - inducing secretion of sodium and water increasing colonic motility
 - stimulating defecation
 - inducing mucus secretion
 - damaging the mucosa, thereby increasing mucosal permeability.

Types: divided into 3 types depending on aetiology:

- type 1: following ileal resection, disease or bypass of the terminal ileum
- type 2: primary idiopathic malabsorption
- type 3: associated with cholecystectomy, peptic ulcer surgery, chronic pancreatitis, coeliac disease or diabetes mellitus.

Causes:

1. **Primary:** due to an excessive production of bile acid,
2. **Secondary:** Due to an underlying gastrointestinal disorder, causing reduced bile acid absorption
 - often seen in patients with ileal disease, such as with **Crohn's**.
 - **cholecystectomy**
 - **coeliac disease**

- small intestinal bacterial overgrowth
- ileal resection
- drugs:
 - Biguanides (metformin),
 - Colchicine, used for treating gout in patients where (NSAIDs) are contraindicated

Investigation

- **the test of choice is SeHCAT**
 - nuclear medicine test using a gamma-emitting selenium molecule in **selenium homocholic acid taurine or tauroselcholic acid (SeHCAT)** (⁷⁵Selenium HomotauroCholic Acid Test)
 - scans are done 7 days apart to assess the retention/loss of radiolabelled ⁷⁵SeHCAT
 - Retention values of less than 15% have been considered abnormal and indicative of bile acid malabsorption.
 - ❖ retention values of 10–15% (mild bile acid malabsorption)
 - ❖ retention values of 5–10% (moderate bile acid malabsorption)
 - ❖ retention values of 0–5% (severe bile acid malabsorption).

Management

- bile acid sequestrants e.g. cholestyramine

Primary biliary cirrhosis

Primary biliary cirrhosis - the M rule

- IgM
- anti-Mitochondrial antibodies, **M2 subtype**
- Middle aged females

Aetiology

- autoimmune condition.

Mechanism

- chronic inflammatory process → damage to interlobular bile ducts → cholestasis & cirrhosis.

Epidemiology

- female: male ratio → 9:1

Associations

- **Sjogren's syndrome (seen in up to 80% of patients)**
- rheumatoid arthritis
- systemic sclerosis
- thyroid disease

Clinical features

The two main conditions causing **pigmentation** and **chronic liver disease** are:

1. primary biliary cirrhosis (PBC) and
2. Haemochromatosis.

- early: may be asymptomatic (e.g. raised ALP on routine LFTs) or fatigue, pruritus
 - classic presentation → itching in a middle-aged woman
- cholestatic jaundice
- **hyperpigmentation**, especially over pressure points
- xanthelasmata, xanthomata
- also: clubbing, hepatosplenomegaly
- Fat malabsorption leading to deficiency of the vitamins A, D, E, K (hence osteomalacia and also bruising).
- **Back pain**

- due to osteomalacia resulting from malabsorption or osteoporosis - hepatic osteodystrophy.
- late: may progress to liver failure

Diagnosis

- anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
 - (AMAs) targeted against pyruvate dehydrogenase.
 - Pyruvate dehydrogenase (PD) is found in the mitochondria, required for the generation of acetyl-CoA from pyruvate for entry into the tricarboxylic acid (TCA) cycle.
- smooth muscle antibodies in 30% of patients
- raised serum IgM
- Liver function tests
 - LFT correlate poorly with histology in PBC – the disease may progress insidiously with normal or near-normal LFTs.

Complications

- malabsorption: osteomalacia, coagulopathy
- **Osteoporosis** is a common complication, possibly due to vitamin D malabsorption and/or premature ovarian failure. All patients with PBC should be screened for the condition → **The patient should undergo bone mineral densitometry.**
- sicca syndrome occurs in 70% of cases
- portal hypertension: ascites, variceal haemorrhage
- **hepatocellular cancer (20-fold increased risk)**

Management

- pruritus: cholestyramine
- fat-soluble vitamin supplementation
- **ursodeoxycholic acid (UDCA)**
 - UDCA delays the need for liver transplantation
 - improves liver biochemistry and may slow disease progression.
 - **The effectiveness of UDCA is monitored by improvements in ALP and GGT, but ALP is more widely used than GGT.**
- liver transplantation
 - e.g. if bilirubin > 100 (PBC is a major indication)
 - **Liver transplantation has a good prognosis (90–95% survival)**
 - recurrence in graft can occur but is not usually a problem
 - occur in 10% to 40% of patients
 - but recurrent PBC does not affect either graft or patient survival rates.
 - **contraindication to liver transplantation:**
 - Psychological factors that may impair compliance with immunosuppression

Primary sclerosing cholangitis (PSC)

4% of patients with UC have PSC, 80% of patients with PSC have UC

Definition

- Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age: The median age at diagnosis is ~ 40.
- primarily seen in middle-aged men with inflammatory bowel disease.

Associations

- ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC
- Crohn's (much less common association than UC)
- HIV

If a patient with pre-existing chronic inflammatory bowel disease displays increased ALP, GGT, and conjugated bilirubin, always consider PSC

Features

- asymptomatic**
 - 50 % of patients
- cholestasis:** (alkaline phosphatase greater than transaminases) → jaundice and pruritus
 - conjugated hyperbilirubinemia.
- right upper quadrant pain
- fatigue
- intermittent diarrhoea.

Investigation

- MRCP** (Magnetic resonance cholangiopancreatography)
 - Non-invasive , often performed **initially**.
 - **the initial diagnostic investigation of choice**
- ERCP**
 - the **standard diagnostic tool**,
 - More invasive but also more accurate than MRCP
 - Good alternative for patients who cannot undergo MRI testing (e.g., patients with pacemaker)
 - showing multiple biliary strictures giving a 'beaded' appearance
- Antibodies:
 - ANCA may be positive (**pANCA 84%**, aCL 66%, , and ANA 53%)
- IgM → increased (hyper gammaglobulinaemia)
- Liver biopsy
 - there is a limited role for liver biopsy,
 - may show fibrous, obliterative cholangitis often described as '**onion skin**'

Complications

- cholangiocarcinoma** (in 10%)
- increased risk of colorectal cancer
- PSC → ↓ secretion of bile acids; → steatorrhea → ↓ fat-soluble vitamins → **Night blindness**

Treatment

- Liver transplant is the definitive treatment**

Prognosis

- The median time to liver failure around 12 years.

Differential diagnoses of primary cholangitis		
	Primary sclerosing cholangitis	Primary biliary cholangitis
Epidemiology	More common among middle-aged men	More common among middle-aged women
Pathophysiology	Progressive chronic inflammation of both intrahepatic and extrahepatic bile ducts	Progressive destruction of only intrahepatic small and medium-sized bile ducts
Antibodies	pANCA	Anti-mitochondrial antibodies (AMA)
Complications	Associated with cholangiocarcinoma and ulcerative colitis	Associated with autoimmune conditions

Cholangiocarcinoma

- The vast majority of cholangiocarcinomas (70%) are sporadic.
- Risk factors:
 - Primary sclerosing cholangitis (PSC) is the most common risk factor
 - Others
 - diabetes
 - fatty liver disease, and
 - inflammatory bowel disease without PSC.
 - Alcohol
 - Smoking
 - Chronic hepatitis B
 - obesity
- The imaging characteristics of a cholangiocarcinoma are hypovascularity with scarring and calcification.
 - CT contrast is delivered in early (hepatic arterial) phase and delayed (portal venous) phase.
 - 80% of normal liver tissue derives its blood supply from the portal vein, but tumours generally derive their blood supply from the hepatic artery and are therefore hypervascular.
 - Cholangiocarcinomas are an exception as hypovascular lesions.
- The Bismuth-Corlette classification is as follows:
 - Type I - below confluence of left and right hepatic ducts
 - Type II - reaching confluence but not involving left or right hepatic ducts
 - Type III - occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct

Liver conditions

Hepatomegaly

Common causes of hepatomegaly

- Cirrhosis: if early disease, later liver decreases in size. Associated with a non-tender, firm liver
- Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular, liver edge
- Right heart failure: firm, smooth, tender liver edge. May be pulsatile

Other causes

- | | |
|--|--|
| <ul style="list-style-type: none"> • viral hepatitis • glandular fever • malaria • abscess: pyogenic, amoebic • hydatid disease | <ul style="list-style-type: none"> • haematological malignancies • haemochromatosis • primary biliary cirrhosis • sarcoidosis, amyloidosis |
|--|--|

Hepatosplenomegaly

Causes of hepatosplenomegaly

- chronic liver disease* with portal hypertension
- infections: glandular fever, malaria, hepatitis
- lymphoproliferative disorders
- myeloproliferative disorders e.g. CML
- amyloidosis

*the latter stages of cirrhosis are associated with a small liver

Gaucher's disease is a lysosomal storage disease, **due to deficiency of the lysosomal hydrolase beta-glucuronidase**. most commonly seen in Ashkenazi Jews. Its features include hepatosplenomegaly, haematological abnormalities and skeletal involvement.

Liver function test

- **Gamma-glutamyl-transferase (GGT)**
 - ↑↑ by drugs such as phenytoin and alcohol.
 - Mild raises in GGT can occur with any alcohol intake, and a rise does not always indicate liver pathology.
 - ↑↑ in fatty liver
- **Transaminase**
 - differential diagnosis for elevated serum aminotransferases:
 - viral hepatitis,
 - hepatotoxicity from drugs or toxins,
 - alcoholic liver disease,
 - hepatic ischemia, and
 - malignant infiltration
 - Only ischaemic hepatitis and paracetamol overdose tend to produce transaminase levels that are raised to very high degree (more than 100 times the upper limit of normal).
 - hypotension (particularly in an individual who is normally hypertensive) is the usual precipitant for ischaemic hepatitis.

- Remember that the level to which transaminases are elevated cannot be used to judge the degree of liver damage and impairment of hepatic function.
- Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings.
- AST/ALT ratio:
 - fatty liver: AST/ALT usually <1
 - alcohol abuse: AST/ALT ratio >2:1
- **Alkaline phosphatase (ALP)**
 - Causes of raised (ALP):
 - liver: cholestasis, hepatitis, fatty liver, neoplasia
 - ❖ In cholestasis, ALP is typically elevated to at least four times the upper limit of normal.
 - ⇒ Lesser degrees of elevation are nonspecific and may be seen in other liver diseases
 - Paget's
 - osteomalacia
 - bone metastases
 - hyperparathyroidism
 - renal failure
 - physiological: **pregnancy**, growing children, healing fractures

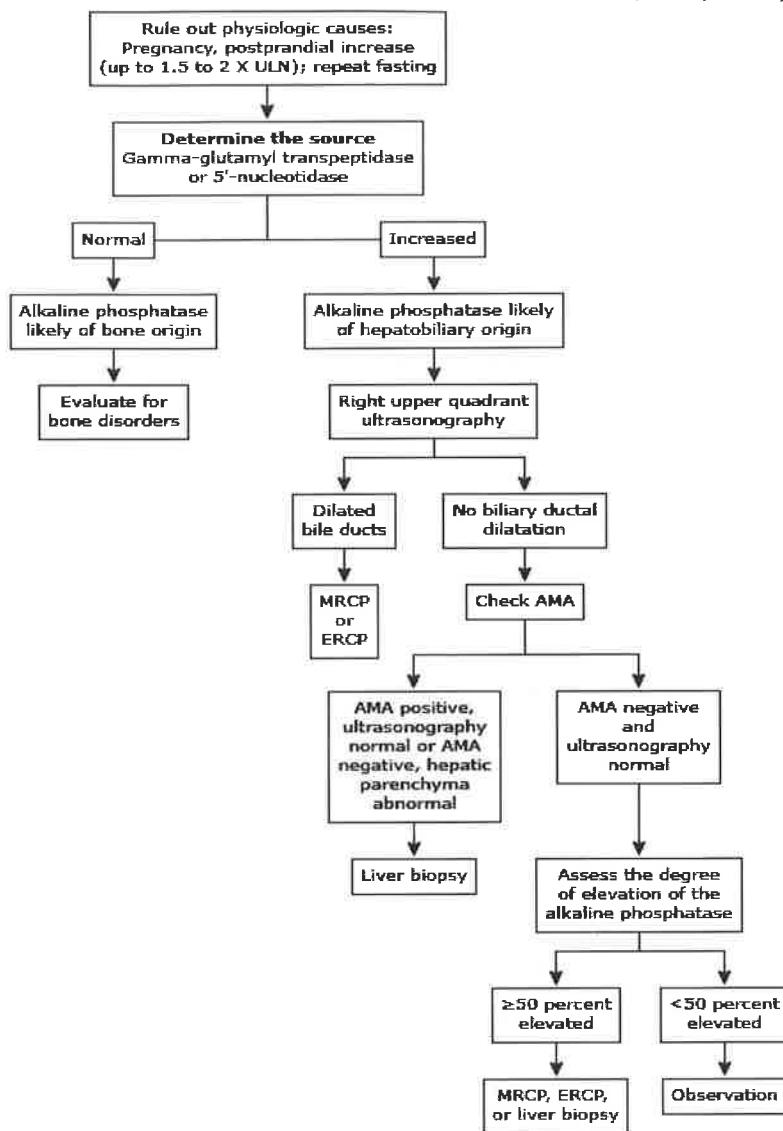
The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
<ul style="list-style-type: none"> • Bone metastases • Hyperparathyroidism 	<ul style="list-style-type: none"> • Osteomalacia • Renal failure

↑ALP → do ultrasonography:

- presence of biliary dilatation → extrahepatic cholestasis (gallstones, strictures, or malignancy).
- absence of biliary dilatation → intrahepatic cholestasis (drug toxicity, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, and total parenteral nutrition).

Evaluation of elevated serum alkaline phosphatase (2019 UpToDate)



AMA: antimitochondrial antibodies; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; ULN: upper limit of normal.

Liver biopsy

Contraindications to percutaneous liver biopsy

- deranged clotting (e.g. INR > 1.4)
 - Percutaneous liver biopsy should be avoided if the INR is greater than 1.3 (prothrombin time greater than three seconds above normal).
 - If the INR is >1.4, **fresh frozen plasma (FFP)** may be administered and liver biopsy then carried out if the INR is less than 1.4.
- low platelets (e.g. < 60 * 10⁹/l)
 - The minimum safe lower limit of platelets is 60.
 - Where the platelet count is 40-60 biopsy can be performed immediately after **platelet transfusion** provided there has been an increment to the recommended level.
- Anti-platelet medication
 - should be stopped for at least one week prior to liver biopsy.
- anaemia
- **extrahepatic biliary obstruction**
- hydatid cyst
- haemangioma
- **uncooperative patient**
- ascites
 - Significant volume ascites is a contraindication to percutaneous liver biopsy but a **trans-jugular biopsy can be performed as an alternative**.

Acute liver failure

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes

- paracetamol overdose
- alcohol
- viral hepatitis (usually A or B)
- acute fatty liver of pregnancy

Features*

- jaundice
- coagulopathy: raised prothrombin time
- hypoalbuminaemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

Note:

- *remember that 'liver function tests' do not always accurately reflect the synthetic function of the **liver. This is best assessed by looking at the prothrombin time and albumin level**.

Ascites

Causes

- **The serum ascites albumin gradient (SAAG) is the most sensitive and specific method of categorising ascites.**
 - To calculate the ascitic fluid albumin should be subtracted from the serum albumin.
 - A value that is ≥ 11 g/L (high SAAG) indicates a transudate (e.g. cirrhosis, cardiac failure),
 - <11 g/L (low SAAG) indicates an exudate (e.g. malignancy, pancreatitis).
- The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11 g/L as per the table below:

SAAG > 11g/L	SAAG <11g/L
Cirrhosis Alcoholic hepatitis Cardiac ascites Mixed ascites Massive liver metastases Fulminant hepatic failure Budd-Chiari syndrome Portal vein thrombosis Veno-occlusive disease Myxoedema Fatty liver of pregnancy	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites Bowel obstruction Biliary ascites Post operative lymphatic leak Serositis in connective tissue diseases

Characteristics of ascitic fluid

- **Causes of a transudate (protein < 30 g/l, assuming a normal albumin level):**
 - Hepatic cirrhosis
 - Right-sided cardiac failure
 - Hypoalbuminaemia (nephrotic syndrome)
 - Acute nephritis
 - Budd-Chiari syndrome
- **Causes of an exudate (protein > 30 g/l):**
 - Infection (tuberculosis, peritonitis)
 - Inflammation (vasculitis)
 - Malignancy
 - **inhaler.**

Treatment

- **Large, symptomatic ascites → therapeutic paracentesis.**
 - Several large randomised, controlled trials have shown that repeated large volume paracentesis (4-6 L) is safer and more effective for the treatment of tense ascites compared with larger than usual doses of diuretics.
 - Paracentesis is relatively contraindicated if the patient is encephalopathic,
 - **Paracentesis is less likely to be successful if the patient has peripheral oedema**
 - Whilst therapeutic paracentesis will be necessary in light of the large volume tense ascites it would be advisable to consider doing this with FFP cover.
- Not large, asymptomatic ascites → dietary salt restriction (to no more than 90 mmol/day) + spironolactone.
 - **The initial management would be spironolactone**
 - Initial dose of spironolactone is 100 mg/day and may be titrated up to 400 mg/day.
 - Once the maximum dose of spironolactone has been reached furosemide can be added if there is still significant ascites accumulation and the renal function and electrolytes will tolerate further diuresis.
 - Doses of furosemide are advised start at 40 mg/day titrating up to 160 mg/day as tolerated or needed.
 - Furosemide alone has poor efficacy in cirrhosis.
 - A major reason for so-called diuretic-resistant ascites is an excess sodium intake,
 - no-added salt diet is recommended for all patients with ascites secondary to chronic liver disease.
 - Spironolactone is more effective than furosemide because the site of sodium retention in cirrhosis is the distal nephron
 - **The ideal weight loss is 0.5 kg/day**, as any more than this may cause cardiovascular strain.

- transcutaneous liver biopsy is contraindicated with ascites (use transjugular biopsy if absolutely necessary).
- **Management of hyponatraemia in patients with chronic liver disease and ascites:**
 - serum sodium is 126-135 mmol/L → No specific intervention other than monitoring
 - serum sodium is 121-125 mmol/L + normal creatinine → Reduce diuretics
 - serum sodium is 121-125 mmol/L + high creatinine → Stop diuretics + give volume expansion
 - **serum sodium is ≤ 120 mmol/L → Stop diuretics + give volume expansion with colloid or normal saline.**
- **Management of hypoproteinemia in patients with chronic liver disease**
 - Cirrhotic ascites has significantly lower protein and complement levels than non-cirrhotic ascites.
 - This can result in less opsonic activity of the peritoneal fluid predisposing to spontaneous bacterial peritonitis.
 - indications for the use of albumin in cirrhosis:
 - post-paracentesis circulatory dysfunction,
 - spontaneous bacterial peritonitis, and
 - hepatorenal syndrome.
 - Albumin replacement treatment is warranted in this diagnosis and can also decrease the development of the hepatorenal syndrome.
 - **20% salt poor albumin (human albumin solution)**
 - The salt-poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload.

What is the most characteristic physiological activity that retains sodium in the face of salt and water overload?

→ **Arterial underfilling**

- In liver cirrhosis, **arterial vasodilatation** due to nitric oxide overactivity, coupled with hypoalbuminemia, which drives low colloid osmotic pressure, leads to **arterial underfilling**.

Meig's syndrome → ovarian fibroma associated with a pleural effusion and ascites

Complications of cirrhosis	Albumin use	
PPCD	8 g/l of ascites removed (above 5 l)	According to guidelines
SBP	1.5 g/kg on day 1 and 1g/kg on day 3 (in association with antibiotics)	
HRS	Loading and maintenance dose + terlipressin until HRS resolution	
Non-SBP Infections	Improvement in renal and circulatory function (no effect on survival, only one study available)	
HE	Only two discordant studies available (effect on oxidative stress)	
Ascites	Not yet enough evidence for the utility of chronic use (<i>ANSWER Study currently ongoing</i>)	Controversial indications (more studies needed)
ACLF	Albumin dialysis (MARS and Prometheus systems)	

Summary table of the current uses of albumin in hepatology, according to the main international guidelines and looking at future perspectives (PPCD: post-paracentesis circulatory dysfunction; SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome; HE: hepatic encephalopathy; ACLF: acute-on-chronic liver failure).

Liver cirrhosis

Pathophysiology

- which hepatic cells are central to the process of fibrosis?
 - The hepatic **stellate cells** are central to the process of fibrosis within the liver.
- What is the pro-inflammatory factor in fibrotic liver injury which activate the stellate cells?
 - **Tumour necrosis factor-a** is a pro-inflammatory effector in fibrotic liver injury, through activation of the **stellate cells**. These cells then secrete the fibrillar collagen constituting the defining features of hepatic fibrosis.
 - Interleukin-10 is thought to exert anti-inflammatory effects on the stellate cell.
- Which mediator is released by stellate cells that causes fibrosis seen in cirrhosis?
 - **Transforming growth factor-beta** is the mediator **released by stellate cells** that causes fibrosis
- Which factor causing contraction of the hepatic stellate cells?
 - **Endothelin** is a **vasoconstrictor in the hepatic sinusoids** (similarly in the endothelium of the systemic circulation) and functions by causing **contraction of the hepatic stellate cells** thus increasing **intrahepatic sinusoidal resistance** and promoting **portal hypertension**.
 - Nitric oxide antagonises the effects of endothelin in the liver.
- Pathogenesis includes the replacement of type IV collagen in the perisinusoidal space (space of Disse) with type I and III collagen.

Features

- **Cardiac**
 - Cardiac output is often elevated
 - The cardiomyopathy of **alcoholism** is a dilated or congestive form.

- **Dilated cardiomyopathy**
- hyperdynamic circulation
- systemic vasodilatation
- ↓ vascular resistance,
- increased plasma volume → low serum sodium.
 - Most patients have **sodium and water retention**.
 - Secondary hyperaldosteronism will result in total body sodium overload but not necessarily hypernatraemia.
 - Remember that the sodium level is a concentration, therefore if the amount of solvent (water) is increased then it will not necessarily rise.
- **Abdominal symptoms**
 - Hepatomegaly (possibly causing RUQ pain)
 - Splenomegaly
 - Ascites
- **Portal hypertension**
 - Hepatic intrasinusoidal pressure is elevated
 - **Which features is most indicative of decompensated portal hypertension?**
 - ⇒ **Caput medusae**
- Which sign is a direct result of **decreased hepatic oncotic** function in cirrhotic patients?
 - **Lower limb swelling**
- **Hormone disorders**
 - Hyperestrogenism
 - Gynecomastia, decreased body hair (e.g., chest hair)
 - ❖ Gynaecomastia
 - ⇒ **What is the cause of gynaecomastia in cirrhosis?**
 - ⇒ **Altered oestrogen metabolism**
 - * ↓↓ metabolism of sex steroids → ↑↑ oestrogen level.
 - * there is associated testicular atrophy and loss of body hair.
 - * May occur as a result of spironolactone therapy (an aldosterone antagonist).
 - Hypogonadism (testicular atrophy)
 - Reduced libido, erectile dysfunction, infertility
 - Amenorrhea

Why do patients get oedema in liver disease?

1. Low albumin
2. Stimulation of RAAS leads to fluid retention

Classifications

- **Child-Pugh classification of liver cirrhosis**

- The Child-Pugh classification is a scoring system to **assess the severity** of liver cirrhosis

Score	1	2	3
Bilirubin (μ mol/l)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin	<4	4-6	>6

Score	1	2	3
time, prolonged by (s)			
Encephalopathy	None	mild	marked
Ascites	None	mild	marked

- Summation of the scores allows the severity to be graded either A, B or C:
 - ❖ < 7 = A
 - ❖ 7- 9 = B
 - ❖ 9 = C

- Cirrhosis can be micro- or macronodular in type.
 1. **micronodular** form: the nodules are less than 3 mm across with uniform liver involvement - seen in **alcohol or biliary disease**.
 2. **macronodular** form: there are larger nodules, classically seen in **chronic viral hepatitis**.

Investigations

- **ALT is more specific than other liver enzymes in diagnosing hepatic injury.**
- **the most important immediate investigation for patient with hepatic cirrhosis presented in a confused and drowsy state → Blood glucose** (hepatic gluconeogenesis can be significantly down-regulated)
- $\uparrow\uparrow$ plasma volume
- $\downarrow\downarrow$ serum sodium
 - **Patients with cirrhosis are frequently hyponatraemic.**
 - This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).
- Urinary sodium concentration is usually less than 10 mmol/l
 - **Reduced urinary sodium excretion**
 - Patients with cirrhosis are frequently hyponatraemic. This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).

Thrombocytopenia is a common finding in chronic liver disease.

Sex hormones in liver cirrhosis

- Clinical features of male cirrhotic subjects are feminization(gynecomastia etc) and hypogonadism(testicular atrophy, reduced fertility, loss of libido, impotence etc).
- sex hormones
 - decrease in serum testosterone levels
 - increase in serum estrogen levels
 - increase in ratio of estrogen to testosterone
 - Hyperestrogenization may be related with feminization of male cirrhotic subjects, whereas hypogonadism is the result of alcohol abuse per se, rather than the indirect consequence of liver cirrhosis.

What are the causes of decompensation in liver disease

- Infection
- Spontaneous bacterial peritonitis
- GI bleeding
- Sedatives
- HCC

Prognosis

- Five-year survival after liver transplantation is now 75%.

Liver transplant

Guidelines for referral to a liver unit following paracetamol overdose include

- Metabolic acidosis (**pH <7.3** or bicarbonate **<18 mmol/L**).
- INR **>3** (or prothrombin time **>50 seconds**)
 - **INR >2.0 at or before 48 hours or >3.5 at or before 72 hours should prompt referral to a specialist unit.**
 - Peak elevation occurs around 72-96 hours.
- Oliguria
- Creatinine **>200 µmol/L**,
 - (use haemodialysis if **>400 µmol/L**)
- Hypoglycaemia.
- Systolic BP **<80 mm Hg** despite adequate fluid resuscitation
- Any degree of encephalopathy 48 hours after ingestion.
- raised intracranial pressure (ICP)
 - signs of CNS oedema include:
 - BP **>160/90 mmHg** (sustained) or brief rises (systolic **>200 mmHg**),
 - bradycardia,
 - decerebrate posture,
 - extensor spasms, and
 - poor pupil responses

Criteria for liver transplant in fulminant failure in cases of paracetamol overdose include:

- arterial pH lower than 7.3 or
- all of the following:
 - Prothrombin time greater than 100 seconds
 - Creatinine greater than 300 µmol/L, and
 - Grade 3-4 encephalopathy.

Criteria for liver transplant in fulminant failure in non-paracetamol cases include:

- INR greater than 6.7 or
- prothrombin time greater than 100 seconds, or
- any three of the following:
 - Aetiology that is not due to hepatitis A, hepatitis B or a drug reaction
 - Age less than 10 years or more than 40 years
 - Jaundice more than seven days before encephalopathy
 - INR greater than 4 or prothrombin time greater than 50 seconds, and
 - Bilirubin greater than 300 µmol/L.

When referral/discussion with the liver transplant unit is required for a patient with acute liver failure?

Paracetamol induced acute liver failure	Non-paracetamol induced acute liver failure
<ul style="list-style-type: none"> ► Arterial pH < 7.30 or HCO₃ < 18 ► INR > 3.0 on day two or > 4.0 thereafter. ► Oliguria and/or AKI ► Altered level of consciousness ► Hypoglycaemia ► Elevated arterial lactate (>4 mmol/L) unresponsive to fluid resuscitation 	<ul style="list-style-type: none"> ► pH < 7.30 , or HCO₃ < 18mmol/l ► INR >1.8 ► Oliguria/renal failure or Na < 130mmol/L ► Encephalopathy, hypoglycaemia or metabolic acidosis ► Bilirubin >300 umol/L (17.6mg/dL)

Ref: Adult liver transplantation: A UK clinical guideline.

March 2020. www.bsg.org.uk (PassOnExam)

Portal hypertension

Basics

- The liver receives approximately 1500 ml of blood each minute, **two-thirds of which is provided by the portal vein.**

Definition:

- abnormally high pressure in the hepatic portal vein (hepatic venous pressure gradient of 10 mm Hg or more).
- Portal hypertension is present when the wedged hepatic vein pressure is more than 5 mmHg higher than the inferior vena cava pressure.

Mechanism of porto-systemic collaterals

- Because the **veins in the portal system lack valves**, increased resistance to flow at any point between the splanchnic venules and the heart will increase the pressure in all vessels on the intestine site of the obstruction.
- This is manifest clinically by the development of porto-systemic collaterals (oesophageal varices), splenomegaly and/or ascites.

Site of Anastomosis	Clinical Sign	Portal ↔ Systemic
Esophagus	Esophageal varices	Left gastric ↔ esophageal
Umbilicus	Caput medusae	Paraumbilical ↔ superficial and inferior epigastric
Rectum	Anorectal varices (sometimes referred to as internal hemorrhoids though they are different)	Superior rectal ↔ middle and inferior rectal

Causes : (Vascular resistance and blood flow are 2 important factors in its development).

- **Pre-hepatic** - (pre-sinusoidal) **blockage of the portal vein before the liver**
 - Congenital atresia or stenosis.
 - **Portal vein thrombosis** (idiopathic, **umbilical and portal sepsis**, malignancy, hypercoagulable states, pancreatitis).
 - **Longstanding portal vein thrombosis is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care.**
 - ❖ **the best initial investigation is → Ultrasound with Doppler**
 - Splenic vein thrombosis.
 - Extrinsic compression - eg, tumours.
- **Hepatic** (sinusoidal)
 - Cirrhosis. (**the most common cause**)
 - Chronic hepatitis.
 - Schistosomiasis.
 - Myeloproliferative diseases.
 - Idiopathic portal hypertension.
 - Granulomata - eg, sarcoid.
 - Nodular (nodular regenerative hyperplasia, partial nodular transformation).
 - Toxins (arsenic, vinyl chloride).
 - Fibropolycystic disease (including congenital hepatic fibrosis).
- **Post-hepatic** - (post-sinusoidal) **blockage of hepatic veins or venules**
 - Budd-Chiari syndrome (hepatic vein obstruction).
 - Constrictive pericarditis.
 - Right heart failure.
 - Veno-occlusive disease of the smaller hepatic veins/venules (due to ingestion of pyrrolizidine alkaloids; antileukaemic drugs, radiation).
 - Sclerosing hyaline necrosis.

Portal hypertension measurement:

- Portal pressure is indirectly measured in clinical practice by the hepatic venous pressure gradient (HVPG).
- The HVPG is calculated by subtracting the free hepatic venous pressure (which reflects intra-abdominal pressure) from the wedged hepatic venous pressure (which reflects portal venous pressure). These values are obtained by hepatic venous catheterization.
- Normal HVPG values are <5 mm Hg.
- HVPG >10 mm Hg predicts the development of oesophageal varices.
- However, HVPG is moderately invasive and its clinical role is uncertain.
- The normal hepatic venous pressure gradient (normal HVPG = 1-5 mmHg) means that the portal hypertension is not related to post-sinusoidal intrinsic liver disease such as cirrhosis

(caused in children by metabolic disorders such as A1ATD) or post-hepatic venous obstruction (HV thrombosis).

- The haemodynamic goal of treatment is reduce the HVPG by 20% or to less than 12 mmHg, using a non-selective beta blocker. If this is not achievable despite titrating the beta-blocker dose, then endoscopic variceal ligation must be considered.

- Wedged hepatic venous pressure**

- the pressure recorded by a catheter wedged in a hepatic vein. It reflects the portal venous pressure in the hepatic sinusoids.
- **↑↑ in sinusoidal and post-sinusoidal portal hypertension,**
- remains normal in pre-sinusoidal portal hypertension.

Complications of portal hypertension:

- Haematemesis or melaena - suggest bleeding varices.
- Lethargy, irritability and changes in sleep pattern - suggest encephalopathy.
- Increased abdominal girth, weight gain - suggest ascites.
- Abdominal pain and fever - suggest spontaneous bacterial peritonitis.
- Pulmonary involvement is common in patients with portal hypertension

Trans-jugular intrahepatic porto-systemic shunt (TIPSS)

- Indications are:
 - Diuretic resistant ascites (**Intractable ascites**)
 - Intractable portal hypertensive bleeding and
 - Hepato-renal failure.
- contraindications to shunting:
 - Severe hepatic encephalopathy
 - Severe heart failure
 - Septicaemia

Hepatic encephalopathy

- Hepatic encephalopathy may be seen in liver disease of any cause.
- The aetiology is not fully understood but is thought to include excess absorption of ammonia from bacterial breakdown of proteins in the gut

Features

- confusion, altered GCS (see below)
- hepatic flap
 - Asterixis (also called the flapping tremor, or liver flap) is a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings.
 - **hepatic encephalopathy is unlikely to be present if a liver flap (asterixis) cannot be detected.**
- constructional apraxia: inability to draw a 5-pointed star
- triphasic slow waves on EEG
- raised ammonia level (not commonly measured anymore)

Grading of hepatic encephalopathy

- Grade I: mood changes like depression or irritability, and sleep abnormalities (typically sleep inversion)
- Grade II: Confusion, inappropriate behaviour
- Grade III: Incoherent, restless

- Grade IV: Coma

Precipitating factors

- infection e.g. spontaneous bacterial peritonitis
- GI bleed
- constipation
- drugs: sedatives, diuretics
- hypokalaemia
- renal failure
- increased dietary protein (uncommon)

Treatment

- Treat precipitating cause (e.g., give K⁺ if hypokalemic)
- Lactulose
 - metabolized to lactic acid by colonic flora, converts NH₃ to NH₄⁺ which can be absorbed
- Neomycin
 - replaced with rifamixin, neomycin no longer routinely used
 - antibiotics kill colonic flora leading to decreased NH₃ production

Hepatorenal syndrome (HRS)

Hepatorenal syndrome is primarily caused by splanchnic vasodilation

Pathophysiology

- vasoactive mediators cause → **splanchnic vasodilation** → ↓↓ systemic vascular resistance → 'underfilling' of the kidneys → activation of the renin-angiotensin-aldosterone system by the juxtaglomerular apparatus → renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Types

- Hepatorenal syndrome has been categorized into two types:

Type 1 HRS	Type 2 HRS
<ul style="list-style-type: none"> • Rapidly progressive • Doubling of serum creatinine to > 221 mmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks • Very poor prognosis 	<ul style="list-style-type: none"> • Slowly progressive • characterised by a moderate and stable reduction in renal function, hypotension and diuretic resistance. • Prognosis poor, but patients may live for longer

Management

- The **ideal treatment** is liver transplantation, but patients are often too unwell to have surgery and there is a shortage of donors
- Other Management options
 - agonists of vasopressin V1 receptors such as **terlipressin** → vasoconstriction of the splanchnic circulation
 - volume expansion with 20% albumin
 - transjugular intrahepatic portosystemic shunt

Wilson's disease

Wilson's disease - serum caeruloplasmin is **decreased**

Wilson's disease is an **autosomal recessive**

Definition

- Wilson's disease is an autosomal recessive disorder characterised by impaired copper transport via caeruloplasmin results in excessive copper deposition in the tissues.
- **Wilson disease** is a disorder resulting from **impaired copper excretion into bile**. Copper overload and deposition in tissues leads to predominantly hepatic and neuropsychiatric symptoms.
- Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion.

Aetiology and pathophysiology

- autosomal recessive
- caused by a defect in the ATP7B gene located on chromosome 13.
- Mutations within the ATP7B gene result in disruption of an ATPase within hepatocytes which is responsible for the movement of copper across intracellular membranes. This results in **hepatic retention of copper, and low serum levels**.
- The mechanism of tissue damage in Wilson disease is **copper-mediated hydroxyl free radical tissue damage**.

Features

- The onset of symptoms is usually between 10 - 25 years.
- Children usually present with liver disease whereas **the first sign of disease in young adults is often neurological disease**
- liver: hepatitis, cirrhosis
- neurological:
 - **basal ganglia degeneration, speech and behavioural problems are often the first manifestations.**
 - **The most common early neurological sign is an asymmetrical tremor,**
 - Also: the initial sign is usually increased clumsiness.
 - parkinsonism,
 - dystonia,
 - asterixis,
 - chorea,
 - dementia
- Kayser-Fleischer rings
 - Golden corneal rings
 - **in the posterior surface of the retina, within its Descemet's membrane.**
 - Detected by **Slit lamp examination**
 - Present in up to 90% of symptomatic patients but is not pathognomonic.
- renal tubular acidosis (esp. Fanconi syndrome)
- haemolysis
- blue nails

Diagnosis

- **Reduced serum caeruloplasmin**
 - Ceruloplasmin is normal in approximately 5% of cases
- **Slit lamp examination**

- slit lamp examination will detect Kayser-Fleischer corneal rings in **approximately 98% of untreated cases** and the sunflower cataract will be more obvious.
- ↓ Total serum copper
- increased 24hr urinary copper excretion
 - greater than 1.6 µmol/day
- **Liver biopsy**
 - **The most reliable investigation to confirm the diagnosis**
 - Shows:
 - increased hepatic parenchymal copper concentration
 - steatosis, glycogenated nuclei, focal hepatocellular necrosis, fibrosis and cirrhosis.
- MRI of the brain
 - commonly shows increased density in the basal ganglia.
- Genetic testing for ATP7B mutation
 - usually reserved for patients where the diagnosis is in doubt, or for screening of siblings.

Complications

- higher risk of hepatocellular carcinoma.

Management

- **General management**
 - Low-copper diet: avoid foods such as **organs, shellfish, nuts, and chocolate**
 - Hepatotoxic drugs, alcohol and foods high in copper (liver, chocolate, shellfish etc.) should be avoided.
 - Regular check-ups: liver biochemical tests every 6 months if disease is stable^[9]
 - Liver transplantation in cases of fulminant liver failure
- **Medical therapy**
 - **Initial therapy: chelating agents**
 - **Penicillamine:**
 - ❖ first-line treatment
 - ❖ side effects in ~ 30% of cases
 - ⇒ (e.g., sensitivity reactions)
 - ⇒ bone marrow suppression
 - Alternatives: trientine or zinc salts
 - ❖ **Trentine**
 - ⇒ may become first-line treatment in the future
 - ⇒ better tolerated than penicillamine, and is therefore used as an alternative where side effects are seen when penicillamine is initiated.
 - **Maintenance therapy: zinc salts** or low dose chelating agents
- **Zinc acetate is the intervention of choice for patients with asymptomatic Wilson's disease (i.e. those who present with elevated transaminases without evidence of cirrhosis or neurological dysfunction).**
- screening of first degree relatives
 - Once a diagnosis of Wilson's disease is made, screening of first degree relatives (with genetic testing) should be done.

Treatment with a chelating agent should be administered gradually over the course of 3 to 6 months, as mobilizing the copper stored in tissues too rapidly may exacerbate neurological symptoms

Prognosis

- Early treatment allows a normal length of life,
- however without treatment Wilson's disease is usually fatal by the age of 40 years.

MRCPUK-part-1-September 2014 exam: A 23-year-old woman developed unilateral hand tremor at rest, behaviour & mood changes, speech problems & bradykinesia. Dark circular marks noted around the iris. her uncle died of liver cirrhosis at the age of 40 years. Given the likely diagnosis, what is the mode of inheritance?

→ Autosomal recessive

Hyponatraemia in Patients with chronic liver disease

- Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.
- Diuretic therapy for the management of ascites often contributes to the hyponatraemia.
- **The British Society of Gastroenterology guidelines** suggest that:
 - serum sodium is $\leq 120 \text{ mmol/L} \rightarrow$ normal saline + stop diuretic
 - serum sodium is 126-135 mmol/L → No intervention other than careful monitoring.
 - serum sodium is 121-125 mmol/L + normal serum creatinine → reduce diuretics or stop it if necessary
 - serum sodium is 121-125 mmol/L + ↑↑ serum creatinine → volume expansion + stop diuretics
 - fluid restriction should only be used in patients who are clinically euvoalaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.

Alcohol

After drinking excessive amounts alcohol

- **Mechanism of polyuria → Ethanol inhibits ADH secretion**
- Mechanism of nausea → vagal stimulation to the vomiting centre.
- Mechanism of tremors → increase glutamate production by neurones to compensate for the previous inhibition by ethanol.
- **Mechanism of hypoglycemia → hepatic sequestration of Reduced nicotinamide adenine dinucleotide (NADH)**
 - In the liver alcohol dehydrogenase converts ethanol to acetaldehyde but to do so requires the reduction of oxidized nicotinamide adenine dinucleotide (NAD^+) to reduced nicotinamide adenine dinucleotide (NADH).
 - Acetaldehyde is then further oxidized to acetate by aldehyde dehydrogenase, which requires the reduction of another NAD^+ to NADH.
 - When excess alcohol is consumed then the system becomes overwhelmed and NADH accumulates in hepatocytes.
 - This sequestration of NADH reduces the amount of NAD^+ available to oxidize gluconeogenic precursors → hypoglycemia

Alcohol induced hypoglycemia

- Alcohol metabolized to acetyl-CoA.
- **NADH produced during alcohol metabolism interferes with gluconeogenesis.**
- NADH causes production of: lactate, malate, and glycerol 3-phosphate.
- Thus, glycerol 3-phosphate causes lipid accumulation in liver alcoholic disease.
- **NAD, required for lactate metabolism (and lactate is used for gluconeogenesis), is being used for alcohol metabolism.**

The large anion gap and hypoglycemia in alcoholic patients can be explained by which mechanism?

→ Inhibition of dehydrogenase enzymes by NADH

- Excess alcohol intake leads to accumulation of NADH that decreases gluconeogenesis as well as impairs fatty acid oxidation.
- (Key gluconeogenic dehydrogenases are inhibited by the elevated levels of NADH, including:
 - ❖ lactate dehydrogenase,
 - ❖ glycerol 3-phosphate dehydrogenase, and
 - ❖ malate dehydrogenase).
)

Alcohol - drinking problems: management

Nutritional support

- SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- disulfiram: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo-controlled trials

Disulfiram

- **Indication:** used as an aid to stop alcohol abuse.
- **Mode of action:** irreversible inhibitor of aldehyde dehydrogenase, therefore if alcohol is ingested, aldehyde accumulates causing unpleasant reactions including vomiting, palpitations and breathlessness.
- The reaction with alcohol only occurs at least 12 hours after the start of disulfiram therapy and may occur up to 10 days after stopping disulfiram therapy.
- **Disulfiram is active against scabies**, although other treatments are usually preferred.

Alcoholic liver disease

The recommended maximum alcohol intake per week is 21 units for men and 14 units for women. Governmental guidelines suggest that women should not have more than 2-3 units per day and men should not have more than 3-4 units per day

Alcoholic liver disease includes fatty liver, alcoholic hepatitis and cirrhosis.

- **fatty liver** (hepatocyte steatosis)
 - accumulation of fat within the hepatocytes.
 - Mechanism:
 - ❖ increased generation of NADH reduces the activity of the TCA cycle, the acetyl-Co A is diverted to fatty acid synthesis.
 - ❖ reduction in cytosolic NAD⁺ leads to reduced activity of glycerol-3-phosphate dehydrogenase resulting in increased levels of glycerol 3-phosphate which is the backbone for the synthesis of the triglycerides, lead to fatty acid deposition in the liver leading to **fatty liver syndrome**.
 - asymptomatic and detected incidentally.
 - Elevated transaminases and a background of alcoholism are clues to the diagnosis.
 - **macrovesicular** fatty changes.
 - Microvesicular fatty changes are not found in hepatic steatosis.
 - An ultrasound demonstrates hyper-echogenicity and a bright liver.
 - This is **reversible with abstention from alcohol**.

- **Alcoholic hepatitis** presents as:
 - acute right upper quadrant (RUQ) pain
 - Tender hepatosplenomegaly
 - jaundice
 - fever
 - frequently occurs on a background of cirrhosis
 - marked derangement of LFTs
 - **LFT typically show an AST elevated greater than the ALT with at least a 2:1 ratio**
 - AST:ALT ratio can be useful in diagnosing alcoholic liver disease, because more than two-thirds of patients will have a ratio greater than 2.
 - transaminases are typically only slightly elevated rarely over 300 and virtually never over 500.
 - The alkaline phosphatase may well be significantly elevated giving the liver profile an 'obstructive' appearance.
 - High IgA levels are seen in alcoholic liver disease.
 - At a microscopic level there is inflammation of the liver.
- **liver cirrhosis,**
 - the hepatocytes are damaged so much that they are replaced by scar tissue which is permanent.
 - Alcoholic hepatitis and cirrhosis may co-exist.
 - Alcoholic hepatitis and cirrhosis may lead to encephalopathy, portal vein hypertension and hepato-renal syndrome, increase risk of infections and they are usually malnourished.
 - There is no specific therapy for alcohol-related hepatitis and cirrhosis.
- **Cardiomyopathy of alcoholism is a dilated or congestive form.**
- **Gout**
 - **Gout is a common finding in chronic alcoholics.**
 - Mechanism:
 - ❖ Lactate accumulate in alcoholics causes lactic acidosis (Metabolic acidosis).
 - ❖ **Lactate competes with uric acid for excretion, decreasing its excretion and thus aggravating gout.**

**Chronic alcohol abuse is typically associated with →
Increased carbohydrate deficient transferrin (CDT)**

Which feature would suggest a diagnosis of hepatic steatosis rather than non-alcoholic fatty liver disease?

→ **Reversible hepatic damage after discontinuing alcohol consumption**

The common abnormalities in chronic alcohol dependence

- **Macrocytosis**
- Hypertriglyceridaemia - can contribute to pancreatitis
- Hyperuricaemia - can cause gout
- Hypoglycaemia - can contribute to seizures and coma
- Increased carbohydrate deficient transferrin - considered a marker of chronic abuse and sometimes checked to ensure abstinence, for example, while awaiting liver transplantation
- Hypogonadism
- Thiamine deficiency
- Abnormal iron
 - Iron levels are variable in alcohol dependence: hepatitis causes increased serum iron while poor diet can result in iron deficiency
 - Ferritin can be elevated in the acute phase response, but reduced in advanced liver disease due to possible reduced synthesis rates

- Abnormal electrolytes
 - Hyponatraemia and hypokalaemia are often seen in established liver disease
 - Hypomagnesaemia
 - **hypocalcaemia** which may be linked to alcohol-related hypomagnesaemia and poor dietary intake of calcium and vitamin D;
- Elevated liver enzymes
 - Elevated GGT - this is due to enzyme induction but does not necessarily indicate that there is liver damage
 - ALT is elevated in liver disease and hepatocellular damage
 - AST is elevated (but can also be increased in cardiac or muscular damage).
 - AST:ALT ratio can be elevated due to the mitochondrial effects of alcohol causing a **disproportionate increase in AST**. However, this is not specific.

Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution.

(eg: a patient prescribed dihydrocodeine regularly for abdominal pain associated with chronic pancreatitis, became drowsy with deterioration in his Glasgow coma scale. What is the agent should be administered initially? → **Naloxone**)

Alcoholic ketoacidosis

Definition

- Alcoholic ketoacidosis is a non-diabetic euglycaemic form of ketoacidosis.

Features

- Metabolic acidosis
- Elevated anion gap
- Elevated serum ketone levels
- Normal or low glucose concentration

Treatment

- **The most appropriate treatment is an infusion of saline & thiamine.**
 - Thiamine is required to avoid Wernicke encephalopathy or Korsakoff psychosis.

Non-alcoholic fatty liver disease (NAFLD) (Non-alcoholic steatohepatitis (NASH))

Obese T2DM with abnormal LFTs - ? non-alcoholic fatty liver disease

Definition

- liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse.
- NAFLD is subdivided into:
 - ⇒ nonalcoholic fatty liver (NAFL): hepatic steatosis without inflammation
 - ⇒ nonalcoholic steatohepatitis (NASH): hepatic steatosis with hepatic inflammation that may be histologically indistinguishable from alcoholic steatohepatitis
- the diagnosis is made only by histology of liver biopsy which shows lesions suggestive of ethanol intake in a patient known to consume less than 40 g of alcohol per week.

Epidemiology

- Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world.
- relatively common and thought to affect around 3-4% of the general population.
- It is projected to become a leading indication for liver transplantation, superseding hepatitis C.

Mechanism

- NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis

Associated risk factors

- Obesity
- Hyperlipidaemia
- **Type 2 diabetes mellitus**
- Jejuno-ileal bypass
- Sudden weight loss/starvation

Complications

- Liver cirrhosis
- NASH is associated with insulin resistance and diabetes.

Features

- Usually asymptomatic
- Hepatomegaly
- Some patients with NASH may complain of fatigue, malaise, and vague right upper abdominal discomfort.

Investigations

- **LFT**
 - ⇒ ALT is typically greater than AST ($ALT > AST = \text{Lipids}$)
 - ⇒ normal aminotransferase levels do not exclude NAFLD
- **Radiographic finding:**
 - ⇒ U/S → increased echogenicity on ultrasound
 - ⇒ CT → decreased hepatic attenuation
 - ⇒ MRI → an increased fat signal
- **Liver biopsy**
 - ⇒ The hallmark of the condition on liver biopsy is the association of inflammation with fatty infiltration of the liver. This can progress to fibrotic change and eventually to cirrhosis.
 - ⇒ fatty infiltration of hepatocytes causing cellular "ballooning" and eventual necrosis.

Diagnosis

- A definitive diagnosis of NAFLD requires all of the following:
 1. Demonstration of hepatic steatosis by imaging or biopsy
 2. exclusion of common liver disorders like viral hepatitis, alcoholic liver disease, drug induced and autoimmune liver disease (e.g. primary biliary cirrhosis). Exclusion of other causes of hepatic steatosis: e.g:

- Significant alcohol use
- Hepatitis C (particularly genotype 3)
- Wilson disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications
- Reye syndrome
- Acute fatty liver of pregnancy
- HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome
- The confirmatory test for diagnosis is liver biopsy.

Management

- Non pharmacological: life style management
 - Weight loss: the mainstay of treatment
 - abstinence from alcohol
- Pharmacological
 - there is ongoing research into the role of gastric banding insulin-sensitising drugs (e.g. Metformin)
 - **For patients with NASH and diabetes mellitus:**
 - ❖ Although initial therapy for type 2 diabetes mellitus is typically with metformin, but metformin does not improve liver histology
 - ❖ the beneficial impact on liver histology with certain other insulin-sensitizing agents could be a consideration when choosing a second-line agent for patients with NASH who cannot take metformin or need additional glucose-lowering therapy. In this setting, **pioglitazone** and **liraglutide** are reasonable options.
 - ❖ In patients with diabetes mellitus and biopsy-proven NASH, **pioglitazone** improves fibrosis as well as inflammation and steatosis.
 - ❖ use of pioglitazone is limited because it is associated with increased risk of weight gain, heart failure, and fractures.
 - ❖ Although less well studied, **liraglutide** also appears to improve liver biopsy evidence of NASH.
 - **Liraglutide** is a GLP-1 agonist which results in significant weight loss of up to 7% over 1 year at high dose, (3mg). By driving weight loss it **leads to a significant reduction in hepatic fat** and may **impact on the long-term prognosis of fatty liver disease.**

Prognosis

- Approximately 20% develop cirrhosis

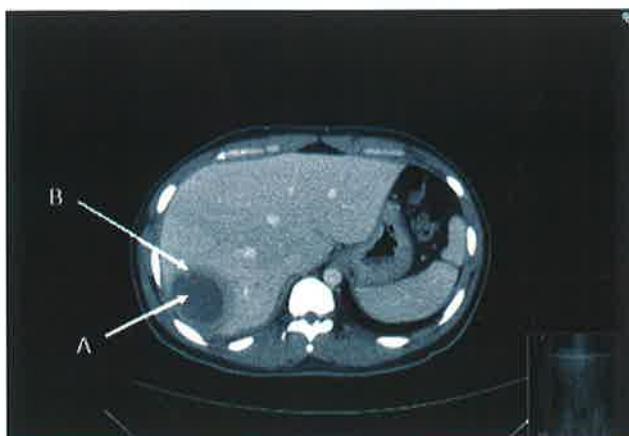
Which liver function test is the best marker of non-alcoholic fatty liver disease in type 2 diabetes mellitus?

→ alanine aminotransferase

Liver abscess

Pyogenic liver abscess

- The most common organisms found in pyogenic liver abscesses are *Staphylococcus aureus* in children and *Escherichia coli* in adults.
- usually complicates pre-existing biliary and gastrointestinal tract infections.
- Management
 - Ideally, a penicillin-based β -lactamase antibiotic combined with metronidazole to provide anaerobic cover would be the treatment of choice.
 - amoxicillin + ciprofloxacin + metronidazole
 - if penicillin allergic: ciprofloxacin + clindamycin



The CT demonstrates a hypodense lesion (A) with surrounding oedema (B).

Amoebic liver abscess

- A solitary abscess in the right lobe of the liver is typical of amoebic liver abscess.
 - The collection is commonly single and confined to the right lobe, but multiple left-sided abscesses may also occur.
- Liver abscesses due to amoebae mainly occur in endemic tropical countries.
- A history of chronic diarrhoea might be elicited in patients with amoebic liver abscess.
- Clinical presentation can be indistinguishable from pyogenic abscesses.
- Specific anti-*E. histolytica* antibodies can be found in 90%
- Management
 - 10-day course of metronidazole.
 - For larger liver abscesses aspiration is the intervention of choice, combined with antibiotic therapy.



CT showing a pyogenic liver abscess in the right lobe of the liver.

Hydatid cysts

Asymptomatic, calcified cystic lesions in the liver are typical of hydatid cysts.

- Hydatid cysts are endemic in Mediterranean and Middle Eastern countries.
- Hydatid infection was endemic in sheep farming regions (such as Wales or New Zealand) in the past and sheep dogs were infected by eating infected offal. Humans contract hydatids via faecal/oral spread from dogs.
 - most commonly seen in farming and rural communities
- They are caused by the tapeworm parasite ***Echinococcus granulosus***.
- Up to 90% cysts occur in the liver and lungs
- An outer fibrous capsule is formed containing multiple small daughter cysts.
- These cysts are allergens which precipitate a **type 1 hypersensitivity reaction**.

Clinical features:

- Can be asymptomatic, or symptomatic if cysts > 5cm in diameter
 - The liver cysts are usually asymptomatic, and calcification usually denotes a non-viable cyst.
- Morbidity caused by cyst bursting, infection and organ dysfunction (biliary, bronchial, renal and cerebrospinal fluid outflow obstruction)
- In biliary rupture there may be the classical triad of; biliary colic, jaundice, and urticaria

Investigations

- Ultrasonography is the most helpful **initial test** since it can usually differentiate a simple cyst from other cystic lesions. It should also be used for follow up studies.
- CT scan shows characteristic daughter cysts.
- **Hydatid serology has a sensitivity of 80-90%.**
- **If hydatid serology is negative, then further imaging (CT/MRI) +/- aspiration may be required to make a diagnosis.**
- **CT is the best investigation to differentiate hydatid cysts from amoebic and pyogenic cysts.**

Treatment

- Surgery is the mainstay of treatment (the cyst walls must not be ruptured during removal and the contents sterilised first).
- benzimidazoles

Drug-induced liver disease

Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis

Hepatocellular Picture	Cholestasis (+/- Hepatitis)	Liver Cirrhosis
<ul style="list-style-type: none"> Alcohol Amiodarone Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide Ketoconazole Halothane MAOIs Methyldopa Paracetamol Sodium valproate, phenytoin Statins Nitrofurantoin → chronic active hepatitis. 	<ul style="list-style-type: none"> Anabolic steroids, testosterone Antibiotics: flucloxacillin, co-amoxiclav*, erythromycin**, nitrofurantoin Fibrates Oral contraceptive pill Phenothiazines: <ul style="list-style-type: none"> > chlorpromazine, > prochlorperazine Rarely: nifedipine Sulphonylureas 	<ul style="list-style-type: none"> Amiodarone Methotrexate Methyldopa

Notes

- with co-amoxiclav, a four-week delay in symptoms and signs is not unusual.
- ** with erythromycin risk may be reduced with erythromycin stearate

Epidemiology

- commoner in women

Features

- jaundice (elevated bilirubin)
- hepatomegaly,
- deranged transaminases
- associated with anti-LKM2 autoantibodies.

Differential diagnosis

- autoimmune hepatitis**
 - may also be associated with anti-LKM positivity,
 - short history and drug exposure make drug-induced hepatitis more likely .**

Prognosis

- Liver function can improve after drug withdrawal, but relapses are possible.

Budd-Chiari syndrome

Triad of abdominal pain, ascites and liver enlargement.

Definition

- obstruction of the main hepatic veins by thrombus.
- Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition

Causes

- polycythaemia rubra vera

- thrombophilia: activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies
- **pregnancy**
- **oral contraceptive pill**

Features

- abdominal pain: sudden onset, severe
- ascites
- **tender hepatomegaly**
- Signs of portal hypertension are present and patients may develop acute variceal haemorrhage as a complication.

Diagnosis

- Ultrasound Doppler or contrast CT scan is often used to make the diagnosis.
 - Hypertrophy of the caudate lobe on imaging is a characteristic sign but is seen in only 50% of cases.
- Ascitic tap usually demonstrates a high SAAG (>11 g/L).

Management

- Thrombolysis and subsequent anticoagulation

Prognosis

- **Three-year survival in patients with chronic Budd-Chiari syndrome has been reported as 50%.**

Gilbert's syndrome

- Gilbert's syndrome is an autosomal recessive condition of defective bilirubin conjugation due to a **deficiency of UDP glucuronyl transferase**.
- The prevalence is approximately 1-2% in the general population

Features

- unconjugated hyperbilinaemia (i.e. not in urine)
- normal dipstick urinalysis excludes Dubin-Johnson and Rotor syndrome as these both produce a conjugated bilirubinaemia.
- jaundice may only be seen during an intercurrent illness

Investigation

- rise in bilirubin following prolonged fasting or **IV nicotinic acid**

Management

- no treatment required

Crigler-Najjar syndrome

- Crigler-Najjar syndrome refers to a condition of **absent** UDP-glucuronyl transferase.
- This condition presents early in life with jaundice, increased unconjugated bilirubin and kernicterus.
- This disease is life threatening and the only cure is liver transplant.

Dubin-Johnson syndrome

- benign autosomal recessive disorder
- Resulting in hyperbilirubinaemia (conjugated, therefore present in urine).
- It is due to a defect in the canalicular multispecific organic anion transporter (cMOAT) protein. This causes **defective hepatic bilirubin excretion**
- patients have a **black liver on gross examination** of the tissue.
- On microscopic examination, patients have **epinephrine metabolite accumulations in their hepatocytes**.
- No treatment is necessary.

Autoimmune hepatitis

The combination of **deranged LFTs** combined with **secondary amenorrhoea** in a **young female** strongly suggest → **autoimmune hepatitis**

- Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females.
- more common in females.

Pathophysiology

- T-cell mediated progressive necro-inflammatory process resulting in fibrosis and cirrhosis.

Associations

- Other autoimmune disorders including:
 - coeliac disease,
 - pernicious anaemia,
 - thyroiditis
 - type 1 diabetes mellitus.
- **IgG hypergammaglobulinaemia**
- sicca syndrome (xerostomia/dry eyes, **keratoconjunctivitis sicca**) may occur.
- HLA B8, DR3 and Dw3.

Disease	Associated raised immunoglobulin subtype
Alcoholic liver disease	IgA
Primary biliary cirrhosis	IgM
Autoimmune hepatitis	IgG

Types

- Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present

Type I	Type II	Type III
Anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA) . Affects both adults and children	Anti-liver/kidney microsomal type 1 antibodies (LKM1) Affects children only	Soluble liver-kidney antigen Affects adults in middle-age

Features

- may present with signs of chronic liver disease
- acute hepatitis: fever, jaundice etc (only 25% present in this way)
- **amenorrhoea (common)**

Investigations

- ANA/SMA/LKM1 antibodies,
- raised **IgG** levels
- liver biopsy:
 - **The gold standard for diagnosis**
 - inflammation extending beyond limiting plate 'piecemeal necrosis', **bridging necrosis**

Management

- steroids, other immunosuppressants e.g. azathioprine
- **Prednisolone (with or without azathioprine) is better than azathioprine alone.**

- Steroid therapy produce symptomatic, biochemical and histological improvement, with improvement in survival.
- It does not, however, prevent progression to frank cirrhosis.
- liver transplantation

Prognosis

- The prognosis with long-term immunosuppression is excellent even in the presence of cirrhosis and few patients subsequently develop liver failure.

Ischaemic hepatitis

- Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver').
- **It is diagnosed in the presence of an inciting event (eg: cardiac arrest) and marked increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal).**
- Often, it will occur in conjunction with acute kidney injury (tubular necrosis) or other end organ dysfunction.

Pregnancy: jaundice

Physiological liver changes during pregnancy

- albumin level decreases earlier in 1st trimester due to hemodilution
- **ALT & AST aminotransferase remains normal.** Thus, serum aminotransferase levels is the most useful test for the routine diagnosis of liver diseases during pregnancy.
- total and free **bilirubin decreases during all three trimesters.** Conjugated bilirubin ↓ in 2nd & 3rd trimesters.
- **ALP ↑ in late pregnancy**, due both to the production of the placental isoenzyme and to the increase in bone isoenzyme. (Thus ALP levels is not a suitable test for the diagnosis of cholestasis during pregnancy).
- Serum gamma-glutamyl transferase ↓ in 2nd & 3rd trimesters,
- serum 5'nucleotidase slightly ↑↑ in 2nd & 3rd trimesters.
- Serum total bile acid concentrations not changed during pregnancy. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits.
- Intrahepatic cholestasis of pregnancy would not occur in the first trimester.

Gilbert's & Dubin-Johnson syndrome,

- may be exacerbated during pregnancy

HELLP syndrome

- HELLP syndrome is a mnemonic that stands for **Hemolysis, Elevated Liver enzymes, and Low Platelets** in a patient with severe preeclampsia.
- HELLP syndrome is a manifestation of severe preeclampsia that can lead to hepatic subcapsular hematoma formation.
- Schistocytes are an erythrocyte variant that may be seen in HELLP syndrome.
- **Immediate delivery is the only definitive treatment**

Obstetric cholestasis

Epidemiology

- Obstetric cholestasis affects around 0.7% of pregnancies in the UK
- most common in the third trimester

Pathophysiology

- Caused by a bile acid transporter defect

Features

- pruritus - may be intense - typical worse palms, soles and abdomen
- Jaundice occurs in less than 10% of patients.

Diagnosis (cholestatic picture of (LFTs) with a high ALP and, with a lesser rise in ALT.)

- ↑ Total Serum bile acid levels (cholic acid and chenodeoxycholic acid) >10 micromol/L
- ↑↑ GGT
- ↑ ALT, AST
- ↑ direct bilirubin
 - bilirubin < 100
 - only slightly elevated in about 10%
- ↑ ALP
 - ALP is not useful as it is normally raised in late pregnancy anyway.
- prothrombin time may be prolonged in any cholestatic process due to vit k deficiency

Complications

- increased risk of prematurity and still birth.

Differential diagnosis:

- Viral hepatitis is the commonest cause of jaundice in pregnancy but the **elevated bile acids** make this unlikely

Management

- ursodeoxycholic acid
 - First-line medication
 - widely used but evidence base not clear
 - early therapy with ursodeoxycholic acid reduces the risk of preterm birth and stillbirth.
- Cholestyramine
 - SE: may cause a deficiency in fat-soluble vitamins
 - Rarely, there are cases of cerebral hemorrhage associated with vitamin K shortage under cholestyramine therapy.
- induction of labour at 37 weeks is common practice but may not be evidence based
- vitamin K supplementation
- phenobarbital

Prognosis

- fully reversible postpartum
- Recurrence in following pregnancies (40–60%)

Cardiac output and blood volume increase in pregnancy but hepatic blood flow does not.

Acute fatty liver of pregnancy (AFLP)

Definition

- a rare disease most common in the third trimester characterized by extensive fatty infiltration of the liver, which can result in acute liver failure

Risk factors

- older maternal age,
- primiparity,

- multiple pregnancies,
- pre-eclampsia,
- male foetus
- previous AFLP.

Pathophysiology

- dysfunction of fatty acid β -oxidation \rightarrow microvesicular fat deposition.

Features

- abdominal pain
- nausea & vomiting
- headache
- jaundice
- hypoglycaemia
- severe disease may result in pre-eclampsia
- Coagulopathy with an increased risk of disseminated intravascular coagulation (DIC)
- Hypoalbuminemia \rightarrow ascites
- encephalopathy later.

Investigations

- ALT is typically elevated e.g. 500 u/l
- \uparrow WBC, \downarrow platelets

Management

- support care
- once stabilised delivery is the definitive management

Haemochromatosis

Haemochromatosis is autosomal recessive

- Haemochromatosis is an **autosomal recessive** disorder of iron absorption and metabolism resulting in iron accumulation.

Aetiology

- It is caused by inheritance of **mutations in the HFE gene** on both copies of **chromosome 6***.
 - *there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene
- 90 % of cases are caused by the **substitution of tyrosine for cysteine at position 282** of the HFE gene found on chromosome 6.
- **HLA-A3 is associated with haemochromatosis**

Epidemiology

- 1 in 10 people of European descent carry a mutation genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200
- Haemochromatosis is the most prevalent genetic condition in Caucasian population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people
- Males and females are affected equally but females are often 'protected' from the clinical features by menstrual blood loss.

Pathophysiology

- Iron absorption is regulated in the duodenal crypts.
- **HFE** is a protein that **regulates iron absorption**.
- **HFE** \rightarrow forms a complex at the basolateral membrane that if bound to transferrin + iron at the basolateral membrane of the duodenal crypt cells prevents maturation and consequently absorption of iron in the bowel.
- mutation in the **HFE gene** \rightarrow failure of complex formation and constant maturation of duodenal crypt cells \rightarrow subsequent unregulated uptake of iron.

Presenting features

- often asymptomatic in early disease
 - early symptoms include
 - fatigue,
 - erectile dysfunction
 - arthralgia (often of the hands)
 - Joint x-rays characteristically show chondrocalcinosis
 - 'bronze' skin pigmentation
 - diabetes mellitus
 - liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition)
 - cardiac failure (2nd to dilated cardiomyopathy)
 - hypogonadism (2nd to cirrhosis and pituitary dysfunction - hypogonadotropic hypogonadism)
 - arthritis (especially of the hands). Joint x-rays characteristically show chondrocalcinosis
- Questions have previously been asked regarding which features are reversible with treatment:

Reversible complications	Irreversible complications
<ul style="list-style-type: none"> • Cardiomyopathy • Skin pigmentation 	<ul style="list-style-type: none"> • Liver cirrhosis** • Diabetes mellitus • Hypogonadotropic hypogonadism • Arthropathy

**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not

Investigation

Screening for haemochromatosis

- general population: transferrin saturation > ferritin
- family members: HFE genetic testing

The best investigation to screen for haemochromatosis

- **General population:** transferrin saturation is considered the most useful marker.
 - Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation.
- **testing family members: genetic testing for HFE mutation**

These guidelines may change as HFE gene analysis become less expensive

Diagnostic tests

- **liver biopsy:** Perl's stain
 - **the gold standard investigation** (as it quantifies iron deposition and also stages the amount of fibrosis)
- molecular genetic testing for the C282Y and H63D mutations
 - found in 90%
 - there is substitution of tyrosine for cysteine at position 282 of the HFE gene on chromosome 6.
 - However, there is low penetrance of clinical disease and haemochromatosis also occurs in patients who are negative for this mutation.
 - **genetic testing for HFE gene mutations is indicated for an individuals meeting one of the following criteria:**
 - Elevated serum ferritin (> 300 microgram / L in males; > 200 microgram / L in females)
 - Elevated transferrin saturation (> 45 %)
 - **First degree relative with haemochromatosis**
- MRI has high specificity but low sensitivity for demonstrating iron overload in the liver - it has not replaced the need for biopsy in the majority of cases.

Typical iron study profile in patient with haemochromatosis

- transferrin saturation > 55% in men or > 50% in women
- raised ferritin (e.g. > 500 ug/l).
 - Ferritin is measured to help guide further investigation and treatment:
 - if more than 1000 a liver biopsy should be performed, and treatment initiated.
- low TIBC

Diabetes and impotence associated with high ferritin → haemochromatosis

- The combination of DM and hypogonadotropic hypogonadism (HH) (low testosterone & FSH) is compatible with a diagnosis of haemochromatosis and measuring ferritin would be a reasonable investigation.
- The next investigation would be measurement of transferrin saturation

Treatment

- **Venesections**
 - survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.
 - weekly or twice weekly (if tolerated) **venesections** of 500 cm^3 until the serum ferritin is less than 50 ng/mL & transferrin saturation less than 50%
- **Chelation with desferrioxamine**
 - When iron overload and anaemia are present concomitantly.
 - may be utilised where venesection cannot be continued and there is still evidence of iron overload.
 - It is more commonly used in other conditions associated with iron overload such as thalassaemia major.
- **Avoid vitamin C supplementation**
 - as this can enhance iron toxicity.
- **liver transplantation**
 - End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate **liver transplantation**.

Monitoring adequacy of venesection

- BSCH recommend 'transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l'

MRCPUK-part-1-May 2005 exam: Which feature of haemochromatosis may be reversible with treatment?

→ **Cardiomyopathy**

MRCPUK-part-1-May 2014 exam: H/O fatigue and arthralgia. The joint pain is worse around his metacarpophalangeal joints and knees. polyuria and polydipsia. An x-ray of his knees reveals chondrocalcinosis. What is the mode of inheritance of the likely underlying diagnosis?

→ **Autosomal recessive**

- (This patient has typical symptoms of haemochromatosis: 1/ Lethargy. 2/arthralgia, with evidence of chondrocalcinosis. 3/diabetes mellitus (polyuria and polydipsia))

MRCPUK-part-2-march-2018: abnormal liver function, low testosterone level, diabetes mellitus and elevated serum ferritin level. What is the most effective intervention to treat

iron overload?

→ **Venesection**

- △ haemochromatosis.

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma

- hepatitis B most common cause worldwide
- hepatitis C most common cause in Europe
- Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide.
- Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

Risk factors

- **The main risk factor** for developing HCC is
 - Liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.
 - *Wilson's disease is an exception
 - 75% to 90% of patients with HCC have cirrhosis.
 - HCC develops in 4% of cirrhotics per year.
 - Patients with chronic hepatitis B have 100-fold higher risk of developing HCC.
- **Other risk factors** include:
 - alpha-1 antitrypsin deficiency
 - hereditary tyrosinosis
 - glycogen storage disease
 - aflatoxin
 - drugs: oral contraceptive pill, anabolic steroids
 - porphyria cutanea tarda
 - male sex
 - diabetes mellitus, metabolic syndrome

Features

- tends to present late
- features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options

- early disease: surgical resection
- liver transplantation
- radiofrequency ablation
- transarterial chemoembolisation
- sorafenib: a multikinase inhibitor

Management of liver capsule pain

- Stretching of the liver capsule by a primary hepatoma or metastases within the liver can cause chronic cancer pain.
- This commonly presents as dull, right-sided subcostal pain.
- Referred pain at the top of the ipsilateral shoulder occurs due to diaphragmatic irritation if the superior aspect of the capsule is involved.

- Corticosteroids can be used in the management of liver capsule pain and dexamethasone is usually the choice of steroid.
- Which analgesics would be most suitable for the management of liver capsule pain?**
→ Dexamethasone

Carcinoid syndrome

Flushing, diarrhoea, bronchospasm, tricuspid stenosis, pellagra → carcinoid with liver mets - diagnosis: urinary 5-HIAA

Which biochemical markers is most likely depleted in carcinoid syndrome?

- Biosynthesis of serotonin begins with tryptophan, so **tryptophan depletion** is most likely.

- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features

- flushing (often earliest symptom)**
- diarrhoea
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
 - (mostly tricuspid insufficiency) and pulmonary stenosis,
 - Endocardial fibrosis is due to constant exposure of the right heart to serotonin.**
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation

- urinary 5-hydroxy-indole-acetic acid (5-HIAA) (**specificity 100%**, sensitivity 70%)
- plasma chromogranin A y (**The most sensitive marker 100%**)

Management

- somatostatin analogues e.g. Octreotide (Side effects of octreotide therapy include increased risk of gallstones)
 - The best treatment for symptoms of carcinoid is the somatostatin analogue, octreotide, which improves symptoms and prognosis**
- Other potential treatments following resistance or failure of octreotide include **hepatic artery embolisation**.
- diarrhoea: cyproheptadine may help
 - the treatment for the diarrhoea will be through treating the underlying diagnosis, which is carcinoid → octreotide**
 - Cyproheptadine is not a first line treatment for diarrhoea and in fact may cause diarrhoea as a side effect.
 - Telotristat → inhibits tryptophan hydroxylase, which mediates serotonin biosynthesis. It is indicated for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.
 - Telotristat approved by (FDA) in 2017 for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by an SSA.

Which vitamin deficiency may be associated with carcinoid syndrome?

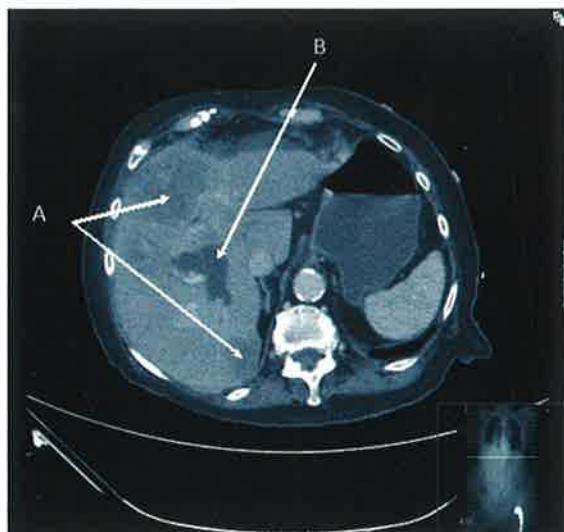
→ Vitamin B₃

- Vitamin B₃, niacin, is used to make NAD and is derived from tryptophan.
- In carcinoid syndrome, the increased synthesis of serotonin would deplete the supply of tryptophan needed to make niacin.
- A deficiency of niacin would result in pellagra, which is characterized by diarrhea, dermatitis, and dementia

MRCPUK-part-1-May 2007 exam: If the patient develops carcinoid syndrome, which one of the following symptoms is most likely to occur first?

→ Facial flushing

hepatic metastases



The abdominal CT demonstrates a number of ill-defined low-density deposits in the liver consistent with hepatic metastases (A) along with significant intrahepatic biliary duct dilatation (B). The likely diagnosis is metastatic pancreatic cancer causing biliary obstruction with a concomitant cholangitis.

Viral hepatitis

Hepatitis A (HAV)

The classic story of (HAV) is initial GIT symptoms then improved condition followed by jaundice and very high alanine aminotransferase (ALT).

Diagnosis

- Anti-hepatitis A IgM antibody will confirm the diagnosis
- IgG antibody would suggest:
 - a previous hepatitis A infection or
 - another underlying cause such as cytomegalovirus.

Indicator of poor prognosis

- Hepatitis A infection on a background of hepatitis C (but not B) has very poor prognosis.

Hepatitis B

Deterioration in patient with hepatitis B - ? hepatocellular carcinoma

- Hepatitis B is a double-stranded DNA hepadnavirus

Spread through

- vertical transmission from mother to child.
 - **Perinatal transmission is the most common route of hepatitis B infection worldwide**
 - the infection rate is **90%** in infants born to HBeAg (hepatitis B envelope antigen) positive mothers.
- exposure to infected blood or body fluids,
 - Sexual transmission comprises **30%** of hepatitis B infections in developed countries.

Incubation period

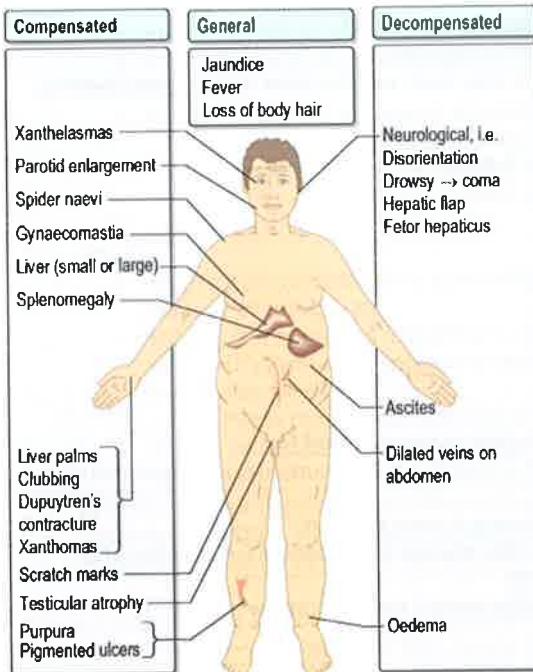
- 6-20 weeks.

Features:

- fever,
- jaundice
- elevated liver transaminases.
 - (ALT) will be elevated more than (AST).

- **Symptoms of decompensated liver disease include:**

- ascites,
- encephalopathy and
- gastrointestinal haemorrhage.



Complications

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- **polyarteritis nodosa**
 - the vascular extrahepatic manifestation of hepatitis B.
 - There is a hepatitis B seropositivity in 30% of patients with polyarteritis nodosa.
- cryoglobulinaemia
- hematologic extrahepatic manifestation of hepatitis B → Aplastic anemia
- renal extrahepatic manifestations of hepatitis B
 - **Membranous glomerulonephritis (more common)**
 - membranoproliferative glomerulonephritis (less common) are.

Prognosis

- Most adults with hepatitis B will progress to full resolution.

Immunisation against hepatitis B

- contains what?:
 - HBsAg adsorbed onto aluminium hydroxide adjuvant
- prepared from what?
 - prepared from yeast cells using recombinant DNA technology
- schedule?
 - give 3 doses of the vaccine + one-off booster 5 years following the initial primary vaccination
- **At risk groups who should be vaccinated** include:
 - healthcare workers,
 - intravenous drug users,
 - sex workers,

- close family contacts of an individual with hepatitis B,
- individuals receiving blood transfusions regularly,
- chronic kidney disease patients who may soon require renal replacement therapy,
- prisoners,
- chronic liver disease patients
- **failure to respond or respond poorly to 3 doses of the vaccine**
 - occur in 10-15% of adults.
 - Risk factors include:
 - age over 40 years,
 - obesity,
 - smoking,
 - alcohol excess and
 - immunosuppression
 - how to check response?
 - testing for anti-HBs levels
 - ❖ testing for anti-HBs is **only recommended for:**
 - ➡ those at risk of occupational exposure (i.e. Healthcare workers)
 - and
 - ➡ patients with chronic kidney disease.
 - ❖ In these patients anti-HBs **should be checked 1-4 months after primary immunisation**
 - ❖ how to interpret anti-HBs levels? the table below shows

Anti-HBs level (mIU/ml)	Response
> 100	Indicates adequate response , no further testing required. Should still receive booster at 5 years
10 - 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	Non-responder . Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

Hepatitis B serology

HBsAg = ongoing infection, either acute or chronic if present > 6 months

anti-HBc = caught, i.e. negative if immunized

Interpreting hepatitis B serology: It is important to remember a few key facts:

- **surface antigen (HBsAg)**
 - is the first marker to appear and causes the production of anti-HBs
 - **appears in the serum 1 to 10 weeks following acute exposure, even before symptoms or (ALT) rise.**
 - normally implies acute disease (present for 1-6 months)
 - if present for > 6 months then this implies chronic disease (i.e. Infective)
 - In those who **recover** HBsAg will usually become undetectable **after 4 to 6 months.**
- **Anti-HBs**

- implies immunity (either exposure or immunisation).
- It is negative in chronic disease
- **Anti-HBc**
 - implies previous (or current) infection.
 - IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months.
 - ❖ Anti-HBc IgM is detectable between 6 and 32 weeks after exposure
 - IgG anti-HBc persists
- **HbeAg**
 - results from breakdown of core antigen from infected liver cells as is therefore a **marker of infectivity**
 - HBeAg is a marker of infectivity in all patients except those who have Hepatitis B virus (HBV) **pre-core mutant** or the core promoter mutant, because they do not synthesise HbeAg.
 - this is most commonly due to a stop-codon mutation at nucleotide 1896.
 - So the learning here is that **although the e antigen is negative, the patient may still be infective.**
- **previous immunisation:** anti-HBs positive, all others negative
- **previous hepatitis B (> 6 months ago), not a carrier:** anti-HBc positive, HBsAg negative
- **previous hepatitis B, now a carrier:** anti-HBc positive, HBsAg positive

IgM anti-HBc jointing HBV-DNA is most effective and most practicable in distinguishing Acute Hepatitis B from Chronic Hepatitis B With Acute Flare.

	Acute Infection	Chronic Carrier	Window Period	Complete Recovery	Immunized
HBs	+	+	-	-	-
Anti-HBs	-	-	-	+	+
Anti-HBc	+ (IgM)	+ (IgG)	+	+ (IgG)	-

HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

HBeAg-positive chronic hepatitis B and compensated liver disease	
1st line	Peginterferon alfa-2a (48-week course)
2nd line (if HBV DNA level has decreased by less than $2 \log_{10}$ IU/ml and/or if HBsAg is > 20,000 IU/ml after 24 weeks from starting 1st line)	Tenofovir. Or alternatively (if tenofovir not tolerable) Entecavir
3rd line (if HBV DNA remains detectable at 96 weeks)	If no history of lamivudine resistance: add lamivudine to tenofovir. If there is history of lamivudine resistance: add entecavir to tenofovir

HBeAg-negative chronic hepatitis B and compensated liver disease	
1st line	Peginterferon alfa-2a (48-week course)
2nd line (if HBV DNA level has decreased by less than $2 \log_{10}$ IU/ml and HBsAg has not decreased after 24 weeks from starting 1st line)	entecavir or tenofovir
3rd line (if HBV DNA remains detectable at 48 weeks)	switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil

Distinguish between acute HBV and a flare of chronic disease

- **originates from** an area of the world with a high prevalence of HBV infection
 - In areas of low HBV prevalence, such as the United Kingdom, a combination of HBsAg positivity and features of acute hepatitis usually indicates acute self-limiting hepatitis B infection.
 - In countries with high prevalence of hepatitis B the majority of infection is acquired vertically during childhood and leads to chronicity rather than acute infection.

- **Anti-HBc-IgM** is typically found in **acute HBV** infection; however it can be found in 10-15% of patients with chronic HBV. This is especially true when considering acute flares of chronic hepatitis.
 - The sensitivity and specificity for HBc-IgM to distinguish between acute HBV and a chronic flare has been reported as low as 77% and 70% respectively.
 - Using high titres to determine cut-offs (1:10,000 or greater) does improve this significantly however.
- **Flares of chronic HBV** are typically associated with **higher levels of HBV DNA and AFP** than acute self-limiting disease.
 - The alpha-fetoprotein is commonly elevated during acute hepatitis due to hepatic regeneration.
- **flares of chronic HBV** tend to be associated with less necroinflammation, and thus ALT tends to be as raised as in acute HBV, but **hepatic synthetic dysfunction is more common**.

Distinguish between patients who have recovered from hepatitis B and those immunized for it

- Although both patients who have recovered from hepatitis B and those immunized for it will test positive for antibody to hepatitis B surface antigen, only patients who have recovered from hepatitis B will be positive for IgG antibody to hepatitis B core antigen.

Assessment of liver disease in secondary specialist care for adults with chronic hepatitis B

- **The initial test** for liver disease in adults newly referred for assessment is → **transient elastography**
 - Transient elastography (FibroScan) is a new, non-invasive, rapid method allowing evaluation of liver fibrosis by measurement of liver stiffness.
 - Interpretation of transient elastography score
 - ≥ 11 kPa → antiviral treatment without a liver biopsy
 - between 6 and 10 kPa → liver biopsy to confirm the level of fibrosis
 - < 6 kPa → liver biopsy, if the:
 - ❖ Age < 30 years and HBV DNA > 2000 IU/ml and abnormal ALT (≥ 30 IU/L for males and ≥ 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.
 - < 6 kPa → NO liver biopsy, if the:
 - ❖ HBV DNA < 2000 IU/ml and normal ALT.
 - Offer annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Interpretation of transient elastography score in chronic HBV

(NICE guidelines 2017)		(PassOnExam)
$\geq 11 \text{ kPa}$	$6 - 10 \text{ kPa}$	$\leq 6 \text{ kPa}$
Offer antiviral treatment without a liver biopsy	Consider liver biopsy to confirm the level of fibrosis	<p>Offer liver biopsy only if:</p> <ol style="list-style-type: none"> 1) younger than 30 years and 2) have HBV DNA greater than 2000 IU/ml and 3) abnormal ALT ($\geq 30 \text{ IU/L}$ for males and $\geq 19 \text{ IU/L}$ for females) on 2 consecutive tests conducted 3 months apart

Management

- Acute HBV
 - the majority of patients will resolve spontaneously,
 - treatment with an oral anti-HBV agent is not necessary.

Patients who are positive for HBsAg for more than six months but are HBeAg negative, HBV DNA negative and have normal ALT do not require liver biopsy nor do they require antiviral therapy, but hepatitis B serology and ALT should be monitored annually.

- Chronic HBV
 - Indications of antiviral treatment in adults with chronic hepatitis B (NICE 2013)
 - age ≥ 30 years + HBV DNA $> 2000 \text{ IU/ml}$ + abnormal ALT ($\geq 30 \text{ IU/L}$ in males $\geq 19 \text{ IU/L}$ in females) on 2 consecutive tests conducted 3 months apart.
 - Age < 30 years + HBV DNA $> 2000 \text{ IU/ml}$ + abnormal ALT if there is:
 - evidence of necro-inflammation or fibrosis on liver **biopsy**
 - or a transient elastography score $> 6 \text{ kPa}$.**
 - HBV DNA $> 20,000 \text{ IU/ml}$ + abnormal ALT regardless of age or the extent of liver disease. (on 2 consecutive tests conducted 3 months apart)
 - cirrhosis + detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.
 - HBV DNA $> 2000 \text{ IU/ml}$ + evidence of necro-inflammation or fibrosis on liver biopsy.
 - with compensated liver disease
 - First-line \rightarrow 48-week course of pegylated **interferon-alpha**
 - $\rightarrow \downarrow \downarrow$ viral replication in up to 30% of chronic carriers.
 - better response** is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
 - Interferon alfa is **usually given short term and is not very effective in patients without an elevated ALT.**
 - stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than $2 \log_{10} \text{ IU/ml}$ and/or if HBsAg is greater than $20,000 \text{ IU/ml} \rightarrow 2^{\text{nd}}$ line
 - second-line \rightarrow **tenofovir** disoproxil (**nucleotide** analogue, reverse transcriptase inhibitor (NRTI)

- ❖ to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.
 - ❖ **would be of most value for long-term treatment of HBV**
 - ❖ Offer entecavir (**nucleoside analogue, reverse transcriptase inhibitor**) as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.
- ⇒ Entecavir is a pro-drug and requires phosphorylation to the triphosphate form before it becomes active.
- Nucleoside = Sugar + Base**
Nucleotide = Sugar + Base + Phosphate
- ❖ Lamivudine would be an alternative, although resistance develops commonly.
 - If HBV DNA remains detectable at 96 weeks:
 - ❖ If No history of lamivudine resistance → add lamivudine to tenofovir disoproxil.
 - ❖ With a history of lamivudine resistance → add entecavir to tenofovir disoproxil.
 - **with decompensated liver disease** (portal hypertension, bleeding varices, ascites and encephalopathy)
 - Do not offer peginterferon alfa-2a → **worsen hepatic decompensation**
 - **First-line → entecavir** (if there is no history of lamivudine resistance).
 - people with a history of lamivudine resistance → **tenofovir** disoproxil
 - When to consider stopping nucleoside or nucleotide analogue treatment?
 - without cirrhosis → 12 months after HBeAg seroconversion
 - with cirrhosis → do not stop
 - Co-infection with chronic hepatitis B and C → peginterferon alfa + ribavirin

Indications of starting antiviral treatment in chronic HBV	
(NICE guidelines 2017) (PassOnExam)	
1	HBV DNA > 2000 IU/ml + abnormal ALT + age > 30 years
2	HBV DNA > 2000 IU/ml + abnormal ALT + age < 30 years + necroinflammation or fibrosis on liver biopsy or a transient elastography score > 6 kPa.
3	HBV DNA > 20,000 IU/ml + abnormal ALT
4	cirrhosis + detectable HBV DNA
5	HBV DNA > 2000 IU/ml + necroinflammation or fibrosis on liver biopsy.

Chronic HBV with decompensated liver disease (NICE guidelines 2017)

Without a history of lamivudine resistance	entecavir
with a history of lamivudine resistance.	tenofovir disoproxil
Do not offer peginterferon alfa-2a to people with chronic HBV and decompensated liver disease.	

Hepatitis B and pregnancy

Risk of vertical transmission

- Without intervention the vertical transmission rate is around 20%,
- increases to 90% if the woman is positive for HBeAg.
- there is little evidence to suggest caesarean section reduces vertical transmission rates

Treatment

- Treatment of the baby:
 - babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a **complete course of vaccination + hepatitis B immunoglobulin**
 - Breastfeeding
 - hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)
 - they may continue antiviral treatment while they are breastfeeding.
- Treatment of the woman:
 - all pregnant women are offered screening for hepatitis B
 - Interferon is contraindicated
 - Offer **tenofovir** disoproxil to women with HBV DNA $> 10^7$ IU/ml in the third trimester **to reduce the risk of transmission of HBV to the baby.**
 - Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.
 - Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment

Hepatitis C

Hepatitis C - 80-85% become chronically infected

- Hepatitis C is likely to become a significant public health problem in the UK in the next decade.
- It is thought around 200,000 people are chronically infected with the virus.
- The most common route of transmission of hepatitis C in the United States is **intravenous drug use.**
- Zone I** of the liver is the zone first affected by hepatitis C infection.
- Hepatitis C virus genotypes**
 - There are 6 genotypes and more than 50 subtypes.
 - In England and Wales genotypes 1 and 3 account for more than 90% of all diagnosed infections.
 - In Japan, North America, and western Europe, the majority of infections are with genotypes **1, 2, and 3.**
 - Subtype **1a** is the most predominant genotype in the US,
 - subtype **1b** predominates in Asia and Europe.

- Genotype 4 is more prevalent in the middle east and in northern and central Africa.
- Genotypes 5 and 6 have been identified in South Africa and southeast Asia, respectively.
- Differences in subtype can result in subtle differences in response to antiviral therapies.
- **Hepatitis C genotype 3 is associated with insulin resistance and hepatic steatosis**
- **Genotype 3a is most strongly associated with a positive response to therapy**
- Genotypes 2 and 3 respond reasonably well to polyethylene glycol (PEG) interferon and ribavirin; genotypes 1 and 4 less well.

Risk factors

- **intravenous drug users**
- patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Pathophysiology

- hepatitis C is a RNA flavivirus
- incubation period: 6-9 weeks

The risk of Transmission:

- vertical transmission rate from mother to child is about **6%**.
- sexual intercourse is probably less than **5%** (**in contrast to hepatitis B, sexual transmission is uncommon**).
- needle stick injury is about **2%**
 - The risk is higher if there is coexistent HIV
- breast feeding is not contraindicated in mothers with hepatitis C

Features

- after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis
- **Chronic hepatitis C is a very common cause of minor elevations in serum transaminases. Other liver function tests can be entirely normal**

Diagnosis

- first → **Arrange an anti-HCV antibody test**
- HCV RNA tests are normally only ordered following a positive antibody test.

Associations

- **chronic hepatitis C associated with insulin resistance**
- insulin sensitising drugs may improve response to anti-viral therapy

Extrahepatic association of hepatitis C

- **Sjögren's syndrome**
- dermatologic
 - Porphyria cutanea tarda
 - Lichen planus
- hematologic
 - Cryoglobulinaemia (mixed essential type)
 - myeloma and monoclonal gammopathies
 - non-Hodgkin lymphoma,
 - immune thrombocytopenia,
 - autoimmune hemolytic anemia
- renal
 - membranoproliferative glomerulonephritis (more common)
 - Membranous glomerulonephritis (less common)

Complications

- chronic infection (80-85%)
- cirrhosis (20-30% of those with chronic disease)
- hepatocellular cancer
- **cryoglobulinaemia**

- porphyria cutanea tarda (PCT)

Management of chronic infection

- chronic hepatitis C is defined as infection that lasts for more than 6 months.
- Combination therapy
 - interferon-alfa and ribavirin
 - recommended for those with moderate-sever disease
 - ❖ (histological diagnosis of significant scarring and/or significant necrotic inflammation).
 - ❖ In cases where a liver biopsy carries a high risk (e.g. haemophilia), treatment can be initiated without histological confirmation.
 - currently a combination of pegylated interferon-alpha, ribavirin and a protease inhibitor (e.g. boceprevir, simprevir and telaprevir) is used
 - Genotype 1 hepatitis C have low rates of viral clearance with dual interferon and ribavirin therapy alone. **the recommended duration of therapy is 48 weeks**
 - **Ledipasvir/sofosbuvir**
 - modern anti-hepatitis C antivirals, which work via inhibition of NS5A and NS5B
 - can be used without ribavirin or interferon and hence lend themselves well to **treatment of hepatitis C in the context of mixed cryoglobulinaemia**.
 - Because they can be used without interferon, they do not increase renal inflammation and reduce the viral load, impacting positively on progression of renal impairment.
- Duration of treatment:
 - The effectiveness of antiviral treatment depends on the viral genotype; the response is generally better in people infected with genotypes 2 or 3 than in those infected with genotypes 1, 4, 5 or 6.
 - The recommended treatment duration is 24 weeks (genotypes 2 or 3) or 48 weeks (all other genotypes)
 - Both treatment-naïve (new) patients and those who have relapsed following initial response to interferon-alfa should be considered for 6 months of combination therapy.
- Cure rates:
 - cure rates are now approaching **90%**, including for some strains which have been previously difficult to treat
- The aim of treatment:
 - the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy
- Contra-indications:
 - **treatment is not generally recommended in those patients who consume large quantities of alcohol**, given the increased risk of liver damage.
- Treatment follow-up:
 - **the best way to assess response to treatment → Viral load**
- Relapses
 - relapse occurs in approximately 5% of people after 5 years.

Complications of treatment

- Ribavirin - side-effects:
 - haemolytic anaemia,
 - cough,
 - teratogenicity
 - Women should not become pregnant within 6 months of stopping ribavirin
- interferon alpha - side-effects:
 - flu-like symptoms,
 - fatigue,

- depression,
 - Peginterferon alfa 2a and 2b are contraindicated in severe psychiatric conditions.
- leukopenia, thrombocytopenia.
 - close monitoring of FBC is recommended, with initial review after 4 weeks of therapy.

Factors Associated with Accelerated Fibrosis Progression	
Host	Viral
Nonmodifiable <ul style="list-style-type: none"> • Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant 	<ul style="list-style-type: none"> • Genotype 3 infection • Coinfection with hepatitis B virus or HIV
Modifiable <ul style="list-style-type: none"> • Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance 	

MRCPUK-part-2-march-2018: A patient with H/O IV drug abuse, deteriorating renal function, spider naevi consistent with chronic liver disease, and the purpuric rash. Hepatitis C is positive. Is the most appropriate intervention?

→ **Ledipasvir/sofosbuvir**

- Δ hepatitis C with mixed cryoglobulinaemia
- do not increase renal impairment
- Ribavirin is less effective than NS5A and NS5B inhibition

Extrahepatic manifestations of chronic HCV infection: (PEN-DG)

- **Porphyria cutanea tarda**
- **Essential mixed cryoglobulinemia**
- **Non-Hodgkin's lymphoma**
- **Diabetes mellitus**
- **Glomerulonephritis**

Hepatitis D

Hepatitis D virus infection can only occur with coexistent hepatitis B infection.

Virology

- Hepatitis D is a single stranded **RNA delta virus**
- It is an incomplete RNA virus that requires hepatitis B surface antigen to complete its replication and transmission cycle.
- It is transmitted in a similar fashion to hepatitis B (exchange of bodily fluids) and patients may be infected with hepatitis B and hepatitis D at the same time.

Hepatitis D terminology:

- Co-infection:
 - Hepatitis B and Hepatitis D infection at the same time.
- **Superinfection:**
 - a hepatitis B surface antigen positive patient subsequently develops a hepatitis D infection.
 - Superinfection is associated with high risk of fulminant hepatitis, chronic hepatitis status and cirrhosis.

Diagnosis

- made via reverse polymerase chain reaction of hepatitis D RNA.

Treatment

- Interferon is currently used as treatment, but with a poor evidence base.

Hepatitis E

Severe hepatitis in a pregnant woman - think hepatitis E

Virology

- RNA hepevirus
- spread by the faecal-oral route
- incubation period: 3-8 weeks

Epidemiology

- common in Central and South-East Asia, North and West Africa, and in Mexico

Features

- causes a similar disease to hepatitis A,
- liver biopsy
 - **Marked cholestasis is a hallmark histological finding in hepatitis E virus infection.**
 - Other liver biopsy features of a hepatitis E patient shows patchy necrosis

Management

- supportive
- In general, hepatitis E is a self-limiting viral infection followed by recovery. **Prolonged viraemia or faecal shedding are unusual**
- a vaccine is currently in development, but is not yet in widespread use

Prognosis

- **does not result in a carrier state**
- **carries a significant mortality (about 20%) during pregnancy**
- does not cause chronic disease or an increased risk of hepatocellular cancer

Hepatitis histology

- hepatitis E → **Marked cholestasis**
- chronic hepatitis → Ground-glass hepatocytes (large hepatocytes containing surface antigen).
- Hepatitis A → Hepatocyte swelling, **monocyte infiltration**, and **Councilman bodies**
- hepatitis B → shows a **granular eosinophilic "ground glass"** appearance; cytotoxic T-cells mediate damage.
- hepatitis C → **Lymphoid** aggregates and a marked increase in the activation of sinusoidal lining cells
- hepatitis D → Microvesicular steatosis

Colorectal conditions

Colorectal cancer (CRC)

Endometrial cancer is the second most common association of HNPCC after colorectal cancer

Epidemiology

- Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths
- **Adenocarcinomas** comprise the vast majority (98%) of colon and rectal cancers
- **Location of cancer** (averages)
 - **rectal:** 40%
 - **sigmoid:** 30%
 - descending colon: 5%
 - transverse colon: 10%
 - ascending colon and caecum: 15%

Risk factors

- Colorectal adenomas
- Family history
- Hereditary syndromes
 - Familial adenomatous polyposis: 100% risk by age 40
 - Hereditary nonpolyposis colorectal cancer (HNPCC): 80% progress to CRC.
- Conditions associated with an increased risk of colorectal cancer
 - Inflammatory bowel disease (IBD): ulcerative colitis and Crohn's disease
 - Endocarditis and bacteremia due to *Streptococcus gallolyticus* is associated with CRC.
 - **Bovis in the Blood = Cancer in the Colon.**
 - Acromegaly
- Diet and lifestyle
 - Smoking
 - Alcohol consumption
 - Obesity
 - Processed meat; high-fat, low-fiber diets
- Older age

Protective factors

- Physical activity
- Diet rich in fiber and vegetables and lower in meat
- Long-term use of aspirin and other NSAIDs

Risks for colorectal carcinoma

Population risk	1 in 40
One first-degree relative more than 45 years old	1 in 17
One first-degree plus one second-degree relative	1 in 12
Two first-degree relatives	1 in 6
Familial polyposis	1 in 2

Which drugs may reduce the risk of colon cancer?

- ⇒ Vitamin D
- ⇒ Aspirin and NSAID

Types

- There are three types of colon cancer:
 1. Sporadic (95%)
 2. Hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
 3. Familial adenomatous polyposis (FAP, <1%)
 - **Sporadic colon cancer**
 - may be due to a series of genetic mutations. For example:
 - allelic loss of the **APC** gene → more than half of colon cancers
 - further gene abnormalities e.g.
 - ❖ activation of the **K-ras** oncogene,
 - ⇒ **RAS** is an intracellular signaling molecular that acts downstream of the epidermal growth factor receptor (EGFR) to stimulate cell division and growth
 - ⇒ present in 30-50% of colorectal cancers
 - ⇒ associated with failure to respond to EGFR based therapies such as the monoclonal antibodies **Cetuximab** and Panitumumab.
 - ⇒ **The presence of a KRAS mutation is a contraindication to treatment with these agents.**
 - ⇒ **Which histopathological subtypes is essential for successful treatment with cetuximab?**
 - ⇒ **K-Ras wild type**
 - ⇒ Cetuximab is licensed by NICE in metastatic colorectal cancer for K-Ras wild type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
 - ⇒ always given in combination with chemotherapy
 - ⇒ major side effect → acne type rash.
 - ❖ deletion of **p53** and **DCC** tumour suppressor genes lead to invasive carcinoma
 - The presence of a KRAS mutation is a contraindication to treatment with these agents.
 - Which histopathological subtypes is essential for successful treatment with cetuximab?
 - ⇒ K-Ras wild type
 - ⇒ Cetuximab is licensed by NICE in metastatic colorectal cancer for K-Ras wild type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
 - ⇒ always given in combination with chemotherapy
 - ⇒ major side effect → acne type rash.
- **Hereditary non-polyposis colorectal carcinoma (HNPCC)**
 - also known as (Lynch syndrome)
 - autosomal dominant mutation of **DNA mismatch repair genes** with **microsatellite instability**.
 - most common form of inherited colon cancer.
 - Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive.
 - The most common genes involved are:
 - **MSH2** (60% of cases) **the function of this gene → DNA mismatch repair**
 - **MLH1** (30%)

- Patients with HNPCC are also at a higher risk of other cancers, with **endometrial cancer** being the next most common association, after colon cancer.
- The **Amsterdam criteria** are sometimes used to aid diagnosis:
 - at least **3** family members with colon cancer
 - the cases span at least **two** generations
 - at least **one** case diagnosed before the age of 50 years
- **Torre-Muir syndrome**, a type of hereditary nonpolyposis colorectal cancer (HNPCC), is **characterized by sebaceous adenomas**.
 - These lesions are usually present on the face, near the eyes and forehead and appear as yellow papules/nodules.



sebaceous adenomas associated with **Torre-Muir syndrome** a type of HNPCC

- Polyp cancers represent T1 disease and have been sub-classified.
- **The Haggitt system is used for pedunculated polyps and describes the deepest invasion of carcinoma cells within the polyp:**
 - Level 1 is limited to the head of the polyp
 - Level 2 is extension into the neck
 - Level 3 is invasion of the stalk, and
 - Level 4 is invasion beyond the stalk but above the muscularis propria.
- The Kicuchi system describes the depth of invasion in sessile polyp cancers.

• **Familial adenomatous polyposis (FAP)**

- FAP is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years.
- Patients inevitably develop carcinoma.
- It is due to a mutation in a tumour suppressor gene called adenomatous polyposis coli gene (**APC**), located on chromosome 5.
- Genetic testing can be done by analysing DNA from a patients white blood cells.
- Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.
- Patients with FAP are also at risk from duodenal tumours.
 - Oesophago-gastroduo-denoscopy (OGD) surveillance is recommended.
- A variant of FAP called **Gardner's syndrome** can also feature:
 - osteomas of the skull and mandible,
 - retinal pigmentation,
 - thyroid carcinoma
 - and epidermoid cysts on the skin

Carcinoembryonic antigen may be used to monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease

Features

- Colorectal cancer on the left side of the body typically presents with bright red rectal bleeding.
- Colorectal cancer on the right side of the body typically presents with iron deficiency anaemia and melena.
 - Colorectal cancer is the most common cause of iron deficiency anaemia in postmenopausal women or in men aged 50 or older.
- In the descending colon, colorectal cancer presents as colicky pain and hematochezia.
- Colorectal cancer on the left side of the body typically presents with obstruction.
- In the ascending colon, colorectal cancer presents as an exophytic mass with iron deficiency anaemia and weight loss.

Colorectal cancer: screening

Colorectal cancer screening - PPV of FOB = 5 - 15%

Overview

- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening
- eligible patients are sent faecal occult blood (FOB) tests through the post
- patients with a single positive results are offered a colonoscopy
- An uncertain or unclear result will result in a request to repeat up to a maximum of two further tests. Persistent unclear results require further investigation with consideration of colonoscopy.
- A negative faecal occult blood does not exclude an underlying diagnosis of colorectal cancer.
- Any patient with symptoms, irrespective of a negative faecal occult blood test, should be investigated for the possibility of underlying bowel cancer as appropriate.

At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

Streptococcus bovis bacteraemia and endocarditis is associated with **colon cancer** (in around half of cases). All patients should, therefore, undergo **colonoscopy**

Colorectal cancer: referral guidelines

NICE updated their referral guidelines in 2015. The following patients should be **referred urgently** (i.e. within 2 weeks) to colorectal services for investigation:

- patients ≥ 40 years with unexplained weight loss **AND** abdominal pain
- patients ≥ 50 years with unexplained rectal bleeding
- patients ≥ 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

An urgent referral (within 2 weeks) should be 'considered' if:

- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding **AND** any of the following unexplained symptoms/findings:

- abdominal pain
- change in bowel habit
- weight loss
- iron deficiency anaemia

Faecal Occult Blood Testing (FOBT)

This was one of the main changes in 2015. Remember that the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening.

In addition FOBT should be offered to:

- patients ≥ 50 years with unexplained abdominal pain **OR** weight loss
- patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
- patients ≥ 60 years who have anaemia even in the absence of iron deficiency

Follow-up period for adenomatous colonic polyps

- The British Society of Gastroenterology (BSG) guidelines on the follow-up period for adenomatous colonic polyps includes:
 - 5-year interval is indicated for low-risk patients
 - (one to two adenomas that are both small, ie < 1 cm)
 - 3-year follow up is recommended for medium-risk patients
 - (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)
 - 1-year follow-up is recommended for high-risk patients**
 - (five or more small adenomas or more than three with at least one at or above 1 cm in size).**

guidance for colonoscopic surveillance

Risk profile	Definition	Surveillance interval
low risk	1 to 2 adenomas that are both small, ie < 1 cm)	5-year
intermediate risk	(3 to 4 adenomas or 1 or 2 adenomas where one adenoma ≥ 1 cm)	3-year
high risk	≥ 5 small adenomas or > 3 with at least one at or above 1 cm in size).	1-year

Post polypectomy follow-up:

- Polyps that are ≤ 10 mm in size can be removed in a single go with biopsy forceps or snares.
- The need for repeat colonoscopy following polypectomy applies to large sessile adenomas removed piecemeal (that is, multiple snares required).
 - Small areas of residual polyp can then be treated endoscopically, with a further check for complete eradication in two to three months.
 - India ink tattooing aids recognition of the polypectomy site at follow up.
 - If extensive residual polyp is seen, surgical resection needs to be considered.
 - If there is complete healing of the polypectomy site, then there should be a colonoscopy at one year, to check for missed synchronous polyps, before returning to three yearly surveillance.

Stages

- The stages of colorectal cancer are based on the TNM staging system by the American Joint Committee for Cancer (AJCC).

TNM Staging	Corresponding Duke's Classification stage	Description
I	A	Tumor confined to intestinal wall (confined to the muscularis propria)
II	B	Infiltration into the visceral peritoneum, adjacent organs, or perirectal tissue
III	C	Lymph node involvement
IV	D	Distant metastases

AJCCC (American Joint Committee) Staging of Colorectal Cancer

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

Residual tumour (R) classification exists in addition to the TNM classification and the histological grade (G):

- RX presence of residual tumour cannot be assessed
- R0 no residual tumour
- **R1 microscopic residual tumour**
- R2 macroscopic residual tumour.

Management: depends upon the stage.

- **Stage I (Duke's A):**
 - Definition
 - Carcinoma in situ limited to mucosa or submucosa (T1, N0, M0).
 - Management
 - surgery to remove the tumour.
 - Additional treatments are not usually needed.
 - **Follow-up**
 - **Colonoscopy - indicated on an annual basis for the first 2 years, then this should be done 3-yearly**
 - Faecal occult blood - should be tested 6-monthly for the first 4 years and then once yearly
 - Carcinoembryonic antigen (CEA) - can be used to monitor for recurrence if it is elevated initially
 - Prognosis
 - the five-year survival rate exceeds 90%.
- **Stage II (Duke's B):**
 - Definition
 - Cancer that extends into the muscularis (B1), into or through the serosa (B2).
 - **Management**
 - **surgical removal of the tumour followed by radiotherapy.**
 - **Radiotherapy has been shown to reduce the rate of recurrence.**
 - The role of adjuvant chemotherapy is less clear in Duke's B than in Duke's C (see below).
 - chemotherapy is not typically given as standard.
 - Prognosis
 - the five-year survival rate is 70% - 80%
- **Stage III (Duke's C):**
 - Definition
 - Cancer that extends to regional lymph nodes (T1-4, N1, M0).
 - **Management**
 - surgery to remove the tumour,
 - **chemotherapy** with 5-FU and leucovorin
 - in some patients radiotherapy may also be needed (especially if the tumour is large and invading the tissue surrounding the colon).

- ❖ There is no role for adjuvant radiation therapy in patients with colon cancer.
- ❖ Adjuvant radiotherapy is useful in patients with rectal cancer in whom the risk for local recurrence is greater.
- Prognosis
 - The five-year survival rate is less than 60% (**40 - 50%**)
- Stage IV (Duke's D):
 - Definition
 - Cancer that has **metastasised** to distant sites (T1-4, N1-3, M1).
 - Management
 - Surgery to remove the tumour or to bypass an obstructing tumour,
 - ❖ **Metastatic lesion resection:**
 - ⇒ Colorectal carcinoma is one of the only oncological diseases where the presence of a metastatic deposit can be treated with curative intent.
 - ⇒ A solitary liver lesion should be surgically resected.
 - ⇒ In fact, the purpose of following patients with CEA is to identify patients with solitary metastatic lesions amenable to surgical resection.
 - palliative chemotherapy and/or radiotherapy for symptom relief;
 - ❖ Trans-arterial chemoembolization & Radiofrequency ablation are used as palliative procedures when the lesions are too numerous or large to resect.
 - use of new agents such as cetumixab (a recombinant human/mouse chimeric epidermal growth factor inhibitor) or bevacizumab (a recombinant human anti-vascular epidermal growth factor (VEGF) antibody).
 - Prognosis
 - Five-year survival is approximately 5%.

Radiation therapy is not a standard modality in the treatment of colon cancers

MRCPUK-part-1-January 2015 exam: A man has hereditary non-polyposis colorectal cancer secondary to a mutation in the MSH2 gene. Which other cancers his daughter will most be at risk from? **Endometrial cancer**

Dysplastic colonic polyps

The British Society of Gastroenterology (BSG) published guidelines on the follow-up period for dysplastic colonic polyps in 2002:

- 5-year interval is indicated for low-risk patients (one to two adenomas that are both small, ie <1 cm)
- **3-year follow up is recommended for medium-risk patients (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)**
- 1-year follow-up is recommended for high-risk patients (five or more small adenomas or more than three with at least one at or above 1 cm in size).

Polyp characteristics: associated with a **higher risk of malignant change:**

- **polyps greater than 1.5 cm, which are sessile or flat**
- Histology demonstrating severe dysplasia, predominantly villous architecture or squamous metaplasia

Peutz-Jeghers syndrome

- Peutz-Jeghers syndrome is an **autosomal dominant** condition
- Characterised by:
 - numerous hamartomatous polyps in the gastrointestinal tract.
 - pigmented freckles on the lips, face, palms and soles.
- Around 50% of patients will have died from a gastrointestinal tract cancer by the age of 60 years.
- incidence of 1:50,000 live births.

Genetics

- autosomal dominant
- **responsible gene encodes serine threonine kinase LKB1 or STK11**

Features

- hamartomatous polyps in GI tract (mainly small bowel)
- pigmented lesions on lips, oral mucosa, face, palms and soles
- intestinal obstruction e.g. intussusception
- gastrointestinal bleeding

Management

- conservative unless complications develop
- **colonoscopy every two years** after the age of 25 for evaluation of the presence of polyps and polypectomy.

Cowden's syndrome is an inherited condition resulting from a defect in the PTEN tumour suppressor gene. Hamartomatous polyps of the GI tract are often the first manifestation along with characteristic muco-cutaneous lesions such as oral mucosal papillomas, palmoplantar keratoses and trichilemmomas (benign tumours of hair follicles). The syndrome is important to diagnose early because of the high risk of malignancy, particularly of the breast and thyroid. Thyroid dysfunction is common even in the absence of cancer.

Familial juvenile polyposis also results in multiple polyps in the colon identical to those found in Cowden's syndrome but the associated oral lesions are absent.

Capsule endoscopy

- Capsule endoscopy is currently used in UK to identify the source of occult gastrointestinal bleeding when an OGD and colonoscopy and failed to show a cause.
- It is particularly useful for identifying pathology in the ileum.

Pseudomyxoma peritonei

- Pseudomyxoma peritonei is a rare mucinous tumour most commonly arising from the appendix.
- The disease is characterised by the accumulation of large amounts of mucinous material in the abdominal cavity.
- It is rare, with an incidence of 1-2/1,000,000 per year

Treatment

- usually surgical and consists of cytoreductive surgery (and often peritonectomy) combined with intra-peritoneal chemotherapy with mitomycin C.

Villous adenoma

Diarrhoea + hypokalaemia → villous adenoma

Overview

- Villous adenomas are colonic polyps with the potential for malignant transformation.
- They **characteristically secrete large amounts of mucus**, potentially resulting in electrolyte disturbances.
- often in the rectum and rectosigmoid.

Features: The vast majority are asymptomatic. Possible features:

- non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

Carcinoid tumours

Carcinoid syndrome

Left-sided valvular lesions are not observed in carcinoid syndrome because the lung metabolizes serotonin (5-HT). Remember the symptoms of carcinoid syndrome as "Be FDR" : Bronchospasm, Flushing, Diarrhoea, and Right-sided valvular lesions.

- Carcinoid syndrome occurs in only 5% of patients with carcinoid tumour
- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- **The most common originating sites of carcinoid is the small bowel, particularly the ileum;**
 - Around 55% of all carcinoid tumours arise from the GI tract,
 - the most common site of origin is the small bowel (45% of those arising within the GI tract).
 - Within the small bowel, the most common site of origin is the distal ileum.
- **carcinoid tumors** are the **most common** malignancy of the appendix.
- 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver
- the caecal-appendiceal region is the commonest location for a carcinoid primary.
- These tumours are slow growing

Features

- flushing (often earliest symptom) **the most common feature** (occurring in 85% of patients) .often provoked by alcohol.
- diarrhoea (75%)and abdominal cramps in the majority of patients.
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
Cardiac abnormalities develop in 50% of patients and consist of tricuspid regurgitation or pulmonary stenosis.
- **Fibrosis of the heart valves is a recognised feature**
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, **Cushing's syndrome**
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation

- **urinary 5-HIAA**
 - 24-hour urine collection for 5-hydroxy-indole-acetic acid (5-HIAA) - excretion is greater than 0.3 mmol.
- plasma chromogranin A
- Biopsy of the lesion show cells staining for chromogranin A on histology → consistent with a neuroendocrine tumour
- **Octreotide scanning** is positive in up to 85% of cases, however a negative scan does not rule out liver metastases.
- **The liver should be imaged by high resolution CT with fine cuts or by USS.**
 - The sensitivity of USS may be increased by the use of microbubble contrast medium (levovist), which is available at some centres.
- **Fasting gut hormones** should be measured as neuroendocrine tumours may co-secrete other hormones such as VIP, which may contribute to the diarrhoea.

Management

- somatostatin analogues e.g. octreotide
 - Octreotide is less likely to be effective **if octreotide scan negative**, but other analogues such as **Lanreotide** have different affinities for different somatostatin receptor subtypes, which may be present on the tumour.
- diarrhoea: cyproheptadine may help
- Other Symptomatic management may include hepatic embolisation, hepatic chemoembolisation and chemotherapy.
- echocardiography to screen for carcinoid heart disease (right-sided valvular lesions).

Prognosis

- generally good.

Gorlin syndrome causes:

1. gastric hamartomas,
2. basal cell carcinomas,
3. mandibular bone cysts,
4. intracranial calcification,
5. pits on the palms and soles.

Diverticular disease

- Diverticulosis → presence of diverticula which are asymptomatic.
- Diverticular disease → diverticula associated with symptoms → **typically painless bleeding**
- **Diverticulitis** → diverticular inflammation (fever, tachycardia) with or without localised symptoms and signs → **painful, No bleeding**

Overview

- Diverticula are bulging sacs that push outward on the colon wall. can occur anywhere in the colon, but **most commonly form near the end of the colon on the left side (sigmoid colon)**.
- A diverticulum consists of a herniation of mucosa through the thickened colonic muscle.
- most common in industrialized countries where diets are lower in fiber and higher in processed carbohydrates.
- **Diverticular disease is by far the commonest cause of severe fresh bleeding per rectum.**

Causes: It is believed diverticula form when there is increased pressure in the colon

- Diets low in **fiber** cause hard stool and slower "transit time" through the colon, increasing pressure.
- repeated straining during bowel movements also increases pressure.

- Drugs: diuretics, and narcotic pain relievers, can increase constipation and increase pressure in the colon.

Epidemiology

- Approximately 50% of all people have diverticula by the time they are 50 years of age, and nearly 70% of all people have diverticula by the time they are 80 years of age
- Diverticular disease is rare in people younger than 40 years**
- Disease is more virulent in young patients, with a high risk of recurrences or complications.**
- The most common fistula is colovesicular and then colovaginal fistulas.**

Risk factors

- The main risk factors are age over 50 years and low dietary fibre.
- Obesity is an important risk factor in young people.
- Complicated diverticular disease has an increased frequency in:
 - patients who smoke,
 - use non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol,
 - and those who are obese and have low-fibre diets

Features

- Approximately 75% of people with diverticula have asymptomatic diverticulosis
- Pain is generally exacerbated by eating and diminished with defecation or flatus.
- Other symptoms, such as bloating, constipation or rectal bleeding, may also occur.
- Diverticulitis**
 - Mechanism**
 - may occur if some faeces get trapped and stagnate in a diverticulum, bacteria then multiply and cause infection.
 - Site of the pain**
 - Generally, presents with left lower quadrant pain.
 - Asian patients have predominantly right-sided diverticula and will usually present with right lower quadrant pain.
 - Pain may be intermittent or constant and may be associated with a change in bowel habits.
 - Fever and tachycardia are present in most patients
 - One third of patients who develop diverticulitis will develop further complications (perforation, abscess, fistula, stricture/obstruction)

Diagnosis: → colonoscopy

- sensitivities and specificities for CT are significantly better than for contrast enemas.
- When an abscess is suspected, CT scanning is the best modality for making the diagnosis and following its course.
- Because of risk of perforation, endoscopy is generally avoided in initial assessment of the patient with acute diverticulitis.
- Haemorrhage:**
 - Flexible sigmoidoscopy is an appropriate initial approach to rule out an obvious rectosigmoid lesion.
 - If no cause is identified, further assessment with non-invasive (nuclear scintigraphy) or invasive (angiography, colonoscopy) techniques can be undertaken in an attempt to localise and treat the bleeding source.

Management

- asymptomatic**
 - No treatment or follow-up needs
 - there may be a prophylactic benefit of a high-fibre diet.
 - The risk of perforation may be increased by the use of NSAIDs and long-term use of opioids.
 - Calcium-channel blockers are associated with a reduction in diverticular perforation but

there is insufficient evidence to recommend their use.

- **Diverticulitis**

- Broad-spectrum antibiotics to cover anaerobes and Gram-negative rods - eg, co-amoxiclav or a combination of ciprofloxacin and metronidazole (if allergic to penicillin).
- Paracetamol should be used for pain.
- Recommend clear liquids only; gradually reintroduce solid food as symptoms improve over 2-3 days.
- Review within 48 hours, or sooner if symptoms deteriorate. Hospital admission should be arranged if symptoms persist or deteriorate.
- Mesalazine has been shown to be more effective in improving the severity of symptoms, bowel habit, and in preventing symptomatic recurrence of diverticulitis, than antibiotics alone
- Most patients admitted with acute diverticulitis will respond to conservative treatment, but 15-30% will need surgery.
- The indications for surgery are:
 - Purulent or faecal peritonitis.
 - Uncontrolled sepsis.
 - Fistula.
 - Obstruction.
 - Inability to exclude carcinoma.
- CT-guided percutaneous drainage of abdominal abscesses is now used in preference to surgery when feasible.
- Risk of recurrent symptoms after an attack of acute diverticulitis is about one in three.
- Recurrent attacks are less likely to respond to medical treatment and they have a high mortality rate.

- **Haemorrhage**

- Haemorrhage ceases spontaneously in 70-80% of patients.. Subsequent colonoscopy should be performed to establish the source of the bleeding and to exclude neoplasia.
- Intra-arterial vasopressin at angiography can control haemorrhage in more than 90% of patients. The benefit is usually only temporary but may allow time to prepare the patient adequately for surgery.
- Angiographic embolisation of very distal bleeding branches is also effective and safe.
- Surgery in lower gastrointestinal bleeding is usually reserved until endoscopic or angiographic treatments fail.
- Segmental resection is most usually done if the bleeding site is clearly identified from a therapeutically unsuccessful angiographic or endoscopic procedure. In patients with persistent bleeding and no angiographic or endoscopic identification of a definite bleeding site, subtotal colectomy may be required.
- The chance of a third bleeding episode can be as high as 50%, so many authorities recommend surgical resection after a second bleeding episode.

- **Prognosis**

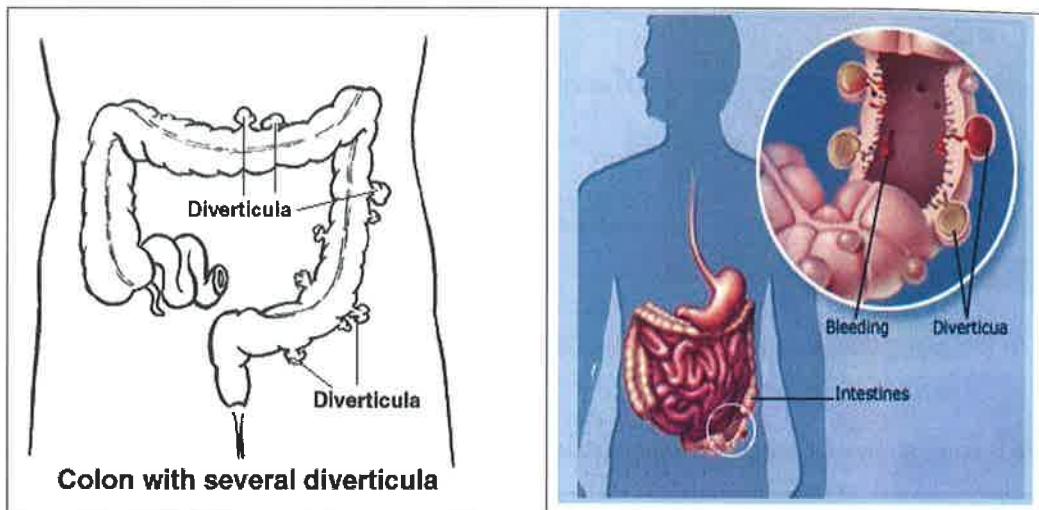
- Approximately three quarters of patients with anatomical diverticulosis remain asymptomatic.
- Most complications of diverticulitis are associated with the initial attack, after which the disease tends to run a benign course.
- Mortality and morbidity are related to complications of diverticulosis, which are mainly diverticulitis and lower gastrointestinal bleeding. These occur in 10-20% of patients with diverticulosis during their lifetime.

- **Prevention**

- Dietary fibre may prevent development of diverticular disease but, once symptoms develop, the benefit from fibre supplementation is unclear.

- Physical exercise has also been shown to help prevent the development of diverticular disease.

The presence of mixed Gram-negative and/or anaerobic organisms is highly suggestive of secondary peritonitis due to a perforated large bowel or appendicitis.



Meckel's diverticulum

- Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct.
- It is normally located in the terminal ileum within ~60 cm of the ileocaecal valve and it averages 6 cm in length.
- the diverticulum is frequently located near the ileocecal valve in the small bowel.
- In Meckel diverticulum, there is persistence of the vitelline duct, an embryologic structure necessary for receiving nutrients. When this structure persists, the Meckel diverticulum may contain ectopic tissue, such as the acid-secreting gastric mucosa
- Although it occurs much more commonly in children it is an important differential consideration for gastrointestinal bleed in adults.
- also quite common in Down's syndrome.

Features

- About 50% of these contain ectopic gastric mucosa, commonly leading to clinical presentations of peptic ulceration and haemorrhage.
- Other complications of Meckel's diverticulum include
 - Diverticulitis
 - Intussusception
 - Perforation
 - Obstruction.

Diagnosis

- **Technetium^{99m} pertechnetate scintigraphy**
 - Tc-99m pertechnetate accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.



The picture shows an excised Meckel's diverticulum.

Meckel diverticula: rule of 2's

- occurs in **2%** of the population,
- commonly located within **2-feet** of the ileocecal valve,
- **2-inches** in length,
- **commonly occurs before the age of two.**

Intussusception

- Hirschsprung disease is aganglionosis of colon, causing obstruction. It usually presents in neonatal period.
- common cause of intestinal obstruction in children in general and in Down's syndrome in particular.
- There is a classic triad in intussusception of:
 1. acute abdominal pain,
 2. currant jelly stool and
 3. palpable abdominal mass, usually in right iliac fossa.

Aorto-enteric fistulae (AEF)

- known to occur following endovascular repair of abdominal aortic aneurysms (AAA) and secondary to aortic grafting of any kind, presumably because of mechanical forces of dislodged or migrating devices.
- May occur after aorto-bifemoral graft as treatment for peripheral vascular disease.
- **Strongly positive faecal occult blood (FOB) suggests significant GI haemorrhage in spite of normal upper GI endoscopy.**

Angiodysplasia

Angiodysplasia is associated with aortic stenosis

Definition

- Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.

Epidemiology

- generally seen in elderly patients (≥ 60 years).
- the most common vascular lesion of the gastrointestinal tract
- Second most common cause of lower GI bleeding in patients >60 years of age.

Location of lesion

- the most common site:
 - predominantly located in the proximal colon (77%) (**located most commonly in the ascending colon and caecum**)

Associations

- associated with aortic stenosis,
- In Heyde's syndrome, a syndrome of aortic valve stenosis and colonic angiodysplasia, a possible mechanism is the induction of von Willebrand's disease type IIA by the valvular stenosis.

Features

- may be asymptomatic,
- gastrointestinal bleeding (estimated incidence of active bleeding being about 10% of affected cases).

Diagnosis

- Colonoscopy
 - If the initial colonoscopy is negative, the most appropriate next investigation is → **repeat colonoscopy**.
 - Pick up of colonic angiodysplasia, (sensitivity), is only 80% by colonoscopy however, this is why it is advisable to move to a **repeat colonoscopy**.
 - Once two colonoscopies have taken place, moving to **capsule endoscopy is a usual next step**.
- The repeated negative upper and lower GI endoscopies suggest that **small bowel angiodysplasia** may be the cause, in an area which is difficult to image via conventional endoscopy. **In this situation capsule endoscopy has a higher yield and would be the appropriate next step.**
 - The pathophysiology of angiodysplasia in this situation isn't known, although it may be due to changes in pressure within the mesenteric venous plexus, as the condition often resolves once the valve is treated.
- mesenteric angiography if acutely bleeding

Management

- Bleeding stops spontaneously in $>90\%$ of cases.
- endoscopic cauterity or argon plasma coagulation
- antifibrinolytics e.g. Tranexamic acid
- oestrogens may also be used

Heyde's syndrome → gastrointestinal bleeding from angiodysplasia in the presence of aortic stenosis.

Angiodysplasia of the gastrointestinal tract

- **Features:**
 - can be silent or cause bleeding
 - most often detected in patients older than 60 years
 - typically present with occult blood loss
- **Most common site → Right colon**
- **Associated conditions:**
 1. end-stage kidney disease
 2. von Willebrand disease
 3. aortic stenosis
- **Diagnosis → endoscopy**
- **Treatment :**
 - if causes bleeding e.g. iron deficiency anaemia → **endoscopic therapy**
 - if found accidentally → **do not treat**

Anal fissure

Anal fissure - topical glyceryl trinitrate

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal. If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks. Around 90% of anal fissures occur on the posterior midline

Management of an acute anal fissure (< 6 weeks)

- dietary advice: high-fibre diet with high fluid intake
- bulk-forming laxatives are first line - if not tolerated then lactulose should be tried
- lubricants such as petroleum jelly may be tried before defecation
- topical anaesthetics
- analgesia topical steroids do not provide significant relief

Management of a chronic anal fissure (> 6 weeks)

- the above techniques should be continued
- topical glyceryl trinitrate (GTN) is first line treatment for a chronic anal fissure
- if topical GTN is not effective after 8 weeks then secondary referral should be considered for surgery or botulinum toxin

Anal fistula

- Goodsall's rule describes the likely location of the internal opening of a fistula-in-ano based on its external opening.
 - If the external opening is anterior to the 9-3 o'clock plane, then the fistula forms a direct radial tract and opens **internally at the same clock face point**.
 - If the external opening is posterior to this line then it will generally follow a more circuitous route opening at 6 o'clock.

Inflammatory bowel disease (IBD)

Crohn's disease

Definition

- Crohn's disease is a form of inflammatory bowel disease.
- Commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

Epidemiology

- IBD is more common in white people than in African-Caribbean people or those of Asian origin.
- has a lower incidence in non-white races; people of Jewish origin are more prone to inflammatory bowel disease than non-Jews; and **Ashkenazi Jews are at higher risk than Sephardic Jews.**
- slightly more common in females (male to female ratio is 1:1.2)
- typically presents in late adolescence or early adulthood. The highest incidence of Crohn's disease in the 15–30 year age
- The ratio of Crohn's disease to ulcerative colitis varies between adults and children. In adults, the ratio of Crohn's disease to ulcerative colitis is 2:3, while the ratio in children is much higher (2.3:1).

Pathology

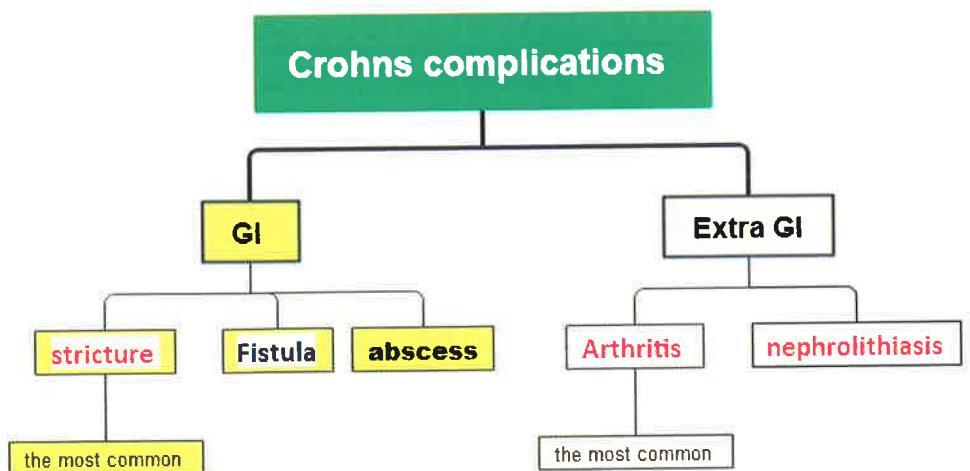
- cause is unknown but there is a **strong genetic susceptibility**
- inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Features

- non-specific symptoms such as weight loss and lethargy
- diarrhoea:
 - the most prominent symptom in adults.
 - Crohn's colitis may cause bloody diarrhea.
 - Nocturnal diarrhoea is indicative of organic disease and is typical of a Crohn's disease flare.
- abdominal pain:
 - the most prominent symptom in children.
 - often in the lower right quadrant
- perianal disease: e.g. Skin tags or ulcers
 - if the patient has sepsis secondary to a perianal abscess, due to underlying Crohn's disease. The priority is to delineate the extent of the abscess and potential fistula by an urgent pelvis MRI before draining it via Examination under anaesthesia (EUA).
 - **the next best investigation to guide further management → Immediate MRI pelvis**
 - CT is inferior to MRI in detecting perianal pathology
- **An abdominal mass is often palpable in the presence of small bowel disease which can lead to Vitamin K malabsorption.**
- extra-intestinal features are more common in patients with colitis or perianal disease

Extra-intestinal manifestations of **IBD** → **A PIE SAC:**

- **A**phthous ulcers
- **P**yoderma gangrenosum
- **I**ritis
- **E**rythema nodosum
- **S**clerosing cholangitis
- **A**rthritis
- **C**lubbing of fingertips



Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

	Common to both Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
Related to disease activity	<ul style="list-style-type: none"> Aphthous oral ulcers Arthritis: pauciarticular, asymmetric Erythema nodosum Episcleritis Osteoporosis 	<ul style="list-style-type: none"> • the most common extra-intestinal feature in both CD and UC <ul style="list-style-type: none"> ➢ Arthritis • more common in CD <ul style="list-style-type: none"> ➢ Episcleritis ➢ Interstitial lung disease
Unrelated to disease activity	<ul style="list-style-type: none"> Arthritis: polyarticular, symmetric Uveitis Pyoderma gangrenosum Clubbing Primary sclerosing cholangitis 	<ul style="list-style-type: none"> • more common in UC <ul style="list-style-type: none"> ➢ Primary sclerosing cholangitis ➢ Uveitis

Smoking in IBD

- Smoking associated with earlier age of onset of disease and more frequent need for immunosuppression **among women** with Crohn's disease **but not men**.
- Smoking cessation is associated with an increased risk of ulcerative colitis.

Investigation

Bloods

- **C-reactive protein correlates well with disease activity**

Faecal calprotectin

- **Calprotectin** is a protein belonging to the S100 family and occurring in large amounts in neutrophil granulocytes
- Increased faecal calprotectin indicates increased migration of neutrophils to intestinal mucosa
- ↑↑ Calprotectin in stool is the direct consequence of neutrophil degranulation due to mucosal damage.

- **The logical next step in excluding inflammatory bowel disease**
- Recommended by NICE to distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases, such as irritable bowel syndrome in people presenting with any of the following lower gastrointestinal symptoms for at least 6 weeks: abdominal pain or discomfort, bloating, or change in bowel habit.
- ↑↑ when there is any intestinal inflammation → Crohn's disease or ulcerative colitis.
- normal value is approximately 25 mg/kg.
- in IBS values may be slightly higher than those of healthy subjects , but in IBD significantly ↑↑
- **Calprotectin** exceeding 50 mg/kg should be considered positive → do endoscopy to confirm IBD
- Non-invasive screen for IBD
- Normal faecal calprotectin → makes IBD unlikely
- ↑↑ faecal calprotectin → drive further imaging

Stool culture

- **should be performed first**
- Even if the presentation is highly suggestive of inflammatory bowel disease. However, it is unforgivable not to do a stool culture in a case of diarrhoea and that should be the starting point before considering the other investigations

Endoscopy

- colonoscopy is the investigation of choice
 - Crohn's disease most typically affects the terminal ileum and proximal colon, therefore **the investigation of choice would be ileo-colonoscopy**.
 - **A flexible sigmoidoscopy may not identify any areas of disease.**
- features suggest of Crohn's include deep ulcers, skip lesions

Histology

- inflammation in all layers from mucosa to serosa
- goblet cells
- granulomas
- **Patchy inflammation**

Small bowel enema

- high sensitivity and specificity for examination of the terminal ileum
- strictures: 'Kantor's string sign'
- proximal bowel dilation
- 'rose thorn' ulcers
- fistulae



Barium study is shown from a patient with worsening Crohn's disease. Long segment of narrowed terminal ileum in a 'string like' configuration in keeping with a long stricture segment. Termed '**Kantor's string sign**'.



The picture shows the typical '**cobblestone mucosa**' of Crohn's disease with isolated areas of normal mucosa surrounded by deep ulceration (ulcerative colitis does not result in such deep ulceration).

Thumb printing

- thumb printing is a predominantly radiological finding due to inflamed, oedematous folds of bowel as a result of mucosal oedema caused by inflammation. Thumb printing may be seen in either Crohn's disease or ulcerative colitis.

Management (NICE 2012)

	CD	UC
Inducing remission	<p>1st line →</p> <ul style="list-style-type: none"> • conventional glucocorticosteroids (oral, topical or I.V.) , OR • Budesonide (less effective and less side effect): (for mild to moderate + distal ileal, ileocaecal or right-sided colonic disease + conventional glucocorticosteroids are contraindicated, or not tolerated) OR • enteral nutrition (If any concern about growth SE of steroids e.g. in children) OR • aminosalicylate (less effective and less side effect): (for mild to moderate + conventional glucocorticosteroids are contraindicated, or not tolerated) 	<p>Mild & moderate UC</p> <p>1st line:</p> <ul style="list-style-type: none"> • Rectal & distal colitis → rectal (topical) Aminosalicylates is superior to rectal steroids • Proximal colitis → oral Aminosalicylates <p>Sever UC → hospital → 1st line (I.V steroid)</p>

	<p>2nd line → adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide (if:</p> <ul style="list-style-type: none"> • there are 2 or more inflammatory exacerbations in a 12-month period or • the glucocorticosteroid dose cannot be tapered. <p>3rd line: add methotrexate to a conventional glucocorticosteroid or budesonide (If azathioprine or mercaptopurine not tolerated , or in whom TPMT activity is deficient),</p> <p>Severe form</p> <p>1st line : conventional glucocorticosteroids</p> <p>2nd line: (not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments) Infliximab or adalimumab</p> <p>(severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3 to 4 or more) diarrhoeal stools daily.)</p>	<p>2nd line → oral prednisolone</p>
Maintaining remission	<p>Stop smoking</p> <p>1st line → azathioprine or mercaptopurine (or methotrexate ONLY if needed to induce remission)</p> <p>2nd line (if azathioprine or mercaptopurine not tolerated or not appropriate) → methotrexate</p> <p>post-surgery → azathioprine in combination with up to 3 months' postoperative metronidazole, OR azathioprine alone for people who cannot tolerate metronidazole</p>	<ul style="list-style-type: none"> • oral 5-ASA e.g. mesalazine • azathioprine and mercaptopurine (methotrexate is NOT recommended for UC)

Inducing remission in Crohn's disease: 2nd, 3rd lines and severe form (NICE 2019) (PassOnExam)

	Case	Treatment
2 nd line	<ul style="list-style-type: none"> ▪ ≥ 2 exacerbations in a 12-month period OR ▪ the glucocorticosteroid dose cannot be tapered. 	Add Azathioprine OR Mercaptopurine to a conventional glucocorticosteroid or budesonide
3 rd line	<ul style="list-style-type: none"> ▪ Azathioprine or mercaptopurine not tolerated OR ▪ in whom TPMT activity is deficient 	add Methotrexate to a conventional glucocorticosteroid or budesonide
Severe form	very poor general health + one or more symptoms such as weight loss, fever, severe abdominal pain and ≥ 3 diarrhoeal stools daily.	<p>1st line : conventional glucocorticosteroids</p> <p>2nd line: (not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments) Infliximab or adalimumab)</p>

Crohn's disease Maintaining remission (NICE 2019)	
1 st line	<ul style="list-style-type: none"> • Azathioprine OR mercaptopurine • Methotrexate ONLY if needed to induce remission.
2 nd line	<ul style="list-style-type: none"> • Methotrexate
post-surgery (complete macroscopic resection)	<ul style="list-style-type: none"> • Azathioprine + in combination with up to 3 months' postoperative metronidazole, OR • azathioprine alone for people who cannot tolerate metronidazole

General points

- **patients should be strongly advised to stop smoking**
- some studies suggest an increased risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy
- **dietary advice**
 - **Short-term use of TPN may be helpful in severe cases**
 - There is a significant portion of Crohn's patients who are lactose intolerant, and hence a **dairy free diet may reduce the frequency of diarrhoea**.

Inducing remission

- glucocorticoids (oral, topical or intravenous) are generally used to induce remission. Budesonide is an alternative in a subgroup of patients
- enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children)
- 5-ASA drugs (e.g. mesalazine) are used **second-line** to glucocorticoids but are not as effective
- azathioprine or mercaptopurine* may be used as an **add-on** medication to induce remission but is not used as monotherapy. Methotrexate is an alternative to azathioprine
- infliximab is useful in **refractory disease and fistulating Crohn's**. Patients typically continue on azathioprine or methotrexate
- metronidazole is often used for **isolated peri-anal** disease

After a diagnosis of small bowel Crohn's disease, a patient asked for therapy that is as **effective as a course of corticosteroids, but with a better adverse event profile.**

What would you recommend?

→ **Defined formula diet**

- One study showed corticosteroids to have an 80% short-term remission rate, while sole-source liquid diets had a 60% remission rate.
- However, the rate of remission rose to 80% with sole-source liquid diets for those who were able to tolerate a course of therapy.

Maintaining remission

- stopping smoking is a priority
 - **(remember: smoking makes Crohn's worse, but may help ulcerative colitis)**
- **first-line** → azathioprine or mercaptopurine
 - *assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine
- **second-line** → methotrexate
- if a patient has had **previous surgery** → 5-ASA drugs (e.g. mesalazine) should be considered

Surgery

- around 80% of patients with Crohn's disease will eventually have surgery

➢ **Side effects**

- **Bile salt malabsorption**
 - ❖ **Loss of the terminal ileum frequently leads to → bile salt malabsorption**
 - ❖ commonly presents with watery diarrhoea.
 - ❖ diagnosis can be confirmed with a SEHCAT scan.
 - ❖ **treatment with the bile salt chelator cholestyramine**

Treatment during pregnancy

- For relapse during pregnancy
 - 1st line → **Prednisolone is the most appropriate initial treatment**
 - 2nd line (in patients who not responds to corticosteroids) → Infliximab
 - Infliximab is thought to be low risk in pregnancy although it does cross the placenta.
 - Patients on maintenance infliximab therapy should stop treatment by week 26 gestation.
 - In patients who require treatment in the last trimester, live vaccines should be avoided in the newborn for the first 6 months.
- For maintenance therapy → azathioprine or 6MP

Complications: There are 3 main serious intestinal complications in Crohn's disease:

1. Stricture (narrowing) of the bowel → intestinal obstruction
2. Fistulas, which are abnormal connections between sections of the bowel, or between the bowel and bladder.
3. colorectal cancer

Prognosis : (Nice 2013)

Prognostic feature	Crohn's disease	ulcerative colitis
prolonged remission	Only 10%	50%
surgery within 10 years of diagnosis	50%	20–30%
risk of mortality compared with the general population	slightly increased	Not increased
General outlook	worse than ulcerative colitis	Better than Crohn's

Renal calculi are increased in Crohn's due to a mixture of dehydration and increased oxalate due to small bowel pathology and previous surgery. (Non-contrast helical CT abdomen is the investigation of choice for suspected renal calculi.)

Crohn's-like enterocolitis with mycophenolate mofetil

- Reported in renal transplant patients who have received mycophenolate mofetil.
- Investigations will reveal mucosal ulceration and skip lesions ordinarily seen in Crohn's.
- Treatment → Withdrawal of mycophenolate → resolution of symptoms

Ulcerative colitis (Nice guidelines 2013)

Ulcerative colitis - the rectum is the most common site affected

- Ulcerative colitis (UC) is a form of inflammatory bowel disease.
- Inflammation always starts at rectum (hence it is the most common site for UC),
- never spreads beyond ileocaecal valve and is continuous.
- The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

Features

The initial presentation is usually following insidious and intermittent symptoms:

- bloody diarrhoea
- urgency
- tenesmus
- abdominal pain, particularly in the left lower quadrant
- extra-intestinal features (see below)

Severity of ulcerative colitis (Mild, moderate and severe)

- In adults the severity criteria are based on the Truelove and Witts' severity index
- In children (≤ 11 years) and young people (12 to 17 years) these categories are based on the Paediatric Ulcerative Colitis Activity Index (PUCAI)

Truelove and Witts' severity index

	Mild	Moderate	Severe
Bowel movements (no. per day)	< 4	4–6	$\geq 6 +$ at least one of the features of systemic upset (Pyrexia, Pulse > 90 , anaemia, ↑ESR)
Blood in stools	small amounts	Between mild and severe	Visible blood
Pyrexia ($> 37.8^{\circ}\text{C}$)	No	No	Yes

Pulse > 90 bpm	No	No	Yes
Anaemia Haemoglobin <105 g/L	No	No	Yes
ESR	≤ 30	≤ 30	> 30
C reactive protein	≤ 30	≤ 30	> 30

Pathology

- red, raw mucosa, bleeds easily
- no inflammation beyond submucosa (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- neutrophils migrate through the walls of glands to form crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent

Barium enema

- loss of haustrations
- superficial ulceration, 'pseudopolyps'
- long standing disease: colon is narrow and short -'drainpipe colon'



Abdominal x-ray from a patient with ulcerative colitis showing **lead pipe appearance** of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroilitis.

Ulcerative colitis: flares

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause flares of inflammatory bowel disease.
- Cytomegalovirus is an uncommon cause of non-responsive colitis.

Flares of ulcerative colitis are usually classified as either mild, moderate or severe:

Mild	Moderate	Severe
<ul style="list-style-type: none"> < 4 stools/day, with or without blood 	<ul style="list-style-type: none"> 4-6 stools/day, with minimal systemic 	<ul style="list-style-type: none"> >6 bloody stools per day, containing blood Evidence of systemic disturbance, e.g.

Mild	Moderate	Severe
<ul style="list-style-type: none"> No systemic disturbance Normal ESR and C-reactive protein values 	disturbance	<ul style="list-style-type: none"> ➤ fever ➤ tachycardia ➤ abdominal tenderness, distension or reduced bowel sounds ➤ anaemia ➤ hypoalbuminaemia

Patients with evidence of severe disease should be admitted to hospital.

Risk factors for the precipitation of toxic colonic dilatation

Ulcerative colitis identify the following as risk factors for the precipitation of toxic colonic dilatation:

- Hypokalaemia
- **Hypomagnesaemia**
- Under-treatment
- Purgative bowel preparations for colonoscopy
- Non-steroidals
- Opioids
- Anti-cholinergics, and
- Anti-diarrhoeal agents.
- inappropriately delayed

Ulcerative colitis: management (NICE 2013)

Treatment can be divided into inducing and maintaining remission..

Inducing remission

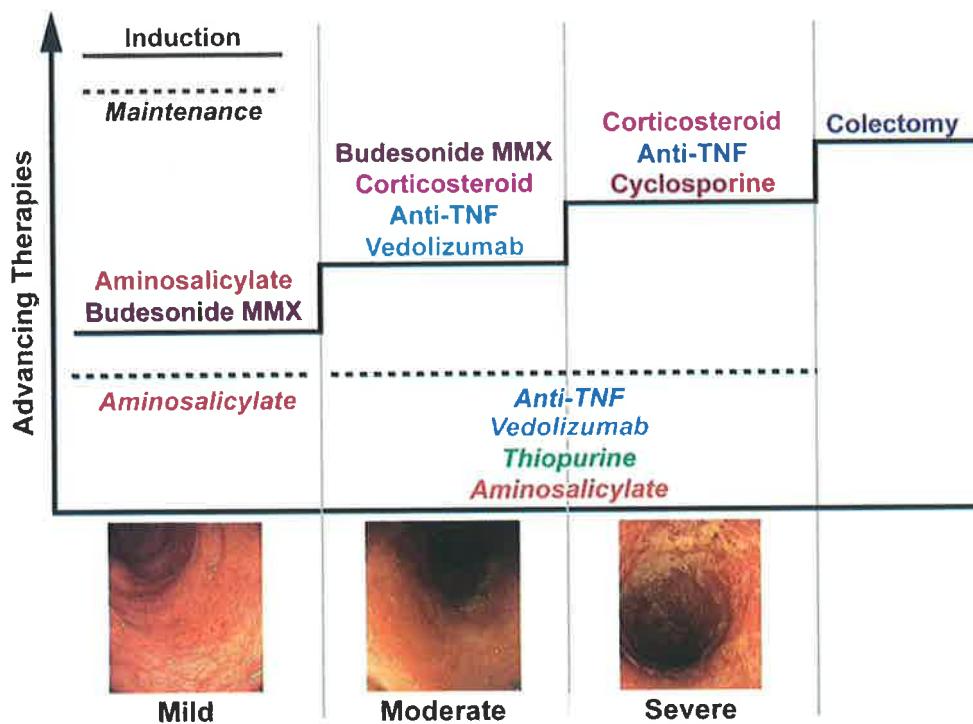
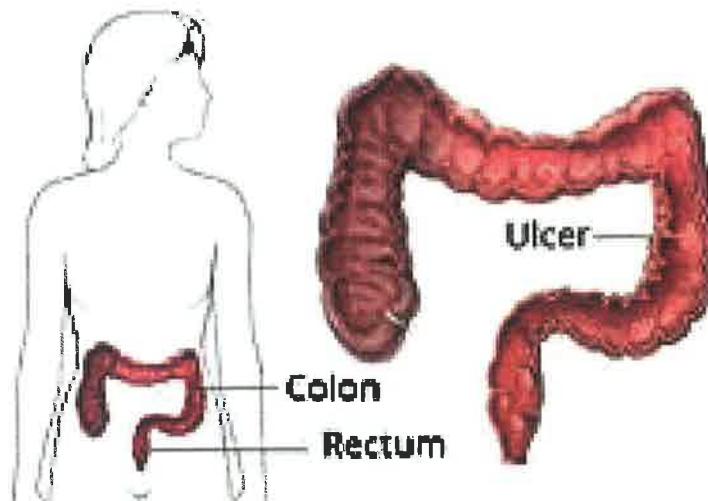
- treatment depends on the extent and severity of disease
- rectal (topical) aminosalicylates or steroids: for distal colitis rectal mesalazine has been shown to be superior to rectal steroids and oral aminosalicylates
- oral aminosalicylates
- oral prednisolone is usually used **second-line** for patients who fail to respond to aminosalicylates. NICE recommend waiting around 4 weeks before deciding if first-line treatment has failed
- **severe colitis should be treated in hospital. Intravenous steroids are usually given first-line**

Maintaining remission

- oral aminosalicylates e.g. mesalazine
- azathioprine and mercaptopurine
- methotrexate is not recommended for the management of UC (in contrast to Crohn's disease)
- there is some evidence that probiotics may prevent relapse in patients with mild to moderate disease

Inactive (quiescent) colitis:

- **(ESR) is not raised in quiescent UC**
- **If the ESR, CRP and platelet counts are not raised, indicating that the patient's symptoms are not due to active disease.**
- Neutrophilic infiltrate is present if disease is active
 - Involves epithelium of surface and crypts
 - Frequently forms crypt abscesses



Step-up approach to treatment based on disease severity. CLINICAL OVERVIEW

Ulcerative colitis. Elsevier Point of Care.

Updated December 21, 2019.

https://www.clinicalkey.com/#!/content/clinical_overview/67-s2.0-0c7ff1f6-29bc-46f1-a7b7-4bcf12316903?scrollTo=%23367-s2.0-0c7ff1f6-29bc-46f1-a7b7-4bcf12316903-99c15915-a11a-451d-9cb0-8db17e1930c9-annotated

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Ulcerative colitis: colorectal cancer

Overview

- risk of colorectal cancer is significantly higher than that of the general population although studies report widely varying rates
- the increased risk is mainly related to chronic inflammation
- worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- lesions may be multifocal

Factors increasing risk of cancer

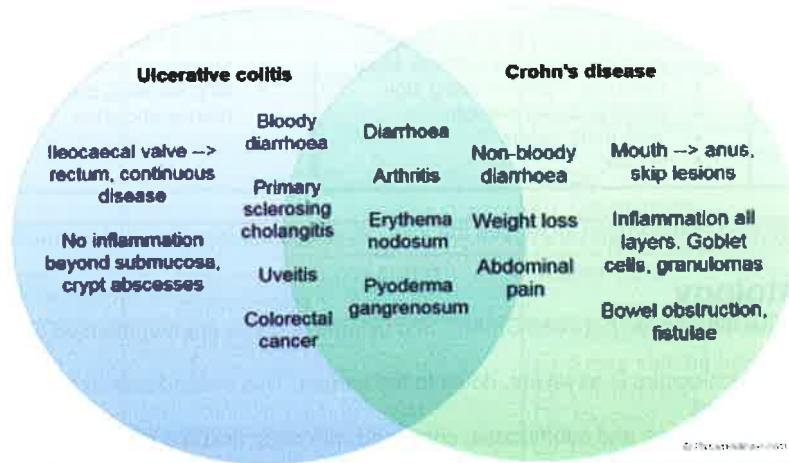
- disease duration > 10 years
- patients with pancolitis
- onset before 15 years old
- unremitting disease
- poor compliance to treatment

Colonoscopy surveillance & Risk stratification of IBD

- All patients with a diagnosis of colitis should have a screening colonoscopy 10 years after index presentation, preferably when they are in remission.
- patients should be decided following risk stratification.
 - **Lower risk** → 5-year follow up colonoscopy
 - Extensive colitis with no active endoscopic/histological inflammation
 - left sided colitis
 - Crohn's colitis of <50% colon
 - **Intermediate risk** → 3-year colonoscopy
 - Extensive colitis with mild active endoscopy/histological inflammation
 - post-inflammatory polyps
 - OR family history of colorectal cancer in a first degree relative aged 50 or over
 - ⇒ **Higher risk** → 1 year follow up colonoscopy
 - Extensive colitis with moderate/severe active endoscopic/histological inflammation
 - stricture in past 5 years
 - dysplasia in past 5 years declining surgery
 - **primary sclerosing cholangitis** / transplant for primary sclerosing cholangitis
 - family history of colorectal cancer in first degree relatives aged <50 years

Inflammatory bowel disease: key differences

- The two main types of inflammatory bowel disease are Crohn's disease and Ulcerative colitis.
- They have many similarities in terms of presenting symptoms, investigation findings and management options.
- There are however some key differences which are highlighted in table below:



Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

	Crohn's disease (CD)	Ulcerative colitis (UC)
Features	Diarrhoea usually non-bloody Weight loss more prominent Upper gastrointestinal symptoms, mouth ulcers, perianal disease Abdominal mass palpable in the right iliac fossa	Bloody diarrhoea more common Abdominal pain in the left lower quadrant Tenesmus
Extra-intestinal	Gallstones are more common secondary to reduced bile acid reabsorption Oxalate renal stones*	Primary sclerosing cholangitis more common
Complications	Obstruction, fistula, colorectal cancer	Risk of colorectal cancer high in UC than CD
Pathology	Lesions may be seen anywhere from the mouth to anus Skip lesions may be present	Inflammation always starts at rectum and never spreads beyond ileocaecal valve Continuous disease
Histology	Inflammation in all layers from mucosa to serosa <ul style="list-style-type: none"> • increased goblet cells • granulomas 	No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria <ul style="list-style-type: none"> • neutrophils migrate through the walls of glands to form crypt abscesses • depletion of goblet cells and mucin from gland epithelium • granulomas are infrequent

	Crohn's disease (CD)	Ulcerative colitis (UC)
Endoscopy	Deep ulcers, skip lesions - 'cobble-stone' appearance	Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
Radiology	Small bowel enema <ul style="list-style-type: none"> • high sensitivity and specificity for examination of the terminal ileum • strictures: 'Kantor's string sign' • proximal bowel dilation • 'rose thorn' ulcers • fistulae 	Barium enema <ul style="list-style-type: none"> • loss of haustrations • superficial ulceration, 'pseudopolyps' • long standing disease: colon is narrow and short -'drainpipe colon'

*impaired bile acid reabsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

IBD: histology

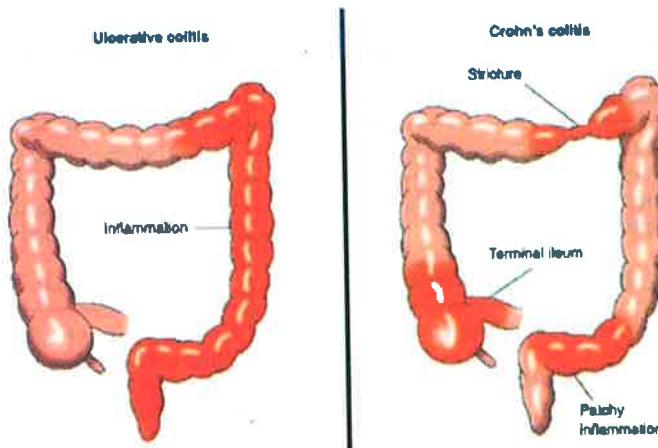
This histological differences between Crohn's and ulcerative colitis are summarised below:

Crohn's

- inflammation occurs in all layers, down to the serosa. This predisposes to strictures, fistulas and adhesions
- oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern
- lymphoid aggregates
- non-caseating granulomas

Ulcerative colitis

- inflammation in mucosa and submucosa only (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent



feature	Ulcerative colitis	Crohn's
Most common site	Rectum	Terminal ileum
Distribution	Rectum to colon "backwash" ileitis	Mouth to anus
Spread	Continuous	Discontinuity "skip" lesions
Gross features	<ul style="list-style-type: none"> ▪ Extensive ulceration ▪ Pseudo-polyps 	<input type="checkbox"/> Focal aphthous ulcers with intervening normal mucosa <input type="checkbox"/> Linear fissures <input type="checkbox"/> Cobblestone appearance <input type="checkbox"/> Thickened bowel wall "plastic" <input type="checkbox"/> Creeping fat
Micro	<ul style="list-style-type: none"> ▪ Crypt abscess 	Noncaseating granulomas
Inflammation	<ul style="list-style-type: none"> ▪ Limited to mucosa and submucosa 	Transmural
Complication	<ul style="list-style-type: none"> ▪ Toxic megacolon 	<input type="checkbox"/> Strictures <input type="checkbox"/> String sign on barium study <input type="checkbox"/> Obstruction <input type="checkbox"/> Abscess <input type="checkbox"/> Fistula <input type="checkbox"/> Sinus tract
Genetic Association	HLA-B27	
Extraintestinal manifestation	Common	Uncommon
Cancer risk	5-25%	Slight 1-3%
Presentation	Bloody diarrhea	Variable : Pain, diarrhea, weight loss

Pseudopolyps are seen in both ulcerative colitis and Crohn's disease.

history of previously well-controlled ulcerative colitis, treated with mesalazine 1.2 g daily. presented with a 5-day history of increasing bowel frequency. A diagnosis of active proctitis was made. What is the most appropriate treatment?

⇒ increase mesalazine dosage

Microscopic colitis (Collagenous colitis and Lymphocytic colitis)

- Microscopic colitis (MC) is an inflammatory condition of the colon that presents with two subtypes: collagenous (CC) and lymphocytic colitis (LC).
- Both types of MC present with watery diarrhea, and normal endoscopic findings. Differentiation is made by histological examination but treatment is the same.
- **Risk factors** for MC are female gender, higher age, concomitant autoimmune disease, past and current diagnosis of malignancy or organ transplant
 - ⇒ Among all autoimmune disorders, celiac disease appears to have the strongest association.
 - ⇒ The use of proton pump inhibitors (PPIs) (lansoprazole), low dose aspirin, β-blockers, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), statins, and bisphosphonates have all been associated with MC

- **Diagnosis**

- ⇒ histological evaluation through lower endoscopy.
 - The histology found in MC (both CC and LC) demonstrates **lymphocytic infiltration of the lamina propria and the epithelium**.
 - CC differs from LC in that there is marked **thickening of the subepithelial layer**.
 - Intraepithelial lymphocytosis (IEL)** can be found in both CC and LC, but is **more pronounced in LC**: ≥ 20 intraepithelial lymphocyte per 100 surface epithelial cells are needed to make the diagnosis

- Both MC respond well to oral budesonide.
- Prognosis is good with resolution of symptoms after medical therapy.
- 38% of the patients achieve spontaneous remission with either no treatment or with simple anti-diarrheals.

Histological features of collagenous colitis and lymphocytic colitis

	Collagenous colitis	Lymphocytic colitis
Lamina propria	Lymphocytic infiltration of the lamina propria with little or no damage in mucosal architecture	
Subepithelial layer	Thickening of subepithelial layer > 10 µm	Subepithelial collagen layer not present or < 10 µm
Intraepithelial	Intraepithelial lymphocytosis could be present, but necessary for the diagnosis	Intraepithelial lymphocytosis (≥ 20 IEL per 100 surface epithelial cells)

- **Management**

- ⇒ discontinue any potentially offending drug.
- ⇒ mild and intermittent symptoms can be treated with anti-diarrheal medication (loperamide).
- ⇒ moderate to severe symptoms: only budesonide has strong supporting evidence and should be the first-line treatment in inducing and maintaining clinical remission in both CC and LC
 - Prednisone is an alternative corticosteroid that has shown some efficacy in treating MC, however it is less effective than budesonide.

Rule out infectious process
and other diseases

Obtain histological evaluation via colonoscopy to confirm diagnosis

Discontinue medications associated with MC

Trial of anti-diarrheal medications (mild)

Trial of budesonide in tapering dose

Collagenous colitis

- Collagenous colitis is one of the forms of microscopic colitis, i.e. a condition in which the colon appears normal on colonoscopy, but where the diagnosis is made based on the abnormal histology of colonic biopsies.
- predominantly affects women (male: female of 1: 4) in the fifth and sixth decades of life.
- aetiology is unknown,
- although associated with
 - ⇒ several medications – in particular, non-steroidal anti-inflammatory drugs
 - ⇒ coeliac disease and other autoimmune disorders.
- chronic watery diarrhoea (which tends to be worse during the day than at night), and is also often accompanied by crampy, diffuse abdominal pain.
- normal blood tests, radiological and macroscopic appearances.
- The diagnosis is made based on the typical histological appearances of a thickened subepithelial collagen band, a moderate inflammatory cell infiltrate, and an increase in intraepithelial lymphocytes.
- Treatments include antidiarrhoeal agents (such as Loperamide), 5-aminosalicylate drugs, corticosteroids, and bile acid sequestrants, all of which are variably effective.

Lymphocytic colitis

- Associations
 - ⇒ occur in patients with other forms of GI pathology, including Crohn's and Coeliac.
 - ⇒ **Sertraline also appears to be associated with the development of lymphocytic colitis.**
- Management

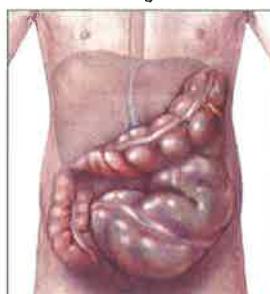
- ⇒ Withdrawal of the offending agent is preferable,
- ⇒ loperamide is often used as a first line therapy to reduce the severity of diarrhoea, with cholestyramine an alternative if there is bile salt malabsorption.
- ⇒ Other alternatives include immune modulating agents such as azathioprine, although a response to therapy may take many months to appear.

Toxic megacolon (Toxic dilatation of the colon)

DON'T GIVE ANTI-DIARRHEAL Rx FOR ACUTE COLITIS → TOXIC MEGACOLON

Flexible sigmoidoscopy is the best investigation - safer than colonoscopy (relative contraindication in active colitis), allowing biopsies to be taken and the viewing of a possible pseudomembrane. Occasionally the mucosa has a characteristic appearance.

Toxic megacolon



Toxic megacolon is characterized by extreme inflammation and distension of the colon. Common symptoms are pain, distension of the abdomen, fever, rapid heart rate, and dehydration. This is a life-threatening complication that requires immediate medical treatment.

- Usually associated with severe colitis.
 - ⇒ usually due to severe UC but also with Crohn's colitis and rarely ischaemic or infective colitis
- The transverse or right colon is usually the most dilated part in toxic megacolon, often greater than 6 cm and occasionally up to 15 cm on supine films.

Diagnostic criteria

toxic megacolon → transverse colon dilatation ≥ 6 cm + signs of systemic toxicity.

- Radiographic evidence of colonic distension
- **plus** at least three of the following:
 - Fever $>38.6^{\circ}\text{C}$
 - Heart rate >120 beats per minute (The most reliable sign is the pulse rate)
 - Neutrophilic leucocytosis $>10.5 \times 10^9/\text{L}$, or
 - Anaemia.
- **Plus**, at least one of the following:
 - Dehydration
 - Altered mental status
 - Electrolyte disturbances, or
 - Hypotension.

Investigation

- **The most helpful investigation is a plain abdominal X-ray.**

- ⇒ Radiological colonic dilatation - widest diameter ≥ 6 cm in the transverse colon.
- ⇒ Other radiological findings include:
 - loss of haustral pattern,
 - mucosal oedema and
 - thumbprinting.

Treatment

The treatment of choice for established dilatation is **colectomy**.

- Treatment includes 3 main goals:
 1. reduce colonic distension to prevent perforation (5-fold increase in mortality after free perforation)
 - Rolling techniques (knee-elbow and prone) may be performed to assist in redistribution of colonic gas and decompression
 - Medical treatment:
 - ❖ antibiotics to cover the colonic bacterial flora, gram-negative and anaerobic bacteria
 - ❖ steroids: either hydrocortisone 100 mg IV every 6 hours or methylprednisolone 60 mg IV every 24 hours is acceptable. The latter has greater relative anti-inflammatory potency and less relative mineralocorticoid potency.
 - ❖ cyclosporine may be effective
 - colectomy: Most authors recommend colectomy if persistent dilatation is present or if no improvement is observed on maximal medical therapy after 24-72 hours.
 2. correct fluid and electrolyte disturbances
 - fluid replacement, electrolyte repletion, and transfusion should be aggressive.
 3. treat toxemia and precipitating factors.
 - Broad-spectrum (IV) antibiotics with coverage equivalent to ampicillin, gentamicin, and metronidazole should be initiated.
 - Possible triggers for TM should be stopped, including:
 - ❖ narcotics
 - ❖ antidiarrheals
 - ❖ anticholinergics

Prognosis

- The mortality rate for non-perforated, acute toxic colitis is about 4%; if perforation occurs, the mortality is approximately 20%.

Gastroenteritis and food poisoning

Radiation enteritis

Overview

- Radiation injury to the rectum and sigmoid colon is commonly seen following treatment of cancers of the cervix, uterus, prostate and bladder.
- It often occurs 9–14 months following radiation exposure and results in a chronically ischaemic intestinal segment that may lead to stricture.
- Symptoms include diarrhoea, obstructed defecation, bleeding, rectal pain or urgency.

Diagnosis

- can be confirmed with colonoscopy, and mucosal features consistent with radiation injury include pallor, friability and telangiectasias.
- Biopsy is not diagnostic but is helpful to exclude other causes.

Treatment

- systemic review of available trials shows promising results for rectal sucralfate and metronidazole combined with topical anti-inflammatory treatment and heater probe.

Gastroenteritis

E. coli is the most common cause of travellers' diarrhoea

Travellers' diarrhoea

- defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool.
- The most common cause is *Escherichia coli*
- **Ciprofloxacin is recommended for first line antibiotic therapy (when needed) before stool culture results are available.**

Acute food poisoning

- Sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.
- typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.
- *Clostridium perfringens*:
 - ⇒ a Gram-positive, rod shaped, anaerobic, spore-forming bacterium.
 - ⇒ The spores can withstand (مُقاوم) cooking temperatures, so if food (meat and poultry) is left to stand for a long time, germination of spores can occur, causing food poisoning.
 - ⇒ The CPE (*Clostridium perfringens* enterotoxin) can be detected in food that has been improperly prepared.
 - ⇒ ***Clostridium perfringens* can also cause gas gangrene, a necrosis of tissues with gas production. The toxin responsible for gas gangrene is called alpha-toxin.**
- **reservoir for this pathogen**
 - ⇒ **Vibrio species are most commonly found in seafood (Fish), are comma-shaped, and prefer alkaline media.**
 - ⇒ Improperly **canned foods** are reservoirs for ***Clostridium botulinum***. This is an anaerobic gram-positive organism that creates spores. If the can is bulging, it is probably contaminated and should not be eaten.
 - ⇒ **Honey** can be a reservoir for ***Clostridium botulinum***. Newborn babies are at risk for contracting spores from eating honey since their immune systems are poorly developed. This can lead to "floppy baby" syndrome.
 - ⇒ Meats, **mayonnaise**, custard and other **cream-based dishes** are food sources commonly associated with ***Staphylococcus aureus*** food poisoning.

Diarrhoea

- **Osmotic diarrhoea** occurs in patients with diabetes who ingest too much sorbitol (a common substitute for glucose in so-called 'diabetic foods').
- **Secretory diarrhoea** commonly occurs in response to endotoxin-producing bacteria, (eg cholera or *Escherichia coli*).

- **Chronic radiation enteritis** is diagnosed if diarrhoea and abdominal pain persist for 3 or more months following irradiation.

Stereotypical histories

Infection	Typical presentation
<i>Escherichia coli</i>	Common amongst travellers Watery stools Abdominal cramps and nausea
Giardiasis	Prolonged, non-bloody diarrhoea
Cholera	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
<i>Shigella</i>	Bloody diarrhoea Vomiting and abdominal pain
<i>Staphylococcus aureus</i>	Severe vomiting Short incubation period
<i>Campylobacter</i>	commonest cause of bacterial gastroenteritis in the UK A flu-like prodrome is usually followed by crampy abdominal pains (often a prominent feature), 'pseudoappendicitis' (RIF pain), fever and diarrhoea which may be bloody. Treatment: <ul style="list-style-type: none"> • the most appropriate therapy → IV fluids • most units advocate no antibiotic treatment. • Antibiotic of choice in this infection is erythromycin, though ciprofloxacin and tetracycline may also be appropriate. Complications include Guillain-Barre syndrome
<i>Salmonella</i>	<ul style="list-style-type: none"> • After <i>Campylobacter</i>, <i>Salmonella</i> is the most commonly isolated bacterial pathogen when laboratory diagnosis of diarrhea is sought. • acute onset of fever, diarrhea, and cramping • antibiotic treatment of patients with nontyphoidal salmonellosis may actually prolong, rather than limit, fecal shedding of these organisms. • the likely sources are poultry (دواجن) and eggs.
<i>Bacillus cereus</i>	Two types of illness are seen <ul style="list-style-type: none"> • vomiting within 6 hours, stereotypically due to rice • diarrhoeal illness occurring after 6 hours
Amoebiasis	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus**
- **12-48 hrs: *Salmonella*, *Escherichia coli***
- 48-72 hrs: *Shigella*, *Campylobacter*

- > 7 days: Giardiasis, Amoebiasis

Amoebic dysentery

- Acute amoebic dysentery is managed with:
 1. a course of **oral metronidazole** or tinidazole,
 2. followed by a ten day course of diloxanide to eradicate colonisation of the gut.
- Amoebic liver abscess may appear at any time from eight weeks after infection, and presents with night sweats, anorexia and right upper quadrant pain.
- mortality from amoebiasis is less than 1%.

Biochemical abnormalities in persistent vomiting

- persistent vomiting → ↓↓ gastric hydrochloric acid → **hypochloraemia and metabolic Alkalosis**
- In the early stages the urine has low chloride and high bicarbonate levels in order to compensate for the loss of gastric hydrochloric acid and is appropriately alkaline.
- With the continued dehydration, sodium is preferentially reabsorbed over the potassium and hydrogen ions which are excreted by the kidneys.
- The urine becomes paradoxically acidic, **hypokalaemia** develops, and alkalosis leads to lower circulating levels of ionised calcium.

To quickly remember the PH changes associated with GI losses, think:

- With vomiting, both the PH and food come up.
- With diarrhoea, both the PH and food go down.

Giardiasis

Pathogenesis

- Giardiasis is caused by the flagellate protozoan *Giardia lamblia*.
- *Giardia lamblia* is capable of causing epidemic or sporadic diarrheal illness.
- It has two morphological forms: cysts and trophozoites. Cysts are the infectious form of the parasite; following cyst ingestion, trophozoites are released in the proximal small intestine. Trophozoites that do not adhere to the small intestine move forward to the large intestine where they revert to the infectious cyst form; these cysts are passed back into the environment in excreted stool.
- Transmission: via the faeco-oral route.
- The incubation period is 1-2 weeks.

Feature

- Often asymptomatic
 - ⇒ ≈ 50% clear the infection without symptoms
 - ⇒ ≈ 15% shed cysts asymptotically (carriers)
- Symptomatic infection ≈ 35%
 - ⇒ lethargy, bloating, abdominal pain
 - ⇒ non-bloody diarrhoea
 - ⇒ malabsorption and acquired lactose intolerance can occur → chronic diarrhoea, **steatorrhoea** & weight loss

Diagnosis

- stool microscopy
 - ⇒ initial investigation, but frequently not positive , need 3 samples, 2- 3 days apart as cyst and trophozoites are shed intermittently

- **Stool antigen tests:** immunoassays (eg: ELISA) using antibodies against cyst or trophozoite antigen
 - ⇒ **the best test** for giardia
 - ⇒ more sensitive and faster than stool microscopy.
- duodenal samples for microscopy: can be obtained by:
 - ⇒ the 'string test' (swallowing a gelatin capsule on a string)
 - ⇒ **endoscopy** → **duodenal aspirates or biopsy.**

Treatment

- Antiprotozoal (tinidazole, nitazoxanide or metronidazole)
 - ⇒ Metronidazole has been the first-line; however, a single-dose tinidazole is superior and the best treatment now (shorter course and fewer side effects)
- For pregnant:
 - ⇒ 1st trimester → paromomycin (Non-absorbable aminoglycoside)
 - ⇒ 2nd & 3rd trimester → either paromomycin or metronidazole

Clostridium perfringens

The food poisoning with Colicky abdominal pain and diarrhoea **without vomiting** after incubation period between 9-13 hours is typical of ***Clostridium perfringens***.

Bacillus cereus

typical case of *Bacillus cereus*, profuse vomiting occurs one to five hours after eating (rice).

- *B.cereus* can cause two patterns of disease:
 1. classic emetic form:
 - caused by the **ingestion of toxin**
 - Characterised by nausea and vomiting, similar to *Staphylococcus aureus*.
 - Rice products are generally the cause of this form.
 2. diarrhoeal form:
 - less common
 - Caused by the **ingestion of the organism**, which releases toxin within the stomach.
 - Produce an illness similar to *C. perfringens* (*but the incubation period is classically shorter (1-6 hours)* with watery diarrhoea and abdominal cramps.
 - Meats, milk, vegetables and fish have been associated with this form.

Shigella

- causes bloody diarrhoea, abdominal pain
- severity depends on type: *S sonnei* (e.g. from UK) may be mild, *S flexneri* or *S dysenteriae* from abroad may cause severe disease
- treat with ciprofloxacin
- Reactive arthritis and Reiter's syndrome can develop following infection with a number of enteric pathogens including *Shigella*, *Salmonella*, *Campylobacter* and *Yersinia*.

Yersinia enterocolitica

- gram-negative bacillus
- *the second most common cause of bacterial gastrointestinal infection in children.*
- most frequently associated with enterocolitis, acute diarrhea, terminal ileitis, mesenteric lymphadenitis and **pseudoappendicitis**

- Pseudoappendicitis syndrome is more common in older children and young adults.
- Enterocolitis, the most common presentation of *Y enterocolitica*, occurs primarily in young children. Most cases are self-limited.
- *Y enterocolitica* is potentially transmitted by contaminated unpasteurized milk and milk products, raw pork, tofu, meats, oysters, and fish.
- The usual presentation of *Y enterocolitica* infection includes diarrhea (the most common clinical manifestation of this infection), low-grade fever, and abdominal pain lasting 1-3 weeks. Diarrhea may be bloody in severe cases. Vomiting is present in approximately 15-40% of cases.
- Stool culture is the best way to confirm the diagnosis.
- Ultrasonography or computed tomography (CT) scanning may be useful in delineating true appendicitis from pseudoappendicitis.
- **Complications**
 - After an incubation period of 4-7 days, infection may result in mucosal ulceration (usually in the terminal ileum and rarely in the ascending colon), necrotic lesions in Peyer patches, and mesenteric lymph node enlargement.
 - In persons with human leukocyte antigen (HLA)-B27, reactive arthritis is not uncommon, possibly because of the molecular similarity between HLA-B27 antigen and *Yersinia* antigens.
- First-line drugs used against the bacterium include aminoglycosides and trimethoprim-sulfamethoxazole (TMP-SMZ). Other effective drugs include third-generation cephalosporins, tetracyclines (not recommended in children < 8 y), and fluoroquinolones (not approved for use in children < 18 y).

- *Yersinia pestis* is the causative agent of the plague.
- *Yersinia* bacteria has an ability to survive, and actively proliferate at temperatures as low as 1–4°C (e.g., on food products in a refrigerator).
- *Yersinia* is one of the causes of reactive arthritis
- ***Yersinia* may be associated with Crohn's disease**
 - Iranian sufferers of Crohn's disease were more likely to have had earlier exposure to refrigerators at home, consistent with its unusual ability to thrive at low temperatures.
- **Which bacteria can multiply and produce endotoxin even in refrigerated blood?**
 - *Yersinia*
 - it is a prominent cause of life-threatening post-transfusion infection.
 - Endotoxins can result in septic shock

Gastrointestinal parasitic infections

Common infections

Organism	Notes
Enterobiasis	<ul style="list-style-type: none"> • Due to organism <i>Enterobius vermicularis</i> • Common cause of pruritus ani • Diagnosis usually made by placing scotch tape at the anus, this will trap eggs that can then be viewed microscopically • Treatment is with mebendazole
Ancylostoma duodenale	<ul style="list-style-type: none"> • Hookworms that anchor in proximal small bowel • Most infections are asymptomatic although may cause iron deficiency anaemia • Larvae may be found in stools left at ambient temperature, otherwise infection is difficult to diagnose

Organism	Notes
	<ul style="list-style-type: none"> Infection occurs as a result of cutaneous penetration, migrates to lungs, coughed up and then swallowed Treatment is with mebendazole
Ascariasis	<ul style="list-style-type: none"> Due to infection with roundworm <i>Ascaris lumbricoides</i> Infections begin in gut following ingestion, then penetrate duodenal wall to migrate to lungs, coughed up and swallowed, cycle begins again Diagnosis is made by identification of worm or eggs within faeces Treatment is with mebendazole
Strongyloidiasis	<ul style="list-style-type: none"> Due to infection with <i>Strongyloides stercoralis</i> Rare in west Organism is a nematode living in duodenum of host Initial infection is via skin penetration. They then migrate to lungs and are coughed up and swallowed. Then mature in small bowel are excreted and cycle begins again An auto infective cycle is also recognised where larvae will penetrate colonic wall Individuals may be asymptomatic, although they may also have respiratory disease and skin lesions Diagnosis is usually made by stool microscopy In the UK mebendazole is used for treatment
Cryptosporidium	<ul style="list-style-type: none"> Protozoal infection Organisms produce cysts which are excreted and thereby cause new infections Symptoms consist of diarrhoea and cramping abdominal pains. Symptoms are worse in immunosuppressed people Cysts may be identified in stools Treatment is with metronidazole
Giardiasis	<ul style="list-style-type: none"> Diarrhoeal infection caused by <i>Giardia lamblia</i>(protozoan) Infections occur as a result of ingestion of cysts Symptoms are usually gastrointestinal with abdominal pain, bloating and passage of soft or loose stools Diagnosis is by serology or stool microscopy First line treatment is with metronidazole

Exotoxins and endotoxins

Definition

- Exotoxins are secreted by bacteria whereas endotoxins are only released following lysis of the cell.

Exotoxins

- Exotoxins are generally released by Gram positive bacteria** with the notable exceptions of *Vibrio cholerae* and some strains of *E. coli*
- It is possible to classify exotoxins by their primary effects:
 - pyrogenic toxins
 - enterotoxins
 - neurotoxins
 - tissue invasive toxins
 - miscellaneous toxins

Pyrogenic toxins

- Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc.
- They are super-antigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

Organism	Toxin	Notes
<i>Staphylococcus aureus</i>	Toxic shock syndrome (TSST-1 superantigen) toxin	Results in high fever, hypotension, exfoliative rash
<i>Streptococcus pyogenes</i>	Streptococcal pyrogenic exotoxin A & C	Results in scarlet fever

Enterotoxins

- Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:
 - diarrhoeal illness
 - vomiting illness ('food poisoning')

Organism	Toxin	Notes
<i>Vibrio cholerae</i>	Cholera toxin	Causes activation of adenylate cyclase (via G _s) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption
<i>Shigella dysenteriae</i>	Shiga toxin	Inactivates 60S ribosome → epithelial cell death
<i>Escherichia coli</i>	1. Heat labile toxin 2. Heat stable toxin	1. Activates adenylate cyclase (via G _s), increasing cAMP → watery diarrhoea 2. Activates guanylate cyclase, increasing cGMP → watery diarrhoea
<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i> enterotoxin	Vomiting and diarrhoeal illness lasting < 24 hours
<i>Bacillus cereus</i>	Cereulide	Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion

Neurotoxins

- Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

Organism	Toxin	Notes
<i>Clostridium tetani</i>	Tetanospasmin	Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis
<i>Clostridium botulinum</i>	Botulinum toxin	Blocks acetylcholine (ACh) release leading to flaccid paralysis

Tissue invasive toxins

Organism	Toxin	Notes
<i>Clostridium perfringens</i>	α -toxin, a lecithinase	Causes gas gangrene (myonecrosis) and haemolysis
<i>Staphylococcus aureus</i>	Exfoliatin	Staphylococcal scalded skin syndrome

Miscellaneous toxins

Organism	Toxin	Notes
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin	ADP ribosylates elongation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue
<i>Pseudomonas aeruginosa</i>	Exotoxin A	Also inhibits EF-2 by the same mechanism as above
<i>Bacillus anthracis</i>	Oedema factor (EF)	Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis
<i>Bordetella pertussis</i>	Pertussis exotoxin	Inhibits G _i leading to increases in cAMP levels, impairing the function of neutrophils/macrophages → reduced phagocytosis

Endotoxins

- Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as *Neisseria meningitidis*.

Pseudomembranous colitis (*Clostridium difficile*)

Pathogen

- *Clostridium difficile* is a **Gram-positive anaerobic rod**
- It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.

Causes

- *Clostridium difficile* develops when the normal gut flora are suppressed by broad-spectrum antibiotics.
 - ⇒ Clindamycin is historically associated with causing *Clostridium difficile* but the aetiology has evolved significantly over the past 10 years.
 - ⇒ **Second and third generation cephalosporins are now the leading cause of *Clostridium difficile*.**
 - ⇒ penicillins and quinolones.

Features

- Symptoms can occur up to 10 weeks following antibiotic therapy.
- Diarrhoea

- ⇒ The commonest symptoms
- ⇒ profuse watery diarrhoea (usually without blood or mucus)
- abdominal pain
- a raised white blood cell count is characteristic
- if severe toxic megacolon may develop

Severity of C. difficile infection

- **Mild infection:** < 3 episodes of loose stools per day, no ↑WCC.
- **Moderate infection:** 3 to 5 loose stools per day, WCC $< 15 \times 10^9$ per litre.
- **Severe infection:**
 - ⇒ WCC $> 15 \times 10^9$ per litre,
 - ⇒ Acutely ↑CRP $> 50\%$ above baseline,
 - ⇒ Temperature > 38.5
 - ⇒ Evidence of severe colitis (abdominal or radiological signs), lactic acidosis
 - ⇒ The number of stools may be a less reliable indicator of severity.
- **Life-threatening infection:** hypotension, partial or complete ileus, toxic megacolon or CT evidence of severe disease.

Diagnosis

- **Clostridium difficile toxin (CDT) in the stool (the most widely used diagnostic tool).**
- ELISA tests are specific but not as sensitive.
- Culture is sensitive but often does not differentiate between toxigenic and non-toxigenic strains.
- **Sigmoidoscopy may show → multiple white plaques adhered to the gastrointestinal mucosa (pathognomonic).**
 - ⇒ 90% of cases can be detected macroscopically by flexible sigmoidoscopy
 - ⇒ mild cases may not be evident macroscopically → microscopic examination of a biopsy sample
 - ⇒ Toxic dilatation should be excluded prior to sigmoidoscopy by doing plain abdominal x-ray.
 - ⇒ not used routinely
- **Plain AXR is useful for diagnosing toxic dilatation**
 - ⇒ would be the investigation of choice if there is abdominal distension.
 - ⇒ To exclude toxic dilatation prior to sigmoidoscopy.
 - ⇒ However it does not establish the diagnosis.

Management

Antibiotic treatment for Clostridium difficile (NICE guideline/July 2021)	
Treatment	Antibiotic
First-line for a first episode of mild, moderate or severe C. difficile infection	Vancomycin: 125 mg orally four times a day for 10 days
Second-line for a first episode of mild, moderate or severe C. difficile infection if vancomycin is ineffective	Fidaxomicin: 200 mg orally twice a day for 10 days
Third-line: if first- and second-line are ineffective	Vancomycin: Up to 500 mg orally four times a day for 10 days With or without Metronidazole.

	500 mg intravenously three times a day for 10 days
For relapse : (a further episode of <i>C. difficile</i> infection within 12 weeks of symptom resolution)	Fidaxomicin : 200 mg orally twice a day for 10 days
For recurrence : (a further episode of <i>C. difficile</i> infection more than 12 weeks after symptom resolution)	Vancomycin : 125 mg orally four times a day for 10 days Or Fidaxomicin : 200 mg orally twice a day for 10 days
For life-threatening <i>C. difficile</i> infection (Need urgent surgical assessment)	Vancomycin : 500 mg orally four times a day for 10 days With Metronidazole : 500 mg intravenously three times a day for 10 days

- Do not offer antimotility medicines such as loperamide.
- For a recurrent episode (2 or more previous episodes) → Consider a faecal microbiota transplant.

Prognosis

- Mortality is high in elderly patients it may be as high as 10%

Top tips

Cephalosporins, not just clindamycin, are strongly linked to *Clostridium difficile*

The main *Clostridium* species

- ***Clostridium botulinum***: produce botulinum toxin in food or wounds and can cause botulism. This same toxin is known as Botox and is used in cosmetic surgery to paralyze facial muscles to reduce the signs of aging; it also has numerous other therapeutic uses.
- ***Clostridium difficile*** can flourish when other gut flora bacteria are killed during antibiotic therapy, leading to pseudomembranous colitis
- ***Clostridium perfringens*** causes food poisoning to cellulitis, fasciitis, and **gas gangrene**.
- ***Clostridium tetani*** causes tetanus.
- ***Clostridium sordellii*** can cause a fatal infection in exceptionally rare cases after medical abortions

Gastroenteritis (GI)

Causes

- **Viral**: Most common causes of GI.
 - ⇒ **norovirus is the most common cause of acute gastroenteritis** and the second most common cause of hospitalisation for acute gastroenteritis.
 - ⇒ Characteristics of the history that suggest a viral aetiology of acute gastroenteritis include: intermediate incubation period (24–60 h), short infection duration (12–60 h) and high frequency of vomiting.
- **Amoebiasis**: caused by *Entamoeba histolytica* (an amoeboid protozoan)
 - ⇒ 10% of the world's population is chronically infected.
 - ⇒ can be asymptomatic, may cause mild diarrhoea

- ⇒ amoebic dysentery → profuse, bloody diarrhoea, stool microscopy may show trophozoites
- ⇒ treatment by metronidazole
- ⇒ Complication → Amoebic liver abscess
 - usually a single mass in the right lobe (may be multiple)
 - features: fever, RUQ pain
 - serology positive in > 90%

Scombrotoxin food poisoning

- Caused by the ingestion of foods that contain **high levels of histamine** and possibly other vasoactive amines and compounds.
- Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, by spoilage of foods such as;
 - ⇒ **fishery products, particularly tuna or mahi mahi.**
 - ⇒ **dark meat fish such as tuna, mackerel and marlin.**
 - ⇒ The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature. Cooking does not inactivate the toxin/histamines.
- **Incubation period**
 - ⇒ **10-60 minutes.**
- **Feature**
 - ⇒ The symptoms are due to ingestions of amines, **predominantly histamines**, produced by bacterial decarboxylation of histidine in fish meat.
 - ⇒ Onset is usually 10-30 minutes post-ingestion of the implicated fish but a delayed onset may occur up to two hours.
 - ⇒ Patients with pre-existing conditions such as bronchial asthma, and those taking isoniazid (a histaminase inhibitor) may be more symptomatic.
 - ⇒ **Presented with diarrhoea, flushing, sweating and a hot mouth, minutes after eating**
 - ⇒ Urticular rash, Bronchospasm

Treatment

- usually self-limiting
- In severe cases, symptoms respond rapidly to antihistamines, for example, chlorpheniramine and intravenous cimetidine by slow intravenous injection over at least five minutes.

Perforated viscus

the most appropriate next step in making the diagnosis → abdominal CT scan

Ascitic fluid is normally sterile and any growth of organisms is indicative of infective pathology.

Mixed growth suggests a large communication of micro-organisms into the abdominal cavity, which makes perforation the most likely cause.

- Ascitic fluid analysis:
 - ⇒ very bloody ascites
 - ⇒ secondary bacterial peritonitis
 - very inflammatory (very high neutrophil count)
 - exudate (low serum albumin ascites gradient - <11 g/L).
 - **Gram stain demonstrates multiple bacteria.**
- X-ray
 - distended bowel loops (dilated, oedematous)

➤ **Rigler's sign**, which indicates a perforated viscus.

- also known as the double wall sign, is seen on an X-ray of the abdomen when the air is present on both sides of the intestine, (luminal and peritoneal side of the bowel wall).

➤ **Dome sign**

- Air on the top of the liquid (fluid level)
- pneumatisos coli which are suggestive of ischaemic bowel but not diagnostic of this or perforation.

Rigler's Sign

Bowel wall visualised on both sides due to intra and extraluminal air

Usually large amounts of free air

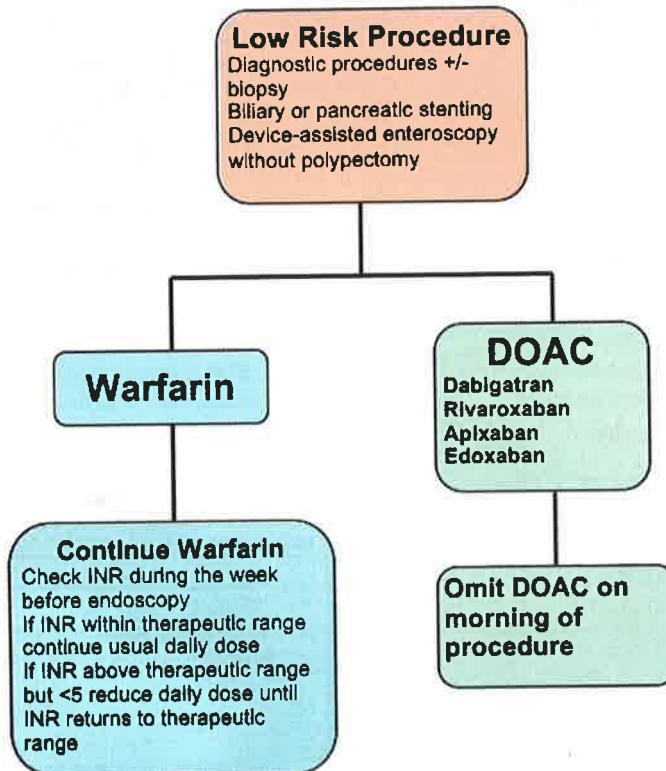
May be confused with overlapping loops of bowel, confirm with upright view

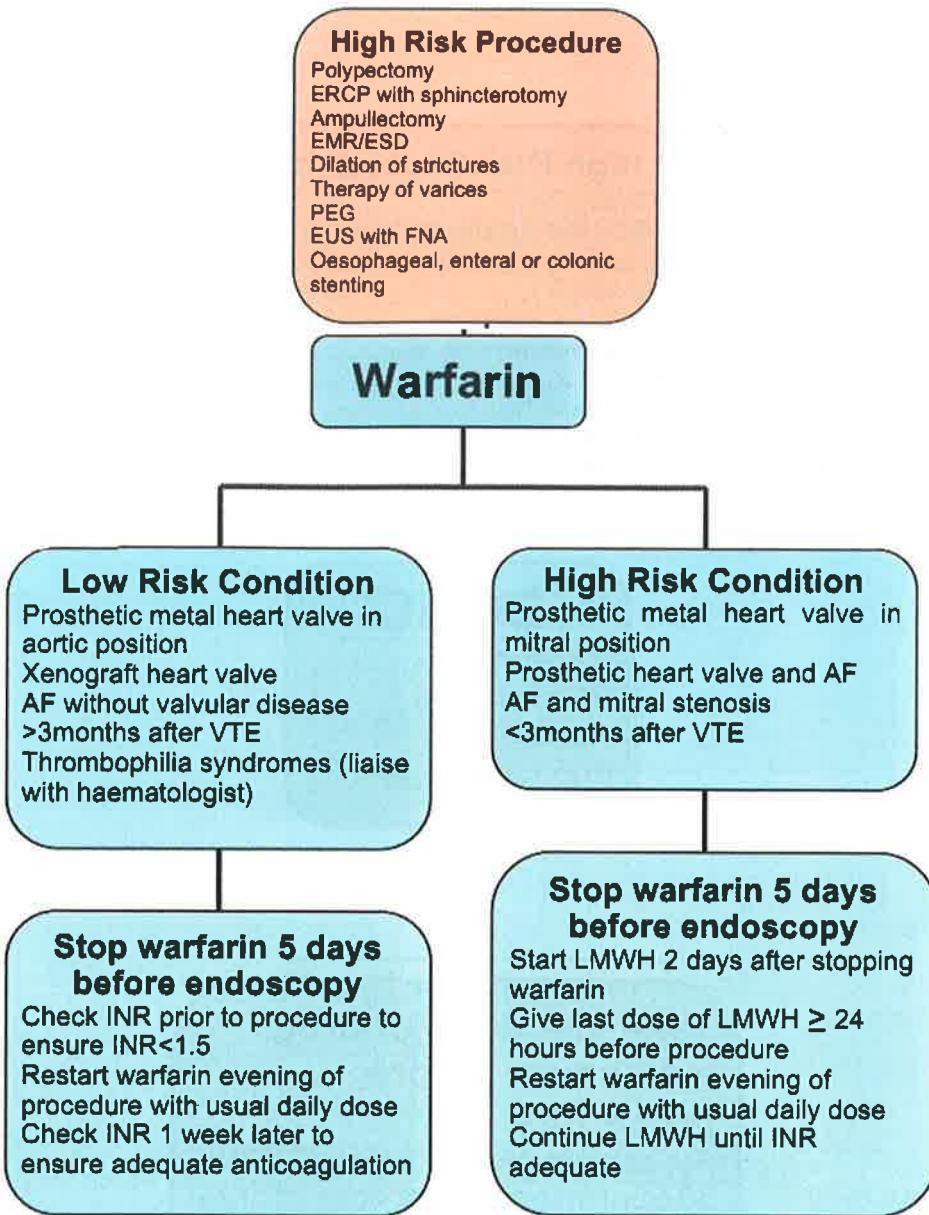


Endoscopy in patients on antiplatelet or anticoagulant therapy

British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines (2016)

- The risk of endoscopy in patients on anti-thrombotics depends on the risks of procedural haemorrhage versus thrombosis due to discontinuation of therapy.
- Where the endoscopic procedure carries a **high risk of bleeding** and the indication for **anticoagulation is low risk** for discontinuation then anticoagulation should be discontinued until the INR is <1.5 and restarted post-procedure. Bridging with heparin is not required.
 - Bridging is only recommended if the **indication for anticoagulation is high risk** - for example, mechanical mitral valve, atrial fibrillation (AF) and prosthetic valve, recent venous thromboembolism (VTE) (less than three months), thrombophilia.
 - Low molecular weight heparin (LMWH) is **relatively contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 30 mls/min**, these patients may require admission for unfractionated heparin (UFH) infusion.
- Where an endoscopic procedure is associated with a **low risk of haemorrhage** then the BSG recommends **continuation of anticoagulation at the current dosage** providing an INR within the last seven days is within the therapeutic range.





High Risk Procedure

Polypectomy
ERCP with sphincterotomy
Ampullectomy
EMR/ESD
Dilation of strictures
Therapy of varices
PEG
EUS with FNA
Oesophageal, enteral or colonic stenting

DOAC

Dabigatran
Rivaroxaban
Apixaban
Edoxaban

Take last dose of drug ≥ 48 hours before procedure

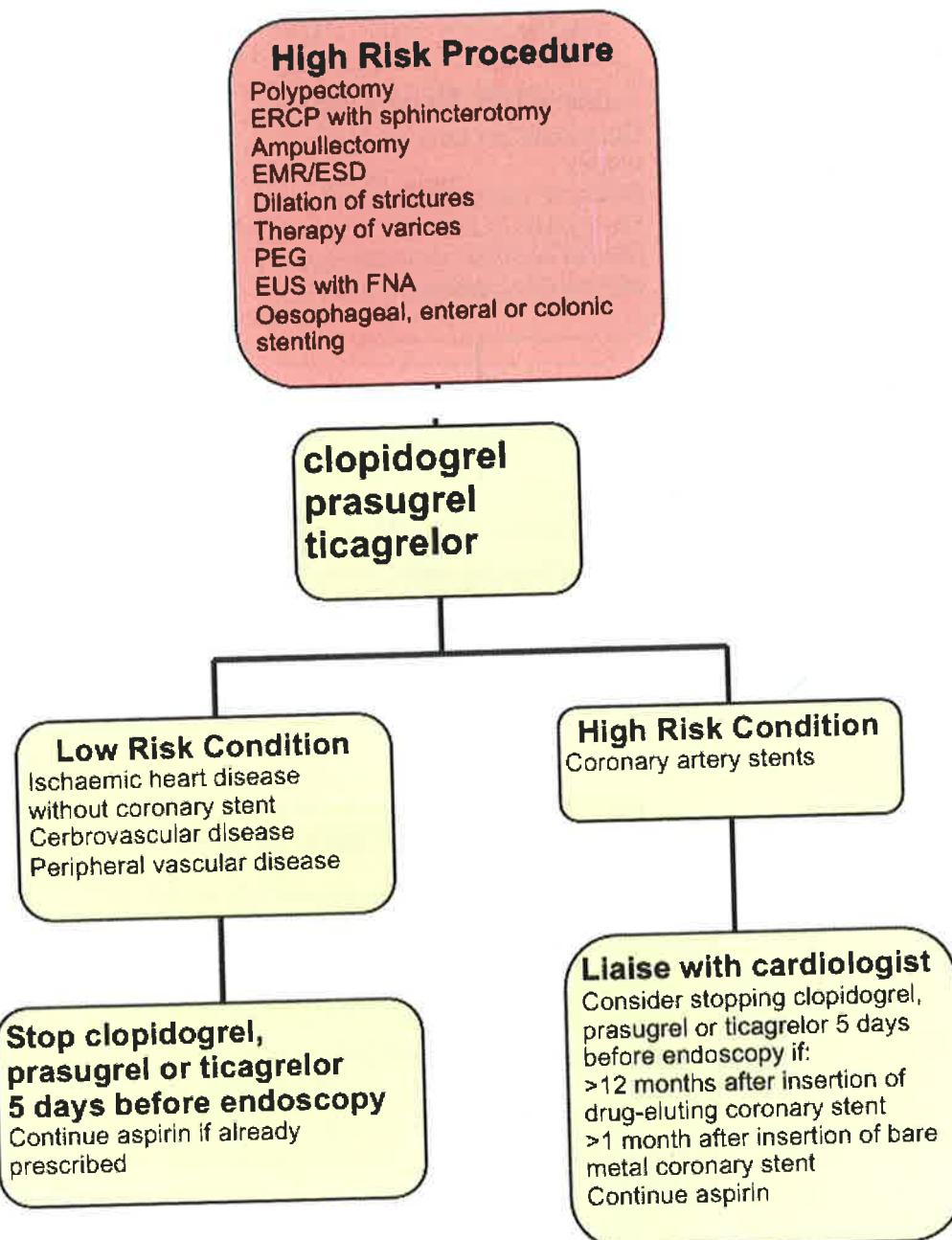
For dabigatran with CrCl (eGFR)
30-50ml/min take last dose of drug
72 hours before procedure
In any patient with rapidly
deteriorating renal function a
haematologist should be consulted

Low Risk Procedure

Diagnostic procedures +/- biopsy
Biliary or pancreatic stenting
Diagnostic EUS
Device-assisted enteroscopy without polypectomy

**clopidogrel
prasugrel
ticagrelor**

Continue therapy





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