

# MEDSTAR

## CLINICAL GUIDE AND SYNOPSIS

SECOND EDITION

### INTERNAL MEDICINE

PREPARED BY

GRADUATING CLASS OF 2015E.C (2022/23)

JIMMA UNIVERSITY, ETHIOPIA



**2<sup>nd</sup> Edition**

**MEDSTAR**

**CLINICAL GUIDE AND SYNOPSIS OF**

**INTERNAL MEDICINE**

**Cover design: Dr. Nahom Asnake(MI)**

**December,2022**

**PREPARED BY JIMMA UNIVERSITY GRADUATING CLASS OF 2023**



## EDITORS NOTE



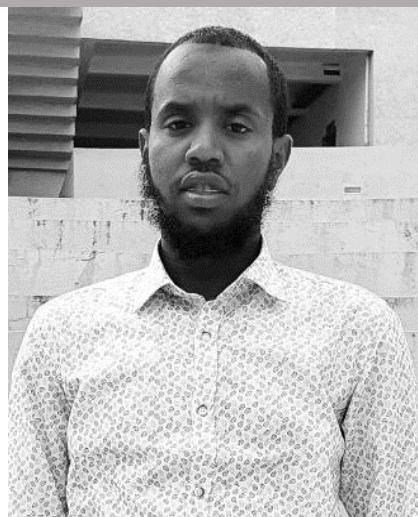
**DR. RAJIF SHAWUL (MI)**  
**CHIEF EDITOR**

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*I'm pleased to offer this second edition of MedStar in a way that is attractive to read.*

In this edition of Medstar Clinical guide and Synopsis we have given due emphasis on the originality, quality and Colour balance of the Textbook. The cover of *MedStar Internal Medicine* has included an image of a bright light. This symbol is used to indicate our motive and core principle of "**Every work of humankind should be a light for the other**".

In this edition, each table, diagram and figure were updated and placed with great care. We have also specified our references after every chapter and/ or Contributors portion, which will specify the source of a specific chapter.



**DR. SALAHADIN**  
**AHMED(MI)**  
**ASSISTANT EDITOR**

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*Be sure, you will feel better and be confident in clinical years with the content of this edition*



## **CONTENTS**

<b>CONTRIBUTORS.....</b>	<b>i</b>
<b>CHAPTER ONE.....</b>	<b>1</b>
<b>CARDINAL MANIFESTATION .....</b>	<b>1</b>
COUGH.....	1
HEMOPTYSIS .....	6
CHEST PAIN OR CHEST DISCOMFORT .....	11
SHORTNESS OF BREATH (DYSPNEA) .....	17
WEAKNESS .....	25
EDEMA.....	34
ABDOMINAL SWELLING AND ASCITES .....	40
ASCITES.....	43
AZOTEMIA AND URINARY ABNORMALITIES.....	46
GASTROINTESTINAL BLEEDING.....	50
<b>CHAPTER TWO.....</b>	<b>60</b>
<b>DISORDERS OF RESPIRATORY SYSTEM.....</b>	<b>60</b>
INFECTIOUS DISEASE OF RESPIRATORY SYSTEM.....	75
CHRONIC OBSTRUCTIVE DISEASES .....	85
BRONCHIECTASIS .....	109
RESTRICTIVE LUNG DISEASE.....	112
OTHER PULMONARY DISORDERS .....	116
<b>CHAPTER THREE.....</b>	<b>126</b>
<b>DISORDERS OF CARDIOVASCULAR SYSTEM.....</b>	<b>126</b>
INTRODUCTION TO CARDIOVASCULAR DISEASE .....	126
HEART FAILURE.....	138
ISCHEMIC HEART DISEASE.....	186
VALVULAR HEART DISEASE .....	201

HYPERTENSIVE HEART DISEASE.....	218
CARDIOMYOPATHIES .....	221
PERICARDIAL DISEASE .....	229
<b>CHAPTER FOUR.....</b>	<b>241</b>
<b>LIVER DISEASE.....</b>	<b>241</b>
LIVER DISEASE.....	241
CHRONIC LIVER DISEASE.....	247
<b>CHAPTER FIVE.....</b>	<b>281</b>
<b>DIABETES MELLITUS.....</b>	<b>281</b>
TYPE 1 DM .....	286
TYPE 2 DM.....	288
COMPLICATIONS OF DIABETES MELLITUS.....	291
DIABETES MELLITUS MANAGEMENT AND THERAPIES.....	321
<b>CHAPTER SIX.....</b>	<b>336</b>
<b>DISORDERS OF KIDNEY AND URINARY TRACT.....</b>	<b>336</b>
ACUTE KIDNEY INJURY (AKI) .....	344
CHRONIC KIDNEY DISEASE (CKD).....	358
GLOMERULAR DISEASES.....	374
POLYCYSTIC KIDNEY DISEASE (PKD).....	395
TUBULO-INTERSTITIAL DISEASES OF KIDNEY .....	399
ACUTE INTERSTITIAL NEPHRITIS (AIN).....	399
NEPHROLITHIASIS .....	403
<b>CHAPTER SEVEN.....</b>	<b>408</b>
<b>INFECTIOUS DISEASE.....</b>	<b>408</b>
TUBERCULOSIS .....	408
RETRO VIRAL INFECTION .....	428
HIV and TB .....	442
ACUTE RHEUMATIC FEVER.....	461

INFECTIVE ENDOCARDITIS .....	475
LEISHMANIASIS .....	494
SCHISTOSOMIASIS.....	500
<b>CHAPTER EIGHT.....</b>	<b>506</b>
<b>HEMATOLOGY.....</b>	<b>506</b>
ANEMIA .....	506
PULMONARY THROMBO EMBOLISM .....	530
DEEP VENOUS THROMBOSIS.....	531
BLEEDING DISORDERS .....	538
<b>CHAPTER NINE.....</b>	<b>551</b>
<b>NEUROLOGY.....</b>	<b>551</b>
STROKE .....	550
BRAIN ABSCESS .....	577
BACTERIAL MENINGITIS.....	582
<b>CHAPTER TEN.....</b>	<b>588</b>
<b>PHYSICAL EXAMINATION AND DISCUSSION.....</b>	<b>588</b>
RESPIRATORY SYSTEM PHYSICAL EXAMINATION.....	587
CVS PHYSICAL EXAMINATION .....	605
ABDOMINAL EXAMINATION.....	624
MOTOR EXAMINATION .....	635

# Preface

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When we envisioned this book of MedStar clinical guide and synopsis of Internal Medicine, our primary aim was to develop a compelling basic guide book in internal medicine which would provide an understanding of how to reach to a specific diagnosis of diseases. We are proud to present this book to you as a result of the hard work and dedication of our team.

As we were clinical year students, we understand the challenges and obstacles you will face in your studies. That is why we have worked tirelessly to compile a comprehensive collection of knowledge and advice to help you navigate your clinical year and beyond.

Revised and improved second edition contains most essential points of internal medicine in a student-friendly format. As per the feedback, suggestion and comments we have received, cardiovascular, Respiratory, Gastrointestinal, renal, infectious, neurology, Hematology, Endocrinology and physical Examination sections of the book have been thoroughly updated in this edition. New chapter of cardinal manifestation and bleeding diathesis are added.

Our team has spent countless hours researching, writing, and reviewing the information contained within these pages. We have drawn upon our own experiences, as well as the expertise of our faculty and mentors, to provide you with a valuable resource that will support you in your medical education and career.

We hope that this book will serve as a useful and practical guide for you as you embark on your journey in the medical field. We wish you the best of luck in your studies and in your future as a healthcare provider.

Your feedback and suggestions are welcome

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We would like to express our heartfelt gratitude towards medical students throughout Ethiopia as they have been encouraging and giving us constructive criticism through different platforms.

The contributors would like to acknowledge its honorable and archetype senior doctors, Dr. Gashahun Mekonen (Internist), Dr. Elsa Tegene (cardiologist), Dr. Amare Hailu (Internist), Dr. Kedir Negaso (internist, Cardiology fellow), Professor Samuel Yoo (Pulmonologist) and Dr. Alefe (internal Medicine, R3) for their Advisory while preparing this edition. We would like to express our special gratitude to Dr. Gashahun Mekonen and Dr. Kedir Negaso for their advisory and immense contribution in both 1<sup>st</sup> and 2<sup>nd</sup> edition of this textbook.

The Editors and contributors would like to thank all Jimma university medical students who have provided valuable feedback on this textbook and whose comments have helped shape this new edition

# CHAPTER ONE

## Cardinal manifestations

Cough

Hemoptysis

Chest pain

Dyspnea

Weakness

Edema

Abdominal swelling and ascites

Azotemia and urinary abnormalities

Gastrointestinal bleeding

### COUGH

- is a common symptom that ranges in significance from trivial to ominous.
- Typically, cough is a reflex response to stimuli that irritate receptors in the larynx, trachea, or large bronchi.
- These stimuli include mucus, pus, and blood, as well as external agents such as dust, foreign bodies, or even extremely hot or cold air.
- Other causes include inflammation of the respiratory mucosa and pressure or tension in the air passages from a tumor or enlarged peribronchial lymph nodes.
- Although cough typically signals a problem in the respiratory tract, it may also be cardiovascular in origin.
- Cough performs an essential protective function for human airways and lungs.
- Without an effective cough reflex, we are at risk for retained airway secretions and aspirated material predisposing to infection, atelectasis, and respiratory compromise.

## COUGH MECHANISM

- Spontaneous cough is triggered by stimulation of sensory nerve endings that are thought to be primarily rapidly adapting receptors and cough C fibers.
- Both chemical (e.g., capsaicin) and mechanical (e.g., particulates in air pollution) stimuli may initiate the cough reflex.
- Sensory signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius vaguely identified as the “cough center.”

## EVALUATION

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- For complaints of cough, a thorough assessment is in order.
  - Duration of the cough is important:
    - Is the cough acute, lasting less than 3 weeks;
    - subacute, lasting 3 to 8 weeks; or
    - chronic, more than 8 weeks?
- Ask whether the cough is dry or produces sputum, or phlegm.
  - If it is productive (produces sputum), ask the patient to describe the volume of any sputum and its color, odor, and consistency.
  - Is the cough worse at any time of day or night?
    - A dry cough at night may be an early symptom of asthma, as may a cough that comes in spasms lasting several minutes.
  - Is the cough aggravated by anything, for example allergic triggers such as dust, animals or pollen, or non-specific triggers like exercise or cold air?
    - The increased reactivity of the airways seen in asthma, and in some normal people for several weeks after viral respiratory infections, may present in this way. Severe coughing, whatever its cause, may be followed by vomiting.
  - The symptoms associated with a cough often lead you to its cause.

## CAUSES OF COUGH

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- Acute cough
  - Upper respiratory infections
  - Common cold
  - Acute bronchitis
  - Pneumonia
  - Pulmonary embolism

- Chronic cough
  - Tuberculosis
  - Chronic obstructive pulmonary disease (COPD)
  - Lung carcinoma
  - Bronchiectasis
  - Interstitial lung disease

**Table: causes of cough**

Origin	Common causes	Clinical features
<b>Pharynx</b>	Post-nasal drip	History of chronic rhinitis
<b>Larynx</b>	Laryngitis, tumor, whooping cough, croup	Voice or swallowing altered, harsh or painful cough Paroxysms of cough, often associated with stridor
<b>Trachea</b>	Tracheitis	Raw retrosternal pain with cough
<b>Bronchi</b>	Bronchitis (acute) and chronic obstructive pulmonary disease (COPD)	Dry or productive, worse in mornings
	Asthma	Usually dry, worse at night
	Eosinophilic bronchitis	Features similar to asthma but airway hyper-reactivity absent
	Lung cancer	Persistent (often with hemoptysis)
<b>Lung parenchyma</b>	Tuberculosis	Productive (often with hemoptysis)
	Pneumonia	Dry initially, productive later
	Bronchiectasis	Productive, changes in posture induce sputum production
	Pulmonary oedema	Often at night (may be productive of pink, frothy sputum)
	Interstitial fibrosis	Dry and distressing
<b>Drug side-effect</b>	Angiotensin-converting enzyme (ACE) inhibitors	Dry cough
<b>Aspiration</b>	Gastro-esophageal reflux disease (GORD)	History of acid reflux, heartburn, hiatus hernia Obesity

## SPUTUM

- Sputum is mucus produced from the respiratory tract.
- The normal lung produces about 100 ml of clear sputum each day, which is transported to the oropharynx and swallowed.
- There are four main types of sputum

**Table: Types of Sputum**

Type	Appearance	Cause
Serous	Clear, watery	Acute pulmonary oedema
	Frothy, pink	Alveolar cell cancer
Mucoid	Clear, grey	Chronic bronchitis/chronic obstructive pulmonary disease
	White, viscid	Asthma
Purulent	Yellow	Acute bronchopulmonary infection Asthma (eosinophils)
	Green	Longer-standing infection Pneumonia Bronchiectasis Cystic fibrosis Lung abscess
Rusty	Rusty red	Pneumococcal pneumonia

## EVALUATION

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- Ask the patient to describe the volume of any sputum and its
  - Color
    - Clear or ‘mucoid’ sputum is produced in chronic bronchitis and COPD with no active infection.
    - Yellow sputum occurs in acute lower respiratory tract infection (live neutrophils) and in asthma (eosinophils).
    - Green purulent sputum (dead neutrophils) indicates chronic infection, e.g.in COPD or bronchiectasis.
    - Rusty red sputum can occur in early pneumococcal pneumonia, as pneumonic inflammation causes lysis of red cells
  - Volume
    - To help patients quantify volume, try a multiple-choice question.

- ↳ “How much do you think you cough up in 24 hours: a teaspoon, tablespoon, quarter cup, half cup, cupful?”
- If possible, ask the patient to cough into a tissue; inspect the phlegm and note its characteristics
- Odor (Taste)
  - **Foul-tasting or smelling sputum** suggests anaerobic bacterial infection, and occurs in bronchiectasis, lung abscess and empyema.
  - In bronchiectasis a change of sputum taste may indicate an infective exacerbation.
- Consistency

## HEMOPTYSIS

- Hemoptysis is the expectoration of blood from the respiratory tract.

### ANATOMY AND PHYSIOLOGY OF HEMOPTYSIS

- Hemoptysis can arise from anywhere in the respiratory tract; from the glottis to the alveolus.
- Most commonly, bleeding arises from the bronchi or medium sized airways, but a thorough evaluation of the entire respiratory tree is often necessary.
- A unique feature of the lung that predisposes to hemoptysis of varied severity is its dual blood supply—the pulmonary and bronchial circulations.
- Most hemoptysis is due to vessels in the bronchial circulation and is, therefore, under systemic pressure, making it more challenging to arrest the bleeding.

### EVALUATION

- For patients reporting hemoptysis,
  - assess the **volume of blood produced** as well as the other sputum attributes;
    - The first step in evaluating hemoptysis is to determine the amount or severity of bleeding.
    - It is crucial to determine whether the amount of blood expectorated is massive;
  - ↳ This determination is clinically important as patients rarely die of exsanguination and, instead, are at risk of death due to asphyxiation from blood filling the airways and airspaces.
  - Ask about the related setting and activity and any associated symptoms.
  - Before using the term “hemoptysis,” try to confirm the source of the bleeding.
  - It is sometimes difficult for the patient to describe whether or not the blood has

#### What is massive hemoptysis?

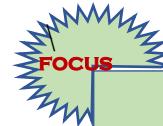
- While there is no agreed-upon volume, **blood loss of 400 ml in 24 hours or 100–150 ml expectorated at one time** are considered **massive hemoptysis**.
- These numbers derive from the volume of the tracheobronchial tree (generally 100–200 mL).

#### FOCUS

- Hemoptysis is rare in infants, children, and adolescents, although common in **cystic fibrosis**.
- Blood originating in the stomach is usually darker than blood from the respiratory tract and may be mixed with food particles

originated from the chest or whether it comes from the gums or nose, or even from the stomach.

- They should always be asked about associated conditions such as epistaxis, or the subsequent development of melena (altered blood in the stool), which occurs in the case of upper gastrointestinal bleeding.
- When vomited, it probably originates in the gastrointestinal tract.
- Occasionally, however, blood from the nasopharynx or the gastrointestinal tract is aspirated and then coughed out.



- World Wide the most common cause of Hemoptysis  
→ **Tuberculosis**
- The most common cause of massive hemoptysis  
→ **Bronchiectasis**

## CAUSES OF HEMOPTYSIS

- Most common causes are: -
  - Lung Cancer
  - Bronchiectasis
  - Acute bronchitis
  - Tuberculosis
  - Pulmonary infarction
  - Acute left ventricular failure

**Table: Causes of Hemoptysis**

<b>Bronchial disease</b>	<i>Cancer</i> <i>Bronchiectasis</i> <i>Acute bronchitis</i> Bronchial adenoma Foreign body
<b>Parenchymal disease</b>	<i>Tuberculosis</i> Suppurative pneumonia Parasites (e.g., hydatid disease, flukes) Lung abscess Trauma Actinomycosis Mycetoma
<b>Lung vascular disease</b>	<i>Pulmonary infarction</i> Goodpasture's syndrome Polyarteritis nodosa

	Idiopathic pulmonary hemosiderosis
<b>Cardiovascular disease</b>	<b>Acute left ventricular failure</b> Mitral stenosis Aortic aneurysm
<b>Blood disorders</b>	Leukemia Hemophilia Anticoagulants

**Table: How Differentiate between hemoptysis and hematemesis**

Hemoptysis	Hematemesis
Blood in the sputum	Blood in the vomitus
The prodromal symptom is either irritation of throat or cough	The prodrome is either nausea or abdominal discomfort
Blood is <b>bright red</b> or frothy	Blood is <b>magenta-colored or brownish-black</b> due to formation of acid hematin
Blood in sputum is alkaline in reaction	Reaction of blood is acidic
It is mixed with sputum	It is mixed with food particles

## INVESTIGATIONS

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### CBC

- WBC count raised in bacterial infection
- Anemia characteristic of chronic disease common
- Eosinophilia in allergic conditions
- Marked lymphocytosis in pertussis

### ESR

- Elevated in infection, inflammation

### Purified Protein Derivative (PPD) Skin Test

- Performed in patients with high risk of pulmonary TB
- Results are read within 48 – 72 hours of placement.
- Test is considered positive if skin erythema measures  $\geq 5$  mm for HIV-infected and other immunocompromised individuals;  $\geq 10$  mm for those at high risk; and  $\geq 15$  for all others.

### Gene Xpert

## CXR

- Helpful in evaluating for:
  - Pneumonia (consolidation)
  - Bronchiectasis (dilated tubular or cystic mucus filled bronchi)
  - COPD (hyperinflation, flat diaphragm)
  - TB (upper lobe infiltrates, hilar lymphadenopathy, cavitary lesions, pleural effusion)
  - Sarcoid (hilar lymphadenopathy)
  - CHF (pulmonary edema, vascular congestion, Kerley B lines, peripheral infiltrates, pleural effusion, cardiomegaly)
  - Bronchogenic carcinoma (hilar mass or a single coin shadow).
- A normal CXR in an immunocompetent patient with chronic cough usually excludes tuberculosis, bronchiectasis, persistent pneumonia, bronchogenic carcinoma, and sarcoidosis. However, chronic cough can be a cause of many disorders in spite of a normal CXR; a few of such conditions are given in Table below

## PEAK EXPIRATORY FLOW RATE (PEFR)

- Serial measurements of peak flow rates on waking, i.e., early morning, during day, and before bed, demonstrating wide variations in airflow limitation is seen in asthma, and facilitates monitoring its treatment.

## CT OF CHEST /MRI

- More sensitive for evaluating patients with equivocal or negative CXR findings.
- Assists in evaluating for mass lesions of neoplasms, sarcoid, ILDs, and bronchiectasis.

## BRONCHOSCOPY

- Generally indicated in patients with:
  - CT/MRI suggesting neoplasm and their biopsy procedures
  - Foreign body aspiration
  - Chronic, persistent cough with negative clinical and lab work out
  - Cough with hemoptysis.

**Table: Causes of chronic cough among adults with normal CXR**

<b>Diagnosis</b>	<b>Differential diagnosis with normal CXR</b>
Environmental	Tobacco exposure; industrial pollutants; occupational allergens
Infections	Postinfectious cough; chronic respiratory bronchitis; TB; bronchiectasis; tropical pulmonary eosinophilia; whooping cough
infections/ Cerumen	Otitis media with disorders—ENT effusion; chronic sinusitis; nasal polyp; vocal cord dysfunction/paralysis; aspiration
Asthma	Cough-variant asthma; postinfectious hyperactivity airways
Cardiac	CHF; mitral stenosis
GI disorders	Gastroesophageal reflux
Neoplasia	Bronchial adenoma; mediastinal mass with tracheal compression; laryngeal papilloma, hemangioma
Iatrogenic Drug induced	Foreign body – nose; ear; trachea; larynx; bronchus
Psychogenic	Habit cough; tic cough; psychogenic cough

## CHEST PAIN OR CHEST DISCOMFORT

- Complaints of chest pain or chest discomfort raise concern about heart disease but often arise from structures in the thorax and lungs as well.
- Lung tissue has no pain fibers. Pain in conditions such as pneumonia or pulmonary infarction usually arises from inflammation of the adjacent parietal pleura.
- Muscle strain from prolonged recurrent coughing may also be responsible.
- The pericardium also has few pain fibers.
- The pain of pericarditis stems from inflammation of the adjacent parietal pleura.
- Chest pain is commonly also associated with anxiety, but the mechanism remains obscure.
- Chest pain can result from cardiac, respiratory, esophageal or musculoskeletal disorders.

## EVALUATION

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- **There are some key features that must be elicited from the history.**
  - Your initial questions should be as open-ended as possible. “Do you have any discomfort or unpleasant feelings in your chest?”
  - Careful assessment of patient’s history and cardiac risk factors is often the most helpful starting point.
  - **Historical features generally useful in the diagnosis of cardiac origin of chest pain include:**
    - Location (**diffuse, anterior retrosternal pain, chest pain, interscapular pain**)
    - Radiation (**to the neck, jaw, shoulders or arms**)
    - Aggravating factors (**exertion, meals, cold weather, and stress**)
    - Duration (**brief pain lasting few seconds to few minutes**)
    - Relieving **factors (rest)**
    - Associated symptoms (**dyspnea, cough, diaphoresis, presyncope, syncope**)
    - Pain that radiates to the left arm and shoulder is often assumed to indicate coronary ischemia, whereas pain that radiates to the right shoulder is thought to suggest a biliary source.
    - However, chest pain that radiates to the right shoulder is more specific for pain of cardiac origin than pain that radiates to the left shoulder. Radiation of chest discomfort to the right arm is also consistent with the diagnosis of acute IHD

**Table: Causes of Chest Pain or Chest Discomfort**

Central	Peripheral
<b>Cardiac</b>	<b>Lungs/pleura</b>
<ul style="list-style-type: none"> <li>▪ Myocardial ischemia (angina)</li> <li>▪ Myocardial infarction</li> <li>▪ Myocarditis</li> <li>▪ Pericarditis</li> <li>▪ Mitral valve prolapse syndrome</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pulmonary infarct</li> <li>▪ Pneumonia</li> <li>▪ Pneumothorax</li> <li>▪ Malignancy</li> <li>▪ Tuberculosis</li> <li>▪ Connective tissue disorders</li> </ul>
<b>Aortic</b>	<b>Musculoskeletal</b>
<ul style="list-style-type: none"> <li>▪ Aortic dissection</li> <li>▪ Aortic aneurysm</li> </ul>	<ul style="list-style-type: none"> <li>▪ Osteoarthritis</li> <li>▪ Rib fracture/injury</li> <li>▪ Acute vertebral fracture</li> <li>▪ Costochondritis (Tietze's syndrome)</li> <li>▪ Intercostal muscle injury</li> <li>▪ Epidemic myalgia (Bornholm disease)</li> </ul>
<b>Esophageal</b>	<b>Neurological</b>
<ul style="list-style-type: none"> <li>▪ Esophagitis</li> <li>▪ Esophageal spasm</li> <li>▪ Mallory–Weiss syndrome</li> <li>▪ Esophageal perforation (Boerhaave's syndrome)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Prolapsed intervertebral disc</li> <li>▪ Herpes zoster</li> <li>▪ Thoracic outlet syndrome</li> </ul>
<ul style="list-style-type: none"> <li>▪ Pulmonary embolus</li> <li>▪ Mediastinal</li> </ul>	
<ul style="list-style-type: none"> <li>▪ Malignancy</li> <li>▪ Anxiety/emotion</li> </ul>	

- Acute, sudden and severe chest pain described as ripping or tearing that is maximal at onset and radiates to interscapular area raises the possibility of aortic dissection. Important diagnostic feature is the inequality in the pulses, e.g., carotid, radial and femoral, and a blood pressure differential of greater than 20 mm Hg
- The pain of diffuse esophageal spasm may mimic that of angina pectoris, including that the relief in many cases is obtained with nitroglycerine.
- Severe chest pain, retrosternal, accompanied by dyspnea, cough, and hemoptysis developing in a patient who has been immobilized or bedridden is suggestive of pulmonary embolism

- Pulmonary hypertensive pain may resemble angina in that it is precipitated by effort.
- Associated moderate or severe dyspnea and evidence of signs of pulmonary hypertension suggest its diagnosis
- Chest discomfort due to pericarditis is typically retrosternal, aggravated by coughing, deep respiration, or change in position; worse in supine, and relieved in sitting upright and leaning forward
- The acute onset of pleuritic pain and dyspnea in a patient with a history of asthma or emphysema is suggestive of pneumothorax.
- Psychogenic chest pain is often associated with hyperventilation and other somatic symptoms such as chronic headache, dizziness, sweating, paresthesia, and a sense of ‘impending doom’.

**Table: Summary of causes of shortness of breath with presentation features**

Causes	Description	
<b>Angina Pectoris</b>	Location	Retrosternal or across the anterior chest, sometimes radiating to the shoulders, arms, neck, lower jaw, or upper abdomen
	Quality	Pressing, squeezing, tight, heavy, occasionally burning
	Severity	Mild to moderate, sometimes perceived as discomfort rather than pain
	Timing	Usually 1–3 min but up to 10 min. Prolonged episodes up to 20 min
	Factors That Aggravate	Exertion, especially in the cold; meals; emotional stress. May occur at rest
	Factors That Relieve	Rest, nitroglycerin
	Associated Symptoms	Sometimes dyspnea, nausea, sweating
<b>Myocardial Infarction</b>	Location	Same as in angina
	Quality	Same as in angina
	Severity	Often but not always a severe pain
	Timing	20 min to several hours
	Factors That Aggravate	-
	Factors That Relieve	-
	Associated Symptoms	Dyspnea, nausea, vomiting, sweating, weakness
<b>Pericarditis</b>	Location	Retrosternal or left precordial, may radiate to the tip of left shoulder

	Quality	Sharp, knifelike
	Severity	Often severe
	Timing	persistent
	Factors That Aggravate	Breathing, changing position, coughing, lying down, sometimes swallowing
	Factors That Relieve	Sitting forward may relieve it.
	Associated Symptoms	Seen in autoimmune disorders, post-myocardial infarction, viral infection, chest irradiation
<b>Pulmonary</b>		
<b>Tracheobronchitis</b>	Location	Upper sternal or on either side of the sternum
	Quality	Burning
	Severity	Mild to moderate
	Timing	Abrupt onset, early peak, persistent for hours or more
	Factors That Aggravate	Hypertension
	Factors That Relieve	
	Associated Symptoms	If thoracic, hoarseness, dysphagia, also syncope, hemiplegia, paraplegia
<b>Pleuritic Pain /as in pleurisy, pneumonia, pulmonary infarction, or neoplasm /</b>	Location	Chest wall overlying the process
	Quality	Sharp, knifelike
	Severity	Often severe
	Timing	Variable
	Factors That Aggravate	Coughing
	Factors That Relieve	Lying on the involved side may relieve it.
	Associated Symptoms	Cough
<b>Chest Wall Pain, Costochondritis</b>	Location	Variable, often unclear Often below the left breast or along the costal cartilages.
	Quality	Stabbing, sticking, or dull, aching
	Severity	Variable
	Timing	Fleeting to hours or days
	Factors That Aggravate	Movement of chest, trunk, arms
	Factors That Relieve	=

	Associated Symptoms	Often local tenderness
<b>Other</b>		
<b>Anxiety</b>	Location	Precordial, below the left breast, or across the anterior chest
	Quality	Stabbing, sticking, or dull, aching
	Severity	Variable
	Timing	Fleeting to hours or days
	Factors That Aggravate	May follow effort, emotional stress
	Factors That Relieve	--
	Associated Symptoms	Breathlessness, palpitations, weakness, anxiety

## INVESTIGATIONS

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### CBC

- Anemia — aggravates cardiac ischemia.
- Leukocytosis in lung infection, infarction, and bacterial pericarditis

### RBS /Lipid Profile

- To assess risk factors for CAD.

### ECG

- When obvious ST-segment elevation is present in patients with acute chest pain, the diagnosis
- of myocardial injury is straight forward. However, significantly more than 50% of patients with AMI have nondiagnostic ECG changes. The ECG becomes even less sensitive with increasing age and in those with a previous
- MI. Also, many ECG patterns interfere with the diagnosis of AMI. These include left bundle branch block, WPW syndrome, early repolarization ST changes, left ventricular hypertrophy, hyperkalemia, digoxin effect, etc.
- Further, ST-T changes in patients with chest pain due to MI, PE, and pericarditis can be similar; therefore, the clinical history and physical examination, as well as ECG clues, must be considered before making a diagnosis

### CARDIAC ENZYMES

- Cardiac troponin and CK-MB are elevated with MI in the setting of acute LVF.

#### **ECHOCARDIOGRAPHY – 2-D and Doppler**

- In patients with acute chest pain due to MI, this technique can be performed at the bedside, and is very useful for assessing right and left ventricular function, wall motion abnormalities, identification of vegetations in endocarditis, and for detecting important complications such as mitral regurgitation, ventricular septal defects, pericardial effusion, and cardiac rupture.
- In aortic dissection, Doppler echo may show aortic regurgitation, a dilated aortic root and, occasionally, the flap of the dissection.

## SHORTNESS OF BREATH (DYSPNEA)

- Literally the term *dyspnea* means difficult of breathing.
- **Dyspnea**, commonly termed *shortness of breath*, is a painless but uncomfortable awareness of breathing that is inappropriate to the level of exertion.
- Clinically, dyspnea is a term applied to sensations experienced by individuals who complain of unpleasant or uncomfortable respiratory sensations.
- The sensation of dyspnea is subjective, and includes both the perception of labored breathing by the patient and the reaction to that sensation, which varies in quality and intensity.
- A recent consensus statement from the American Thoracic Society offered the following definition of dyspnea
  - ↳ “**Dyspnea** is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses
- Thoroughly assess this prominent symptom of cardiac and pulmonary disease.

## EVALUATION

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- For patients with a known prior pulmonary, cardiac, or neuromuscular condition and worsening dyspnea, the initial focus of the evaluation will usually address determining whether the known condition has progressed or whether a new process has developed that is **causing dyspnea**.
- For patients without a prior known potential cause of dyspnea, the initial evaluation will focus on **determining an underlying etiology**.
- Determining the underlying cause, if possible, is extremely important, as the treatment may vary dramatically based upon the predisposing condition.
- Ask, “Have you had any difficulty breathing?”
  - **Mode of onset, duration and progression**
    - Psychogenic breathlessness may occur suddenly at rest or while talking. Patients often say they cannot
  - **Variability and aggravating/ relieving factors**
  - **Severity**
    - Because of variations in age, body weight, and physical fitness, there is no absolute scale for quantifying **dyspnea**.

- Instead, make every effort **to determine its severity based on the patient's daily activities.**
- Find out when the symptom occurs, at rest or with exercise, and how much exertion produces onset
  - How many steps or flights of stairs can the patient climb before pausing for breath?
  - What about carrying bags of groceries, mopping the floor, or making the bed?
  - Has dyspnea altered the patient's lifestyle and daily activities? How?
- Dyspnea while walking on the flat, up gentle inclines or stairs indicates a significant condition.
- Most patients relate shortness of breath to their level of activity. Anxious patients present a different picture. They may describe difficulty taking a deep enough breath, a smothering sensation with inability to get enough air, paresthesia, or sensations of tingling or “pins and needles” around the lips or in the extremities.

**Table: Causes of Shortness of Breath**

Non-cardiorespiratory	Cardiac
<ul style="list-style-type: none"> <li>▪ Anemia</li> <li>▪ Metabolic acidosis</li> <li>▪ Obesity</li> <li>▪ Psychogenic</li> <li>▪ Neurogenic</li> </ul>	<ul style="list-style-type: none"> <li>▪ Left ventricular failure</li> <li>▪ Mitral valve disease</li> <li>▪ Cardiomyopathy</li> <li>▪ Constrictive pericarditis</li> <li>▪ Pericardial effusion</li> </ul>
<b>Respiratory</b>	
Airways	Parenchyma
<ul style="list-style-type: none"> <li>▪ Laryngeal tumor</li> <li>▪ Foreign body</li> <li>▪ Asthma</li> <li>▪ COPD</li> <li>▪ Bronchiectasis</li> <li>▪ Lung cancer</li> <li>▪ Bronchiolitis</li> <li>▪ Cystic fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Tuberculosis</li> <li>▪ Pneumonia</li> <li>▪ Diffuse infections, e.g., <i>Pneumocystis jirovecii</i> pneumonia</li> <li>▪ Pulmonary fibrosis</li> <li>▪ Alveolitis</li> <li>▪ Sarcoidosis</li> <li>▪ Tumor (metastatic, lymphangitis)</li> </ul>
Pleural	Pulmonary circulation

<ul style="list-style-type: none"> <li>▪ Pneumothorax</li> <li>▪ Effusion</li> <li>▪ Diffuse pleural fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pulmonary thromboembolism</li> <li>▪ Pulmonary vasculitis</li> <li>▪ Primary pulmonary hypertension</li> </ul>
<b>Chest wall</b>	<b>Neuromuscular</b>
<ul style="list-style-type: none"> <li>▪ Kyphoscoliosis</li> <li>▪ Ankylosing spondylitis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Myasthenia gravis</li> <li>▪ Neuropathies</li> <li>▪ Muscular dystrophies</li> <li>▪ Guillain–Barré syndrome</li> </ul>

**Table: Summary causes shortness of breath with presentation features**

Causes		Description
<b>Left-Sided Heart Failure (Left ventricular failure or mitral stenosis)</b>	Process	Elevated pressure in pulmonary capillary bed with transudation of fluid into interstitial spaces and alveoli, decreased compliance (increased stiffness) of the lungs, increased work of breathing
	Timing	Dyspnea may progress slowly, or suddenly as in acute pulmonary edema.
	Factors that aggravate	Exertion, lying down
	Factors that relieve	Rest, sitting up, though dyspnea may become persistent
	Associated symptoms	Often cough, orthopnea, paroxysmal nocturnal dyspnea; sometimes wheezing
	Setting	History of heart disease or its predisposing factors
<b>Chronic Bronchitis</b>	Process	Excessive mucus production in bronchi, followed by chronic obstruction of airways
	Timing	Chronic productive cough followed by slowly progressive dyspnea

	Factors that aggravate	Exertion, inhaled irritants, respiratory infections
	Factors that relieve	Expectoration; rest, though dyspnea may become persistent
	Associated symptoms	Chronic productive cough, recurrent respiratory infections; wheezing may develop
	Setting	History of smoking, air pollutants, recurrent respiratory infections
<b>Chronic Obstructive Pulmonary Disease (COPD)</b>	Process	Overdistention of air spaces distal to terminal bronchioles, with destruction of alveolar septa, alveolar enlargement and limitation of expiratory air flow
	Timing	Slowly progressive dyspnea; relatively mild cough later
	Factors that aggravate	Exertion
	Factors that relieve	Rest, though dyspnea may become persistent
	Associated symptoms	Cough, with scant mucoid sputum
	Setting	History of smoking, air pollutants
<b>Asthma</b>	Process	Reversible bronchial hyperresponsiveness involving release of inflammatory mediators, increased airway secretions, and bronchoconstriction
	Timing	Acute episodes, separated by symptomfree periods. Nocturnal episodes common
	Factors that aggravate	Variable, including allergens, irritants, respiratory infections, exercise, and emotion

	Factors that relieve	Separation from aggravating factors
	Associated symptoms	Wheezing, cough, tightness in chest
	Setting	Environmental and emotional conditions
<b>Diffuse Interstitial Lung Diseases</b> (such as sarcoidosis, widespread neoplasms, asbestosis, and idiopathic pulmonary fibrosis)	Process	Abnormal and widespread infiltration of cells, fluid, and collagen into interstitial spaces between alveoli. Many causes
	Timing	Progressive dyspnea, which varies in its rate of development with the cause
	Factors that aggravate	Exertion
	Factors that relieve	Rest, though dyspnea may become persistent
	Associated symptoms	Often weakness, fatigue. Cough less common than in other lung diseases
	Setting	Varied. Exposure to trigger substances.
<b>Pneumonia</b>	Process	Inflammation of lung parenchyma from the respiratory bronchioles to the alveoli
	Timing	An acute illness, timing varies with the causative agent
	Factors that aggravate	
	Factors that relieve	
	Associated symptoms	Pleuritic pain, cough, sputum, fever, though not necessarily present

	Setting	Varied.
<b>Spontaneous Pneumothorax</b>	Process	Leakage of air into pleural space through blebs on visceral pleura, with resulting partial or complete collapse of the lung
	Timing	Sudden onset of dyspnea
	Factors that aggravate	
	Factors that relieve	
	Associated symptoms	Pleuritic pain, cough
	Setting	Often a previously healthy young adult
<b>Acute Pulmonary Embolism</b>	Process	Sudden occlusion of all or part of pulmonary arterial tree by a blood clot that usually originates in deep veins of legs or pelvis
	Timing	Sudden onset of dyspnea
	Factors that aggravate	--
	Factors that relieve	---
	Associated symptoms	Often none. Retrosternal oppressive pain if the occlusion is massive. Pleuritic pain, cough, and hemoptysis may follow an embolism if pulmonary infarction ensues. Symptoms of anxiety
	Setting	Postpartum or postoperative periods; prolonged bed rest; heart failure, chronic lung disease, and fractures of hip or

		leg; deep venous thrombosis (often not clinically apparent)
<b>Anxiety With Hyperventilation</b>	Process	Overbreathing, with resultant respiratory alkalosis and fall in arterial partial pressure of carbon dioxide (pCO <sub>2</sub> )
	Timing	Episodic, often recurrent
	Factors that aggravate	Often occurs at rest. An upsetting event may not be evident.
	Factors that relieve	Breathing in and out of a paper or plastic bag may help
	Associated symptoms	Sighing, lightheadedness, numbness or tingling of the hands and feet, palpitations, chest pain
	Setting	Often occurs at rest. An upsetting event may not be evident.

INVESTIGATIONS	
CBC	<ul style="list-style-type: none"> <li>Anemia aggravates dyspnea of any etiology</li> <li>WBC count may be increased in pulmonary infection</li> <li>Significant eosinophilia is commonly reported in asthma</li> <li>Thrombocytopenia may accompany ARDS.</li> </ul>
RBS / Electrolytes, Urinalysis	<ul style="list-style-type: none"> <li>To exclude hyperglycemia, and DKA</li> <li>Renal and electrolyte abnormalities can precipitate acute dyspnea</li> </ul>
CXR	<ul style="list-style-type: none"> <li>Can demonstrate consolidation, infiltrate, effusion, pneumothorax, bullae, pulmonary edema, tumor, and cardiomegaly</li> <li>In pulmonary embolism, the CXR is usually normal, but abnormalities include focal oligemia (i.e., Westermark's sign); a peripheral wedge-shaped density (i.e., Hampton's hump); pleural effusions; elevated hemidiaphragm; or an enlarged right descending pulmonary artery (i.e. Palla's sign).</li> </ul>
X-ray of Neck — Lateral View	<ul style="list-style-type: none"> <li>May be indicated in patients with stridor. to exclude obstructive lesion or foreign body aspiration.</li> </ul>
ECG	<ul style="list-style-type: none"> <li>Although in most dyspneic patients the ECG does not contribute much to diagnosis, it does indicate whether heart disease of any disorder is present, such as cardiac ischemia, arrhythmia, chamber hypertrophy, and heart block. These cardiac disorders can contribute to acute dyspnea. Also, lung disease eventually affects right side of the heart, and may cause changes suggesting lung disease such as right atrial or right ventricular hypertrophy in pulmonary hypertension</li> <li>The complex of an <b>S wave in lead I, a Q wave in III, and an inverted T wave in lead III</b> is specific for pulmonary embolism, but rarely seen.</li> </ul>
Specific investigations	
Echocardiography	<ul style="list-style-type: none"> <li>This is indicated if CHF, valvular heart disease, or pericardial effusion is suspected. It also helps to identify an embolus in suspected PE. Pulmonary artery pressure can also be estimated to rule out pulmonary hypertension causing dyspnea.</li> </ul>
Bronchoscopy	<ul style="list-style-type: none"> <li>It should be performed if aspiration of foreign body is suspected; the procedure can be both diagnostic and therapeutic.</li> </ul>
Arterial Blood Gases (ABG)	<ul style="list-style-type: none"> <li>Useful in assessing the type, degree of respiratory failure, and measuring the overall acid-base status</li> </ul>

## WEAKNESS

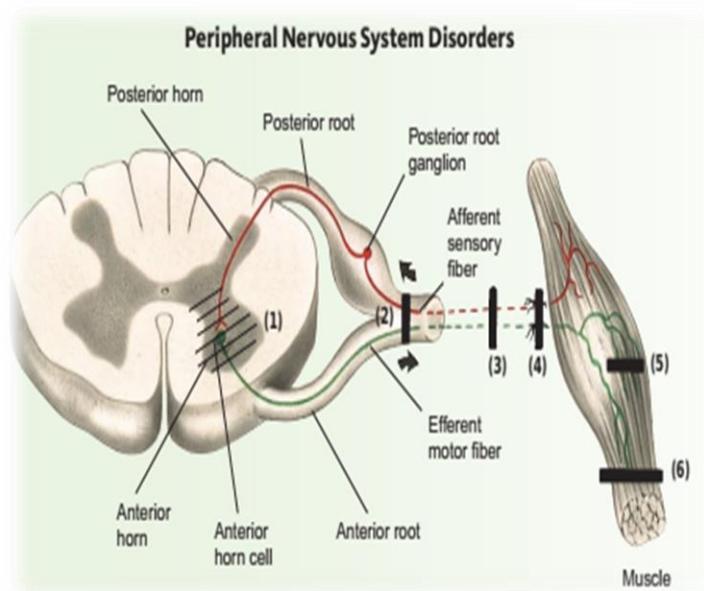
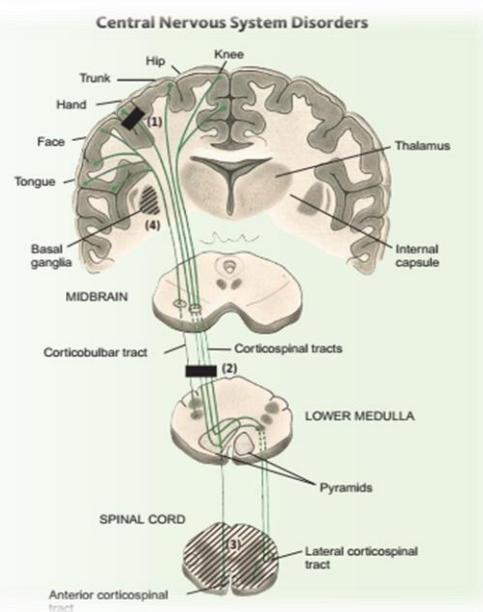
- Is a reduction in the power that can be exerted by one or more muscles.
- It must be distinguished from increased **fatigability**, limitation in function due to pain or articular stiffness, **or** impaired motor activity because severe proprioceptive sensory loss prevents adequate feedback information about the direction and power of movements.
- It is also distinct from **bradykinesia** and **apraxia**.
- **N.B:** -
  - **Fatigability:** the inability to sustain the performance of an activity that should be normal for a person of the same age, sex, and size),
  - **Bradykinesia:** in which increased time is required for full power to be exerted)
  - **Apraxia;** - a disorder of planning and initiating a skilled or learned movement unrelated to a significant motor or sensory deficit.
- The **distribution** of weakness helps to localize the underlying lesion.

### Definitions of paralysis distribution

<b>Paresis</b>	Partial paralysis
<b>Plegia</b>	Complete paralysis
<b>Monoplegia</b>	Involvement of a single limb
<b>Hemiplegia</b>	Involvement of one-half of the body
<b>Paraplegia/diplegia</b>	Paralysis of the legs
<b>Tetraplegia</b>	Paralysis of all four limbs

- **Paralysis** or the suffix “-Plegia” indicates weakness so severe that a muscle cannot be contracted at all, whereas *paresis* refers to less severe weakness.
- The prefix “hemi-” refers to one-half of the body, “para-” to both legs, and “quadri-” to all four limbs.
- Weakness from involvement of upper motor neurons occurs particularly in the extensors and abductors of the upper limb and the flexors of the lower limb.
- Lower motor neuron weakness depends on whether involvement is at the level of the anterior horn cells, nerve root, limb plexus, or peripheral nerve—only muscles supplied by the affected structure are weak.
- Myopathic weakness is generally most marked in proximal muscles.
- Weakness from impaired neuromuscular transmission has no specific pattern of involvement.

- Normal motor function involves integrated muscle activity that is modulated by the activity of the cerebral cortex, basal ganglia, cerebellum, red nucleus, brainstem reticular formation, lateral vestibular nucleus, and spinal cord.
- Motor system** dysfunction leads to **weakness or paralysis**, or to **ataxia or abnormal movements**.
- Neuromuscular diseases that result in limb weakness are best understood on the basis of neuroanatomy of the motor pathways, which consists of four integrated systems
  - The upper motor neuron (UMN) system
  - The lower motor neuron (LMN) system
  - The neuromuscular junction transmission system
  - The skeletal muscle



- Normal muscle strength depends principally on normal functioning of a relay of the above four systems, and any dysfunction at one or more of these four levels, which includes malfunction in the cerebral hemisphere, brainstem, spinal cord, nerve roots, peripheral nerves, myoneural junctions, and within the muscle itself can manifest in neuromuscular diseases.

## 1. Upper Motor Neuron Weakness

- Lesions of the upper motor neurons or their descending axons to the spinal cord produce weakness through decreased activation of lower motor neurons.
- In general, distal muscle groups are affected more severely than proximal ones, and axial movements are spared unless the lesion is severe and bilateral.
- Spasticity is typical but may not be present acutely. Rapid repetitive movements are slowed and coarse, but normal rhythmicity is maintained.

## 2. Lower Motor Neuron Weakness

- This pattern results from disorders of lower motor neurons in the brainstem motor nuclei and the anterior horn of the spinal cord or from dysfunction of the axons of these neurons as they pass to skeletal muscle.
- Weakness is due to a decrease in the number of muscle fibers that can be activated through a loss of a motor neurons or disruption of their connections to muscle.

## 3. Neuromuscular Junction Weakness

- Disorders of the neuromuscular junctions produce weakness of variable degree and distribution.
- The number of muscle fibers that are activated varies over time, depending on the state of rest of the neuromuscular junctions.
- Strength is influenced by preceding activity of the affected muscle.
- In myasthenia gravis, for example, **sustained or repeated contractions of affected muscle decline** in strength despite continuing effort
- Thus, fatigable weakness is suggestive of disorders of the neuromuscular junction, which cause functional loss of muscle fibers due to failure of their activation.

## 4. Myopathic Weakness

- Myopathic weakness is produced by a decrease in the number or contractile force of muscle fibers activated within motor units.
- With muscular dystrophies, inflammatory myopathies, or myopathies with muscle fiber necrosis, the number of muscle fibers is reduced within many motor units.

## 5. Psychogenic Weakness

- Weakness may occur without a recognizable organic basis. It tends to be variable, inconsistent, and with a pattern of distribution that cannot be explained on a neuroanatomic basis.

- On formal testing, antagonists may contract when the patient is supposedly activating the agonist muscle.
- The severity of weakness is out of keeping with the patient's daily activities.

## EVALUATION

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- Elicit a full history to clarify what the patient means—fatigue, apathy, drowsiness, or actual loss of strength.
  - In true motor weakness, the cause may involve a nerve, the neuromuscular junction, or a muscle.
  - Time course and location are especially important.
  - For complaints this complaint (body weakness), a thorough assessment is in order.
    - Is the onset sudden, gradual or subacute, or chronic, over a long period of time?
    - Is it stationary or has progressed? if, yes, then how it progressed?
    - What areas of the body are involved?
    - Is the weakness generalized, or focal to the face or a limb?
    - Does it involve one side of the body or both sides?
    - What movements are affected?
    - As you listen to the patient's story, identify the patterns below:
      - *Proximal*—in the shoulder or hip girdle, for example
      - *Distal*—in the hands or feet
      - *Symmetric*—in the same areas on both sides of the body
      - *Asymmetric*—types of weakness include focal, in a portion of the face or extremity;
        - Monoparesis, in an extremity; paraparesis, in both extremities; and hemiparesis, in one side of the body
- ↳ To identify proximal weakness, ask about difficulty with movements such as combing hair, reaching up to a shelf, getting up out of a chair, or climbing a high step.
- Does the weakness get worse with repetition and improve after rest?
  - Are there associated sensory or other symptoms?
  - To identify *distal* weakness, ask about hand movements when opening a jar or can or using scissors or a screwdriver, or problems such as tripping when walking.

**Table: How to assess weakness**

Clinical finding	Likely level of lesion/diagnosis
<b>Pattern and distribution</b>	
<ul style="list-style-type: none"> <li>▪ Isolated muscles</li> <li>▪ Both limbs on one side (hemiparesis)</li> <li>▪ One limb</li> <li>▪ Both lower limbs (paraparesis)</li> <li>▪ Fatigability</li> <li>▪ Bizarre, fluctuating, not following anatomical rules</li> </ul>	<ul style="list-style-type: none"> <li>→ Radiculopathy or mononeuropathy</li> <li>→ Cerebral hemisphere, less likely cord or brainstem</li> <li>→ Neuronopathy, plexopathy, cord/brain</li> <li>→ Spinal cord; look for a sensory level</li> <li>→ Myasthenia gravis</li> <li>→ Functional</li> </ul>
<b>Signs</b>	
<ul style="list-style-type: none"> <li>▪ Upper motor neuron</li> <li>▪ Lower motor neuron</li> </ul>	<ul style="list-style-type: none"> <li>→ Brain/spinal cord</li> <li>→ Peripheral nervous system</li> </ul>
<b>Evolution of the weakness</b>	
<ul style="list-style-type: none"> <li>▪ Sudden and improving</li> <li>▪ Evolving over months or years</li> <li>▪ Gradually worsening over days or weeks</li> </ul>	<ul style="list-style-type: none"> <li>→ Stroke/mononeuropathy</li> <li>→ Meningioma, cervical spondylotic myelopathy</li> <li>→ Cerebral mass, demyelination</li> </ul>
<b>Associated symptoms</b>	
<ul style="list-style-type: none"> <li>▪ Absence of sensory involvement</li> </ul>	<ul style="list-style-type: none"> <li>→ Motor neuron disease, myopathy, myasthenia</li> </ul>

## CAUSES OF MUSCLE WEAKNESS

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### COMMON

- Cerebrovascular disease (stroke)
  - TIA; cerebral infarction/thrombosis/embolism
  - Intracranial hemorrhage: subarachnoid hemorrhage/Subdural hematoma
- Trauma
  - Head injury;
  - spinal cord injury:
  - Vertebral displacement, fracture
- Infections:
  - Bacterial — Meningitis, TB; tuberculoma.

- Viral — Meningitis, encephalitis, herpes, and HIV
- Cerebral abscess
- Spinal epidural abscess
- Peripheral neuropathies:
  - Diabetes mellitus
  - Alcoholism
  - Nutritional deficiencies—thiamine, vit. B12, folic acid
- Cervical and lumbar radiculopathies:
  - Cervical spondylotic myelopathy
  - Lumbar disc. herniation.
- Intracranial neoplasm (glioma, meningioma)
- Spinal cord neoplasm (both intramedullary and extramedullary)
- Inflammatory (Guillain Barré syndrome, i.e., GBS)

#### **NON-COMMON**

- Cerebral venous sinus thrombosis:
  - Cavernous sinus thrombosis
  - Superior sagittal vein thrombosis
- Multiple sclerosis or other demyelinating disorder
- Motor neuron disease:
  - Progressive muscular atrophy
  - Amyotrophic lateral sclerosis (ALS)
  - Progressive bulbar palsy
- Muscular dystrophy
- Neuromuscular junction disease (Myasthenia gravis)
- Spinal cord disease (syringomyelia, syringobulbia)
- Metabolic (acute porphyria)
- Infections (poliomyelitis, tetanus, rabies, syphilis).

INVESTIGATIONS	
CBC	<ul style="list-style-type: none"> <li>▪ Hb may be reduced in chronic infection /inflammation; exacerbates muscular weakness.</li> <li>▪ Pernicious anemia is common in nutritional deficiency causing weakness.</li> </ul>
ESR	<ul style="list-style-type: none"> <li>▪ Elevated in infection, inflammation, autoimmune disorders</li> </ul>
RBS	<ul style="list-style-type: none"> <li>▪ To monitor hypoglycemia and hyperglycemia associated with weakness, neuropathy.</li> </ul>
LFT, urea, electrolytes, calcium	<ul style="list-style-type: none"> <li>▪ to evaluate associated disorders.</li> </ul>
CT Scan Brain	<ul style="list-style-type: none"> <li>▪ Ideally it should be done on every patient with stroke as soon as possible. If the deficit is secondary to hemorrhage, it will immediately be apparent (and such patients should not be anticoagulated)</li> <li>▪ It is important to correlate CT scan findings with patient's neurologic examination; patients with old or clinically silent infarcts may be irrelevant to the acute situation.</li> </ul>
CSF Analysis	<ul style="list-style-type: none"> <li>▪ Immediate lumbar puncture is indicated in suspected cases of CNS infection (without evidence of increased intracranial pressure)</li> <li>▪ When a CT scan is not available and anticoagulants are anticipated; bloody or xanthochromic CSF should be a contraindication to anticoagulation</li> <li>▪ Gram's stain of CSF sediment will show organisms in majority of untreated bacterial meningitis cases. India ink preparation for cryptococcus and AFB stains for TB bacilli are usually positive</li> <li>▪ CSF culture should include bacteria (aerobic and anaerobic), TB, brucella, fungi, and viruses</li> <li>▪ CSF for cryptococcal capsular antigen should be done when fungal meningitis is suspected, especially in those who are immunocompromised</li> <li>▪ CSF for syphilis serology, e.g., venereal disease research laboratory test (VDRL), fluorescent treponemal antibody absorption test (FTA-ABS)</li> <li>▪ CSF IgG and measles antibody titers must be obtained if subacute sclerosing panencephalitis (SSPE) is suspected</li> <li>▪ PCR amplification of viral gene sequence can be performed in patients suspected with viral encephalitis and myelitis</li> </ul>

<b>MRI—Cervical and Lumbosacral Spine</b>	Useful in obtaining more information about lesions already seen on CT scans and in diagnosing white matter lesions, e.g., multiple sclerosis, and lesions in the posterior fossa.
<b>Nerve Conduction Study (NCS)</b>	In various neuropathies to assess damage to peripheral nerves, and to determine whether the lesion is focal, diffuse, axonal, or demyelinating.
<b>Electromyography (EMG)</b>	Used to investigate disorders of neuromuscular transmission such as myastheniagravis and myopathic disorders such as muscular dystrophies
<b>Serum Acetylcholine Receptor Antibody Titer</b>	Elevated levels in myasthenia gravis.

### FOCUS

- Abrupt onset of motor and sensory deficits occurs in **transient ischemic attack and stroke**.
- Progressive subacute onset of distal lower extremity weakness suggests **Guillain–Barré syndrome**.
- Chronic, more gradual, onset of weakness in the lower extremities can be seen in **metastatic cord lesions and lumbar disc disease**.
- Focal or asymmetric weakness has many causes, both central (ischemic, thrombotic, or mass lesions) and peripheral, which range from nerve injury to the neuromuscular junction disorders, to **myopathies**, or intrinsic muscle diseases.
- Proximal limb weakness, usually symmetric and without sensory loss, occurs in myopathies from alcohol, drugs like glucocorticoids, and inflammatory muscle disorders like **myositis** and **dermatomyositis**.
- In the neuromuscular junction disorder **myasthenia gravis**, there is proximal typically asymmetric weakness that gets worse with effort (fatigability), often with associated **bulbar symptoms** such as diplopia, ptosis, dysarthria, and dysphagia.
- Bilateral predominantly distal weakness suggests a **polyneuropathy**, as in **diabetes**.

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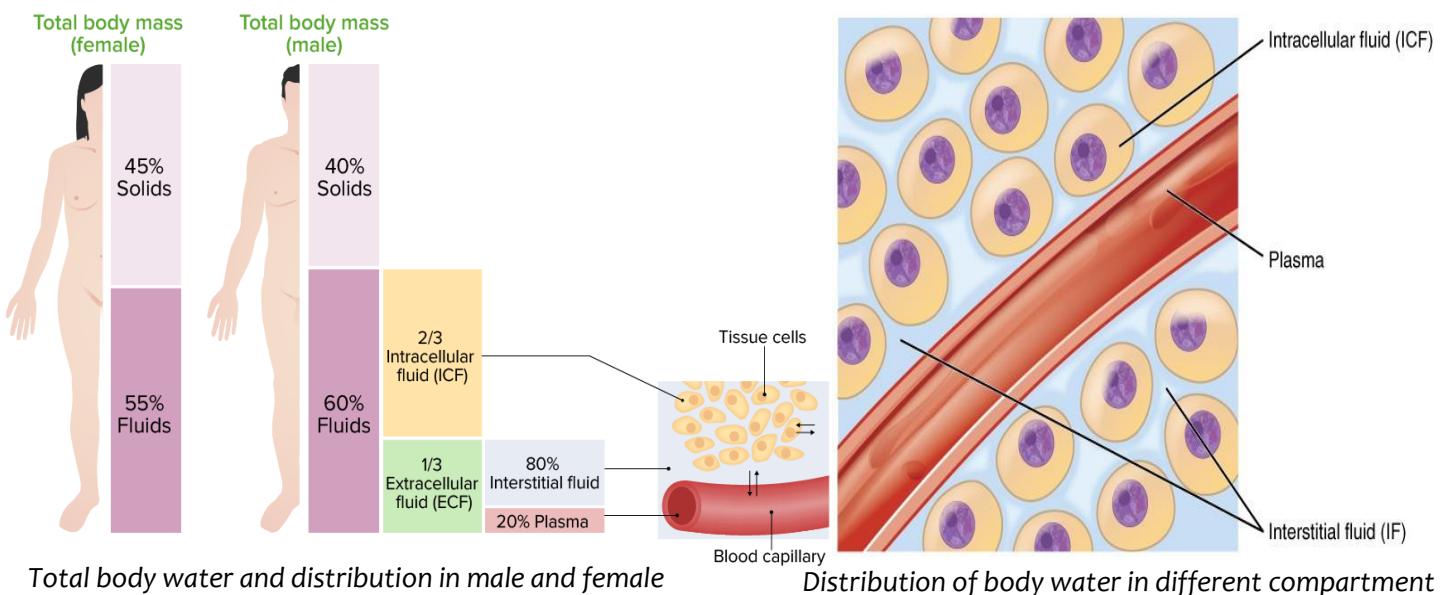
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## EDEMA

- Defined as a palpable swelling produced by expansion of the interstitial fluid volume
- When volume is massive and generalized it's called **anasarca**
- Edema can be generalized or localized
- Causes of localized edema include
  - Venous obstruction (as in DVT)
  - Allergic reaction (such as laryngeal edema)
- In this chapter we will discuss focusing on generalized edema

## TOTAL BODY WATER

- 2/3<sup>rd</sup> intracellular
- 1/3<sup>rd</sup> extracellular
  - 20% plasma
  - 80% interstitial



## NORMAL PHYSIOLOGY

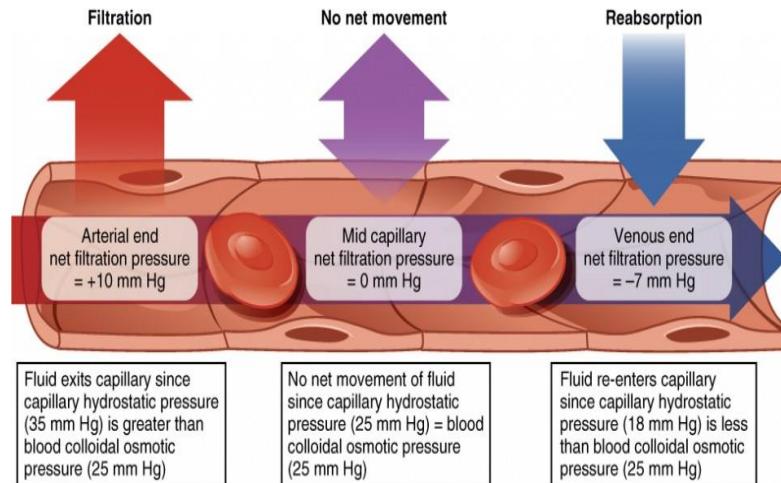
- There is constant interchange of fluid between plasma and interstitial space
- These interchanges are due to two **balancing** forces

a. Hydrostatic pressure in the capillary

- Which favors transcapillary fluid movement
- High relative to oncotic pressure **at arterial end**
- Resulting in shift of fluid to interstitial space

b. Oncotic pressure in the interstitial space

- Favors the retention of fluid within the vessel
- Higher than hydrostatic pressure at **venular end**
- Lymphatic system returns (largely) interstitial fluid to plasma



## PATHOPHYSIOLOGY

- There are 2 basic steps involved in edema formation
  1. Alteration in capillary hemodynamics favoring shift of fluid into interstitial fluid, these can be 2ry to:
    - Increased capillary hydrostatic pressure
    - Increased capillary permeability
    - Decreased capillary oncotic pressure
  2. Retention of Na and water by the kidney
    - Renal failure or Acute glomerulonephritis
    - Heart failure
    - Cirrhosis with hepatorenal syndrome

## EFFECTIVE ARTERIAL BLOOD VOLUME

- Represents the filling of the arterial tree and that effectively perfuses the tissues
  - Reduced in Edema (also called Underfilling)
- Causes for the reduction include
  - Reduction of cardiac output (CHF)
  - Reduction in systemic vascular resistance (Cirrhosis)
  - Hypoalbuminemia
- The most important physiologic response to this Underfilling is:

- **The renal retention of sodium and, therefore, water.**
- thereby restoring effective arterial volume
- sometimes leading to the development or intensification of edema
- The intensification is because as there is retention of Na and water in plasma it further predisposes to shift of fluid into interstitial space.

## CLINICAL MANIFESTATION

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- For edema to be clinically apparent at least **2.5 -3 L** is needed in interstitial fluid
- The following forms are considered special forms of edema
  - **Ascites**, refer to accumulation of excess fluid in the peritoneum and
  - **Hydrothorax**, refer to accumulation of excess fluid in pleural cavities
- **Weight gain** usually precedes overt manifestations of generalized edema
- Persistence of an indentation of the skin after pressure known as “**pitting**” edema
  - **Characteristic clinical finding**
- In its subtle form an indentation by the rim of the bell of stethoscope on chest wall after removing the stethoscope may be noted
- Puffiness of the face is also other form of edema manifestation

## DISTRIBUTION OF EDEMA

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- It is an important guide to its cause
  - **Heart failure**
    - more extensive in the legs
    - accentuated in the evening,
    - when patients are confined to bed, edema may be most prominent in the presacral region.
  - **Hypoalbuminemia (nephrotic syndrome)**
    - Characteristically is generalized
    - Especially evident in the very soft tissues of the eyelids and face
    - Tends to be most pronounced in the morning owing to the recumbent posture assumed during the night
  - **Obstruction of the superior vena cava**
    - Edema is confined to the face, neck, and upper extremities

## CAUSES OF EDEMA

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### HEART FAILURE

- Pathophysiology
  - Impaired systolic emptying of the ventricle(s) and/or the impairment of ventricular relaxation
    - promotes an accumulation of blood in the venous circulation
  - Activation of the sympathetic nervous system and the RAAS
    - Renal vasoconstriction and reduction of glomerular filtration and salt and water retention
- ***These two interrelated and vicious systems raise venous and intracapillary pressure resulting in edema***

### RENAL DISEASE

- Edema results from
  - Primary retention of sodium and water owing to renal dysfunction
  - This state differs from HF, by having a **normal (or sometimes even increased) cardiac output**

### HYPOTALBUMINEMIA

- Causes
  - Protein losses
    - Protein losing enteropathy
    - Nephrotic syndrome
  - Reduced albumin synthesis
    - Liver disease
    - Malnutrition
- Pathophysiology
  - Losses of large quantities ( $\geq 3.5 \text{ g/d}$ ) of protein into the urine and hypoalbuminemia ( $< 3.0 \text{ g/dL}$ )
  - Reduced colloid osmotic pressure,
  - Sodium and water that are retained cannot be confined within the vascular compartment,
  - Resulting decline in total and effective arterial blood volumes
  - Which intern activates edema-forming sequence including RAAS
  - Characteristically, edema is:
    - Diffuse and symmetric

- Most prominent in the dependent areas; periorbital edema
- Most prominent in the morning

### HEPATIC CIRRHOsis

- Pathophysiology
  - Hepatic venous outflow obstruction (**Intrahepatic hypertension**)
  - Which in turn expands the splanchnic blood volume, and hepatic lymph formation
  - Intrahepatic hypertension stimulates renal sodium retention
  - Associated hypoalbuminemia secondary to
    - Reduced hepatic synthesis
    - peripheral arterial vasodilation
  - All the above in concert resulting in reduction of the effective arterial blood volume
  - Which intern activates edema-forming sequence including RAAS
  - Concentration of circulating **aldosterone is elevated**
    - Due to failure of the liver to metabolize this hormone
  - Initially, edema is localized preferentially proximal (upstream) to the congested portal venous system, causing **ascites**
  - In later stages, peripheral edema may develop
    - particularly when there is severe hypoalbuminemia

### DRUG-INDUCED EDEMA

- Mechanism
  - Renal vasoconstriction
    - nonsteroidal anti-inflammatory drugs and cyclosporine
  - Arteriolar dilation
    - Vasodilators (hydralazine, minoxidil, diazoxide)
  - Augmented renal sodium reabsorption
    - steroid hormones
  - Capillary damage

### EDEMA OF NUTRITIONAL ORIGIN

- Pathophysiology
  - A diet deficient in calories and particularly in protein over a prolonged period
    - hypoproteinemia and then edema

- Beriberi heart disease
  - Resulting peripheral arteriovenous fistula
- **Refeeding edema**
  - when famished subjects are first provided with an adequate diet

### OTHER CAUSES OF EDEMA

- Hypothyroidism (myxedema)
  - due to deposition of hyaluronic acid
- Hyperthyroidism
  - pretibial myxedema secondary to Graves' disease
  - typically, nonpitting
- Exogenous hypercortisolism
- Pregnancy
- Administration of estrogens and vasodilators,
  - Particularly dihydropyridines such as nifedipine.

## ABDOMINAL SWELLING AND ASCITES

### ABDOMINAL SWELLING

- Causes of abdominal swelling can be remembered conveniently as the **six Fs**
  1. Flatus
  2. Fat
  3. Fluid (ascites)
  4. Fetus
  5. Feces
  6. Fatal growth (often a neoplasm).

### APPROACH TO THE PATIENT

#### HISTORY

- Malignancy symptoms (**Fatal growth**)
  - weight loss, night sweats, and anorexia
- Bowel obstruction (**Feces**)
  - Failure to pass stool or flatus
  - Nausea or Vomiting
- Severe constipation, or an ileus (lack of peristalsis) (**Feces**)
- Aerophagia or increased intestinal production of gas (**Flatus**)
  - Increased belching and flatus
- Risk factors for or symptoms of CLD (**Fluid**)
  - Excessive alcohol use and jaundice
- Symptoms of HF and Tuberculosis (ascites)

#### PHYSICAL EXAMINATION

##### LGS:

- Supraclavicular lymphadenopathy (Virchow's node)
  - Metastatic abdominal malignancy
- Gynecomastia (liver disease)

##### CVS:

- Elevation of JVP
- Kussmaul's sign (elevation of the JVP during inspiration)

- pericardial knock (seen in heart failure or constrictive pericarditis)
- murmur of tricuspid regurgitation

## ABDOMEN

- Bowel sound
  - Absent or localized high pitched (Intestinal obstruction or ileus)
- Umbilical venous hum
  - Portal hypertension
- Harsh bruit over the liver
  - Hepatocellular carcinoma or alcohol-associated hepatitis.
- Tympanic on percussion
  - Gas
- Dull to percussion
  - Mass or fluid
  - **A minimum of 1500 ml of Ascitic fluid is required for detection on physical examination**
- Palpate for any organomegaly

## I/S

- Suggestive of Liver disease
  - Spiderangiomias
  - palmar erythema
  - dilated superficial veins around the umbilicus (caput medusae)

## IMAGING

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- Abdominal x-rays
  - dilated loops of bowel, air fluid level
  - suggesting intestinal obstruction or ileus
- Abdominal ultrasonography
  - Can detect as little as **100 ml** of ascitic fluid
  - Hepatosplenomegaly
  - Nodular liver, or a mass
  - Not used to detect retroperitoneal lesions b/c of overlying bowel gas
  - CT is recommended for **retroperitoneal lymphadenopathy or a pancreatic lesion**

## LABORATORY

- serum albumin level, and INR
  - to assess hepatic function
- CBC
  - Cytopenias from hypersplenism
  - leukocytosis, anemia, and thrombocytosis (systemic infection)
- Serum amylase and lipase
  - Acute pancreatitis
- Urinary protein quantitation
  - Nephrotic syndrome

## ASCITES

- It is accumulation of fluid within the peritoneal cavity
- Cirrhosis accounts for 84% of cases of ascites

## PATHOPHYSIOLOGY

- In portal hypertension
  - systemic vasodilatation (due to release of NO) → ↓ effective arterial volume  
→ renal Na retention → volume overload and ascites
- In malignant or inflammatory ascites
  - leaking of proteinaceous material occurs from tumor or from inflamed/infected/ruptured intraabdominal structures

Etiologies	
<b>Portal HTN Related (SAAG ≥1.1)</b>	<b>Non-portal HTN Related (SAAG &lt;1.1)</b>
<b>Prehepatic obstruction</b> Portal or splenic vein thrombosis, schistosomiasis, sarcoidosis	<b>Malignancy:</b> peritoneal carcinomatosis; chylous ascites from malignant lymphoma; Meigs' syndrome (ovarian tumor)
<b>Hepatic obstruction:</b> cirrhosis (84%), acute hepatitis, malignancy (HCC or metastasis)	<b>Infection:</b> TB, chlamydia/gonorrhea (i.e., Fitz-Hugh-Curtis syndrome)
<b>post-hepatic obstruction</b> Right-sided CHF (ex: constriction, TR), Budd-Chiari syndrome, SOS	<b>Inflammation:</b> pancreatitis, ruptured pancreatic/biliary/lymph duct; bowel obstruction <b>Hypoalbuminemic states:</b> nephrotic syndrome, protein-losing enteropathy

## EVALUATION

- Etiology of the ascites is best determined by **paracentesis**
- **Paracentesis**
  - A bedside procedure in which a needle or small catheter is passed transcutaneously to extract ascitic fluid from the peritoneum
  - The left lower quadrant is preferred because of **the greater depth of ascites and the thinner abdominal wall**
- **Initial test** which should be performed on the ascitic fluid include
  - Appearance
    - **Clear** → cirrhosis with normal bilirubin
    - **Turbid or cloudy** → SBP

- **Milky** → chylous ascites
- **Bloody** → traumatic tap, malignancy
- **Brown** → bilirubin 40% of serum conc. (Ddx. ruptured gallbladder or perforated duodenal ulcer)
- Serum to ascites albumin gradient determination
  - Portal hypertension if SAAG is  $\geq 1.1$  g/dl (with 97% accuracy)
  - Non portal hypertension if SAAD is  $< 1.1$  g/dl
- Cell count and differential
  - **Single most important test to evaluate for infection**
  - The mere presence of Neutrophil count  $\geq 250$  cells/mm<sup>2</sup> does not diagnose SBP, the presence of 2 out of the following three indicates bowel perforation
    - Total protein  $> 1$  g/dl
    - Glucose  $< 50$  mg/dl
    - LDH  $>$  than upper limit of normal for serum
- Total protein concentration
  - If total ascitic protein (TAP) is  $\geq 2.5$  g/dl → **exudate**
  - If TAP is  $< 2.5$  g/dl → **transudate**
- Additional tests which aid to confirm a diagnosis include
  - Culture
    - 10ml of ascitic fluid per bottle
    - For detecting bacterial growth
  - Glucose concentration
    - Ascitic fluid glucose is normally similar to that in serum
    - Malignant cells (consume glucose) → **low glucose**
    - Bowel perforation → glucose may be undetectable
  - Lactate dehydrogenase concentration
    - Because of its larger molecular size, it enters into ascitic fluid less readily
    - Ascitic fluid/serum (AF/S) ratio is  $\sim 0.4$  in cirrhosis
    - AF/S in **SBP  $\sim 1.0$**
    - If AF/S is  $> 1$  → infection, bowel perforation or tumor
  - Gram stain
    - Though usually sent for SBP, in which concentration of bacteria is 1/ml
    - Approximately 10,000 bacteria/ml are required for detection by gram stain

- So, gram stain is not much useful to diagnose SBP (**positive only in 7%**)
- Rather it is useful to ruling in free perforation of bowel (multiple sheets of bacteria are seen)
- Amylase concentration
  - In Pancreatic ascites (~ 2000 int. unit/ml)
- Tests for tuberculous peritonitis
  - AFB (0–3% sensitivity)
  - Culture of ascitic fluid (35–50% sensitivity)
  - Culture of a biopsy specimen (detecting ~ 100%)
  - Cell count (with mononuclear cell predominance)
  - Adenosine deaminase (30–45 U/L), **90% sensitivity inpatient without cirrhosis**
- Cytology
  - Malignant cells in peritoneal carcinomatosis (almost 100%)
- Triglyceride (TGA) concentration
  - Chylous ascites → 200 mg/dl TGA

## AZOTEMIA AND URINARY ABNORMALITIES

### AZOTEMIA

- Reduced GFR (either acute or chronic) is reflected in a rise in  $P_{Cr}$ , leading to retention of nitrogenous waste products (defined as azotemia) such as urea.
- Creatinine is used to estimate GFR because
  - creatinine is produced from muscle and excreted at a relatively constant rate
  - creatinine is a small, freely filtered solute that is not reabsorbed by the tubules
- Once GFR reduction has been established, the physician must decide if it represents acute or chronic renal injury.
- Features suggestive of chronic renal injury
  - Nonconcentrated urine (isosthenuria; isosmotic with plasma)
  - some proteinuria
  - on ultrasound (**small kidneys, characterized by increased echogenicity and cortical thinning**)
- Acute renal failure can result from
  - Processes that affect blood flow and glomerular perfusion (prerenal azotemia)
  - Intrinsic renal diseases (affecting small vessels, glomeruli, or tubules)
  - Post renal processes (obstruction of urine flow in ureters, bladder, or urethra)

### OLIGURIA AND ANURIA

- **Oliguria** refers to a 24-h urine output <400 mL
- **Anuria** is the complete absence of urine formation (<100 mL)
- **Nonoliguria** refers to urine output >400 mL/d in patients with acute or chronic azotemia

## ABNORMALITIES OF THE URINE

### PROTEINURIA

- Proteinuria is detected by dipstick examination
- Dipstick measurement detects only albumin
- Proteinuria that is not predominantly due to albumin will be missed by dipstick screening
  - E.g. Bence-Jones proteins in multiple myeloma.

- Formal assessment of urinary protein excretion requires a 24-h urine protein collection
- Healthy individuals excrete <150 mg/d of total protein and <30 mg/d of albumin
- Glomerular barriers that prevent proteinuria
  - Both **charge and size selectivity** normally prevent virtually all plasma albumin, globulins, and other high-molecular-weight proteins from crossing the glomerular wall
  - Glomerular endothelial cell forms pores ~ **100nm** that retain blood cells but impedes passage of most proteins
  - Foot processes of epithelial cells (podocytes) produce a series of narrow channels (slit diaphragms) and allow molecular passage of small solutes and water but not proteins

## PATOPHYSIOLOGY

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- Excessive production of an abnormal protein that exceeds the capacity of the tubule for reabsorption
  - Plasma cell dyscrasias, monoclonal production of immunoglobulin light chains
    - Multiple myeloma
    - Amyloidosis
    - and lymphomas
- Fusion of glomerular epithelial cell foot processes
  - minimal change disease
- Disruption of the basement membrane and slit diaphragms

## HEMATURIA, PYURIA, AND CASTS

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- Hematuria is defined as two to five RBCs per high-power field (HPF)
- Common causes of isolated hematuria include
  - Stones
  - neoplasms
  - tuberculosis
  - trauma, and
  - prostatitis
- Gross hematuria with blood clots
  - usually is not an intrinsic renal process
  - it suggests a postrenal source in the urinary collecting system.
- A single urinalysis with hematuria is common and can result from

- Menstruation
- viral illness
- allergy
- exercise, or mild trauma
- Persistent or significant hematuria
  - **>3 RBCs/HPF on three urinalyses, a single urinalysis with >100 RBCs, or gross hematuria**
  - It is associated with significant renal or urologic lesions in 9.1% of cases
- Typically, the RBCs of glomerular origin are often **dysmorphic** when examined by phase-contrast microscopy
- Isolated pyuria is unusual, it usually associated with hematuria
- WBC casts with bacteria are indicative of **pyelonephritis**
- WBCs and/or WBC casts also may be seen in
  - acute glomerulonephritis
  - interstitial nephritis and
  - transplant rejection
- “**Sterile pyuria**” with negative urinary bacterial cultures
  - Suggestive of urogenital tuberculosis

## ABNORMALITIES OF URINE VOLUME

### POLYURIA

Polyuria is defined as a urine output **> 3L/day in adults** ( $2\text{L}/\text{m}^2$  in children)

### DIFFERENTIAL DIAGNOSIS OF POLYURIA

1. **Solute diuresis** (urine osmolality  $> 600 \text{ mosmol/kg}$ )
  - Glycosuria (most common)
    - Hyperglycemia (in uncontrolled DM)
    - SGLT2 inhibitor use
  - Urea
    - Resolution from azotemia
    - Tissue catabolism (eg. Due to glucocorticoids)
  - Iatrogenic
    - Usually caused by administration of large volume IV saline
    - After relief of bilateral urinary tract obstruction

- Exogenous administration of Urea (usually Rx in patients with hyponatremia)
  - High-protein feedings (enteral or parenteral), leading to increased urea production and excretion
  - Mannitol (I.e., given to patients with Increased intracranial pressure)
2. **Water diuresis** (urine osmolality < 600 mosmol/kg)
- Primary polydipsia (psychogenic polydipsia)
    - Characterized by a primary increase in water intake
    - Usually in psychiatric patients taking phenothiazine (leads to sensation of dry mouth)
    - May also be induced by hypothalamic lesions (sarcoidosis)
  - Central diabetic insipidus (neurogenic DI)
    - Is due to deficient secretion of ADH
    - vasopressin-sensitive
    - Causes are usually idiopathic but can be from
      - Autoimmune injury to ADH producing cells
      - Trauma
      - Pituitary surgery or
      - Hypoxic ischemic encephalopathy
  - Nephrogenic diabetic insipidus
    - Normal ADH with renal ADH resistance
    - vasopressin-insensitive
    - Causes are
      - Inherent defect (Almost always in Childhood, [X linked hereditary nephrogenic DI (most common)])
      - Chronic lithium use and hypercalcemia (**most common cause in adults**)

## GASTROINTESTINAL BLEEDING

### DEFINITION

- Intraluminal blood loss anywhere from the oropharynx to the anus

### CLINICAL MANIFESTATIONS

- **Hematemesis:** blood in vomitus (UGIB)
- **Coffee-ground emesis:** emesis of blood exposed to gastric acid (UGIB)
- **Melena:** black, tarry stools from digested blood (usually UGIB, but can be from Right colon)
- **Hematochezia:** bloody or maroon-colored stools (LGIB or rapid UGIB)

**Note:** Decompensation of other underlying illnesses rather than exsanguination is the cause of death in GIB

### Gastrointestinal bleeding (GIB) can be classified

1. Based on the presentation
  - **Overt GIB**, which is manifested by
    - **Hematemesis**
      - vomitus of red blood (when bleeding is rapid and profuse) or
      - “Coffee-grounds” material (when bleeding is less severe)
    - **Melena**
      - indicates blood has been present in the GI tract for **≥14 h up to 3-5 days**
      - occur usually in proximal GI tract bleeding
    - **Hematochezia**
  - **Occult GIB**, which is manifested by
    - symptoms of blood loss or anemia
    - Iron-deficiency anemia (laboratory)
    - Positive fecal occult blood test on colorectal cancer screening
2. Based on the site/source of bleeding
  - **Upper GIB:** above the ligament of Treitz (at the duodenjejunal junction)
    - from the esophagus, stomach, or duodenum
  - **Lower:** below the ligament of Treitz
    - from the colon; small intestinal
  - **Obscure GIB:** if the source is unclear

## UGIB vs LGIB

Presentation	UGIB	LGIB
Hematemesis	present	Not present
Melena	present	May present
Hematochezia	In case of brisk/active UGIB	Common
Hyperactive bowel sounds	Present	Not common
Elevated BUN	Present	Normal BUN commonly
Iron deficiency anemia	-	In chronic LGIB

## CAUSES OF UPPER GASTROINTESTINAL BLEEDING

1. Peptic ulcers (~50%)
  - *H. Pylori* (most common cause)
  - NSAID
2. Esophageal varices (2–40%)
  - Liver disease
  - Portal venous thrombosis
3. Mallory-Weiss tears (2-10%)
  - Retching
4. Erosive disease
  - Erosive gastritis and duodenitis (~10–15%)
  - Erosive esophagitis (primarily due to GERD) ~1–10%

## CAUSES OF LOWER GASTROINTESTINAL BLEEDING

1. Diverticulosis
  - **most common**, if local anal processes are excluded
  - Bleeding is abrupt in onset
  - Usually, painless
  - Diverticula more common in left colon; but
  - Bleeding diverticula more often in right colon
2. Hemorrhoids
  - **most common form**, if local anal processes are considered
3. Vascular ectasias (usually in proximal colon)
4. Neoplasms (primarily adenocarcinoma)

5. Colitis (ischemic, infectious, Crohn's or ulcerative colitis, NSAID-induced colitis or ulcers)
6. Postpolypectomy bleeding
7. Radiation proctopathy

## APPROACH TO THE PATIENT WITH GIB

### INITIAL ASSESSMENT

- Circulatory status
  - HR and BP (the best)
  - significant bleeding
    - tachycardia, and, finally, recumbent hypotension
    - patient may be cold and sweating or agitated
- Evidence of liver disease
  - Signs of decompensated cirrhosis
- Comorbidity
  - If present, may be worsened by acute bleeding
  - increase the hazards of endoscopy and surgical operations
- Initial Risk Assessment
  - **Glasgow-Blatchford score**
  - A score of 2 or less is associated with a good prognosis
  - while progressively higher scores are associated with poorer outcomes

Glasgow-Blatchford Score	
RISK FACTORS AT ADMISSION	SCORE
<b>Blood urea nitrogen (mg/dL)</b>	
18.2 to <22.4	2
22.4 to <28.0	3
28.0 to <70.0	4
≥70.0	6
<b>Hemoglobin (g/dL)</b>	
12.0 to <13.0 (men); 10.0 to <12.0 (women)	1
10.0 to <12.0 (men)	3
<10.0	6
<b>Systolic blood pressure (mmHg)</b>	
100–109	1
90–99	2

<90	3
<b>Heart rate (beats per minute)</b>	
≥100	1
<b>Melena</b>	1
<b>Syncope</b>	2
<b>Hepatic disease</b>	2
<b>Cardiac failure</b>	2

**Score 0:** low risk

**Score > 0:** high risk, keep in hospital as the patient is likely to require transfusion or endoscopic intervention

**Score ≥ 8:** requires ICU admission

- **BASIC INVESTIGATION**

- CBC, Hemoglobin
  - It takes around **72 hrs.** for hgb to fall with **acute GIB**
  - B/c there is proportional reduction in plasma and red cell volumes acutely
  - Transfusion is recommended when the **hgb < 7 g/dl** (without comorbidity) and
  - **9-10 g/dl** in older and severe comorbidity (active coronary disease requiring PRBC transfusion)
- Urea and electrolytes
  - BUN rises as the absorbed products of luminal blood are metabolised by the liver
  - An elevated blood urea with normal creatinine concentration implies **severe bleeding**
- Liver function tests
  - Evidence for chronic liver disease
- Prothrombin time
  - If there is clinical evidence of liver disease or patients are anticoagulated
- Cross-matching
  - At least 2 units if bleeding is significant

## DIAGNOSIS OF UGIB

- Diagnosis of upper GI bleeding is made clinically
  - a history of hematemesis or melena establishes the diagnosis
- upper GI endoscopy is required to identifying the cause
- Upper GI endoscopy has both diagnostic and therapeutic value

## MANAGEMENT OF UGIB

Emergency management of non-variceal bleeding are discussed in detail below

Mang't of Variceal bleeding is discussed in CLD portion

### FOR ALL PATIENTS

- Keep NPO
- Insert two large bore IV line
  - For possible fluid and/or blood transfusion
  - Obtain blood sample for laboratory (CBC, BG and RH)
- Pharmacotherapy
  - Intravenous proton pump inhibitor
    - Omeprazole 80mg IV loading followed by 40mg IV BID OR
    - Esomeprazole 40 mg IV BID OR
    - Pantoprazole 40 mg IV BID
- Pre-Endoscopic Medications
  - Administer anticoagulant reversal if INR is > 2.5
  - Consider withholding antithrombotic agents
  - PPI infusion, decreases high-risk ulcer stigmata (e.g., active bleeding) and need for endoscopic therapy
  - But PPI doesn't improve further bleeding, surgery, or death
  - Promotility agent, Erythromycin 250 mg intravenously ~30–90 min before endoscopy, improve visualization at endoscopy

## STABLE PATIENT

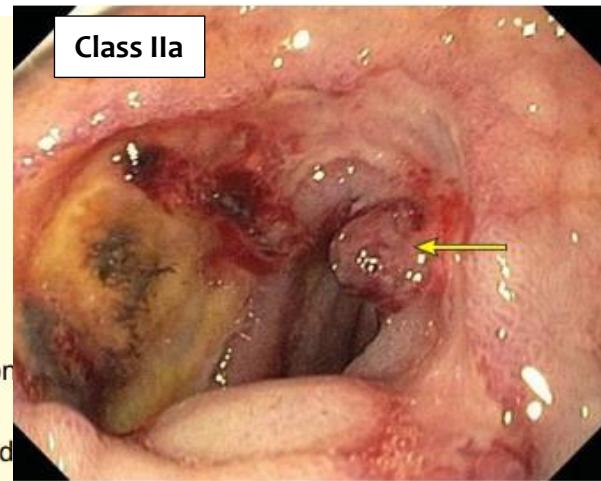
- Provide transfusion if either of the following is present
  - Hemoglobin <9 g/dL in high-risk patients (e.g., elderly, coronary artery disease)
  - Hemoglobin <7 g/dL (70 g/L) in low-risk patients
- Refer for Endoscopy based on the risk stratification

## UNSTABLE PATIENTS

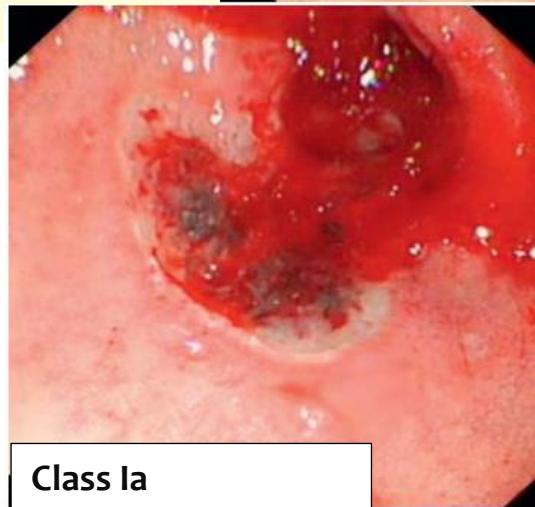
- Follow ABCDE approach
- Consider intubation (in patient with Altered mental state and/or severe ongoing hematemesis)
- Urgent volume resuscitation
  - Bolus IV crystalloid
  - Transfusion, if hypotensive (SBP <90) and Tachycardic (HR >110/min)
- Oxygen
  - If only in shock
- Endoscopy
  - Diagnostic modality of choice for acute UGIB
  - Ideally within 24 hr., after adequate resuscitation
  - Except in high-risk patients within 6 hr. of gastroenterology consultation
  - If variceal bleeding is suspected endoscopy is done within 12 hr. of presentation
  - diagnose 80% of cases
  - Endoscopic findings in bleeding PUD are described using **modified Forrest classification**
  - Based on this risk classification endoscopic therapy is indicated Ia to IIb
  - Class IIc or III do not require endoscopic therapy and receive standard doses of oral PPI
  - Although several types of endoscopic treatment for bleeding PUD are there
    - Thermal coagulation therapy or hemostatic clip are most common
  - **Administration of PPI after endoscopy uses to**
    - sustain intragastric pH >6
    - enhance clot stability
    - decreases further bleeding and
    - decreases mortality in patients with high-risk ulcers

→ If it is variceal bleeding should be treated by band ligation. if this fails, balloon tamponade is another option, while arrangements are made for a transjugular intrahepatic portosystemic shunt (TIPSS)

Modified Forrest classification		Risk of recurring hemorrhage
<b>Class Ia</b>	spurting hemorrhage	90%
<b>Class Ib</b>	Oozing hemorrhage	50%
<b>Class IIa</b>	A nonbleeding visible vessel	50%
<b>Class IIb</b>	An adherent clot	30%
<b>Class IIc</b>	A flat pigmented spot	10%
<b>Class III</b>	A clean ulcer base	<5%

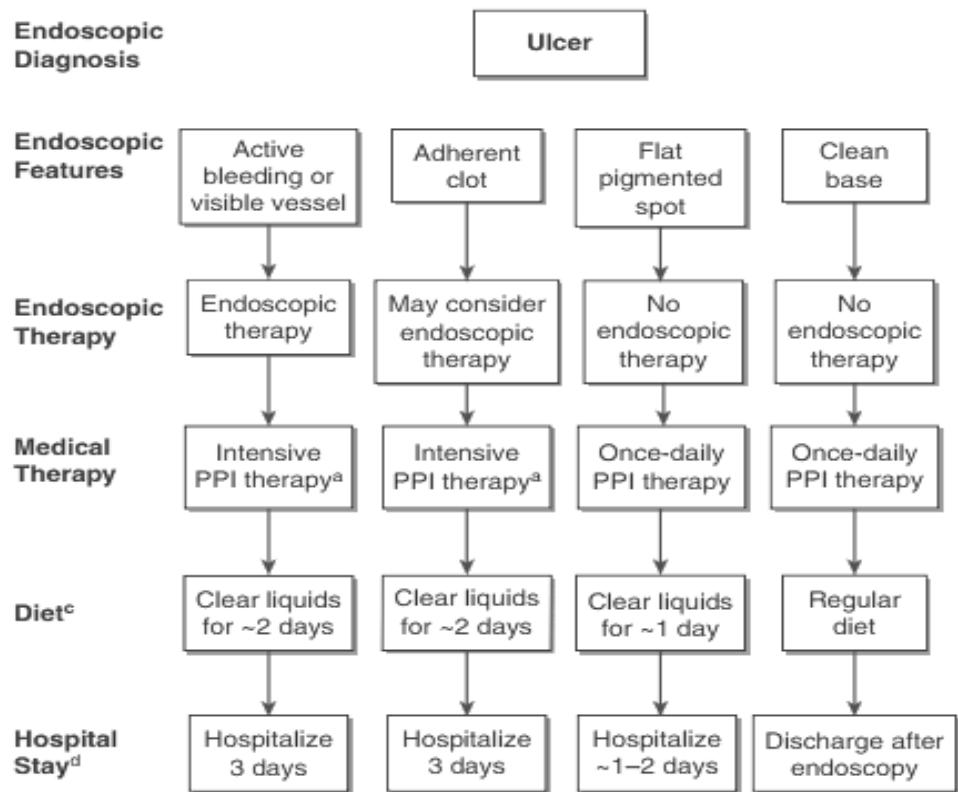


Ulcers with a flat pigmented spot (Forrest classification IIc; panel A) or a clean base (Forrest classification III, panel B) are at low risk for rebleeding and do not need to be treated endoscopically.



- Monitoring
  - hourly measurements of pulse, blood pressure and urine output.
- Surgery
  - indicated when endoscopic hemostasis fails to stop active bleeding and
  - if rebleeding occurs on one occasion in an elderly or frail patient, or twice in a younger, fitter patient.
- Eradication
  - **10–50%** of patients with bleeding ulcers rebleed within the next year if no preventive strategies are employed
  - These strategies include
    - In NSAID or Aspirin associated bleeding ulcers: stop the drug and re-evaluate the need
    - Those who are H. pylori positive should receive eradication therapy (decreases rebleeding rates to <5%)
    - Anticoagulants: stop and re-evaluate for continued need, dose adjustment
    - Variceal bleeding: band ligation and non-selective beta-blocker therapy (propranolol)
    - Idiopathic (non-H. pylori, non-NSAID) ulcers: long-term PPI is recommended

**FIGURE:** Suggested algorithm for patients with acute UGIB based on endoscopic findings.



<sup>a</sup>Intravenous bolus (80 mg) followed by infusion (8 mg/h) for 3 days; or oral or intravenous bolus (e.g., 80 mg) followed by intermittent high doses (e.g., 40–80 mg BID or 40 mg TID) for 3 days. Then twice-daily PPI on days 4–14 followed by once-daily PPI

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## CHAPTER TWO

# Diseases of respiratory system

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Introduction

Infectious diseases of Respiratory System

Chronic obstructive lung disease

Bronchiectasis

Restrictive Lung Disease

Pulmonary Hypertension

Respiratory Failure

Lung Abscess

Lung Cancer

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### INTRODUCTION

The respiratory system is network of organs and tissues (airways, lungs, muscles that power the lung, blood vessels) which works together to move oxygen throughout body and clean out waste gases.

The main function of the respiratory system includes

- Gas exchange
- Acid-base balance
- Phonation
- Pulmonary defense and metabolism, and
- Handling of bioactive materials

### FUNCTIONAL ANATOMY AND PHYSIOLOGY

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The lungs are the major organs of the respiratory system and are divided into lobes; right lung with 3 lobes and left lung with 2 lobes. Each lobe is composed of bronchopulmonary segments.

Airway cross-section is smallest in the glottis and trachea, making the central airway vulnerable to obstruction by foreign bodies and tumors. Foreign body commonly gets lodged in the right main bronchus because of its relative vertical orientation.

Normal breath sounds originate mainly from the rapid turbulent airflow in the larynx, trachea and main bronchi. Small airways within the lung parenchyma has large combined cross-sectional area and airflow is virtually silent here.

The acinus is the gas exchange unit of the lung and comprises branching respiratory bronchioles and clusters of alveoli.

**Inspiration:** involves downward contraction of the dome-shaped diaphragm (innervated by the phrenic nerves from C3-C5) and upward and outward movement of the ribs on the costovertebral joints, caused by contraction of the external intercostal muscles (innervated by intercostal nerves from the thoracic spinal cord).

**Expiration:** is largely passive, driven by elastic recoil of the lung

## **CONTROL OF BREATHING**

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The respiratory motor neurons in the posterior medulla oblongata are the origin of the respiratory cycle and their activity is modulated by:

- Central chemoreceptors in the ventrolateral medulla which sense the pH of the cerebrospinal fluid (CSF) and are indirectly stimulated by a rise in arterial PCO<sub>2</sub>
- The carotid bodies which sense hypoxemia, are mainly activated by arterial PO<sub>2</sub> values below 8 kPa (60 mmHg), but also sensitized to hypoxia by raised arterial PCO<sub>2</sub>
- Muscle spindles in the respiratory muscles sense changes in mechanical load
- Vagal sensory fibers in the lung may be stimulated by stretch, by inhaled toxins or by disease processes in the interstitium
- Cortical (volitional) and limbic (emotional) influences can override the automatic control of breathing

Diseases of respiratory system fall into one of three major categories:

1. obstructive lung diseases
2. restrictive disorders
3. abnormalities of the vasculature

Categories of Respiratory Disease	
Category	Examples
OBSTRUCTIVE LUNG DISEASE	Asthma Chronic obstructive pulmonary disease (COPD) Bronchiectasis Bronchiolitis
RESTRICTIVE PATHOPHYSIOLOGY/PARENCHYMAL DISEASE	Idiopathic pulmonary fibrosis (IPF) Asbestosis Desquamative interstitial pneumonitis (DIP) Sarcoidosis
RESTRICTIVE PATHOPHYSIOLOGY/NEUROMUSCULAR WEAKNESS	Amyotrophic lateral sclerosis (ALS) Guillain-Barré syndrome Myasthenia gravis
RESTRICTIVE PATHOPHYSIOLOGY/CHEST WALL/PLEURAL DISEASE	Kyphoscoliosis Ankylosing spondylitis Chronic pleural effusions
PULMONARY VASCULAR DISEASE	Pulmonary embolism Pulmonary arterial hypertension (PAH) Pulmonary venoocclusive disease Vasculitis
MALIGNANCY	Bronchogenic carcinoma (non-small-cell and small-cell lung cancer) Metastatic disease
INFECTIOUS DISEASES	Pneumonia Bronchitis Tracheitis

## APPROACH TO THE PATIENT WITH DISEASE OF THE RESPIRATORY SYSTEM

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Patient with diseases of the respiratory system can present with cough, shortness of breath, chest pain, hemoptysis, pleural effusion, finger clubbing, respiratory failure, incidental pulmonary nodule, and hence our approach should be symptom wise.

The approach to patient with respiratory system disorder begins with a thorough history, focused physical examination and subsequently pulmonary function testing, chest imaging, blood and sputum analysis, serologic or microbiologic studies, and diagnostic procedures like bronchoscopy.

## HISTORY

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### DYSPNEA

- Onset and duration of a patient's symptoms are helpful in determining the etiology
  - Acute shortness of breath is usually associated with sudden physiological changes, such as laryngeal edema, bronchospasm, myocardial infarction, pulmonary embolism, or pneumothorax
  - Gradually progressing shortness of breath is common in COPD and idiopathic pulmonary fibrosis (IPF)
- Factors that incite shortness of breath and intervention that helps resolve it
  - Most asthmatics experience intermittent episodes of dyspnea, cough, and chest tightness that are usually associated with specific triggers
- Degree of activity that results in shortness of breath: gives the clinician a gauge of the patient's degree of disability

### COUGH

- Duration
- Productive or non-productive
  - Quantity and quality of the sputum
  - whether it is blood-streaked or frankly bloody
- Any specific triggers that induce the cough

#### Example:

- acute cough of phlegm → infection, including the upper airway (sinusitis, tracheitis), the lower airways (bronchitis, bronchiectasis), and the lung parenchyma (pneumonia)
- Chronic cough is commonly associated with

- obstructive lung diseases (asthma, COPD and chronic bronchiectasis),
- Nonrespiratory diseases (GERD, postnasal drip), and
- diffuse parenchymal lung diseases like IPF.

**Cough can be classified based on the duration into**

1. Acute cough: less than 3 weeks
2. Subacute: 3- 8 weeks
3. Chronic: longer than 8 Weeks

All causes of cough and dyspnea are not respiratory problems, and assessment should encompass all differentials, including cardiac and gastrointestinal diseases as well as psychogenic causes. The following table demonstrates the possible causes of dyspnea

Pathophysiology	Etiologies
Air way obstruction ( $\uparrow$ resistance to airflow)	asthma, COPD, bronchiectasis, cystic fibrosis, tumors, foreign body, anaphylaxis
Alveolar/parenchymal	Pulmonary edema (cardiogenic or noncardiogenic), ILD, pneumonia, atelectasis
Vascular (V/P mismatch)	Large vessel: PE, tumor emboli Small vessel: PHT, vasculitis, ILD, PNA, emphysema
Chest wall ( $\uparrow$ resistance to expansion, respiratory muscle weakness)	Pleural disease: large effusion, fibrosis, pneumothorax Chest wall/diaphragm: kyphoscoliosis, $\uparrow$ abdominal girth Neuro-muscular disorders: GBS, ALS, MG Hyperinflation: asthma, COPD
$\downarrow$ Oxygen carrying capacity	Anemia, methemoglobinemia, CO poisoning
Stimulation of receptors	Chemoreceptors: hypoxemia, metabolic acidosis Mechanoreceptors: ILD, pulmonary edema, PE, PHT
Psychological	Anxiety, panic attack, depression, somatization

**HEMOPTYSIS:** warrants urgent evaluation as it can be symptom of a variety of lung diseases, including infections, bronchogenic carcinoma, and pulmonary embolism.

**CHEST PAIN:** As the lung parenchyma is not innervated with pain fibers, chest pain usually results from either diseases of the parietal pleura (pneumothorax) or pulmonary vascular diseases (pulmonary hypertension).

Additionally, all patients should be asked about

- current or previous cigarette smoking (including second hand smoke) as it increases risk of COPD, bronchogenic lung cancer, desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis

- Possible inhalational exposures at work (asbestos, silica) or home (wood smoke, excrement from pet birds)
- Travel predisposes to certain infections of the respiratory tract, most notably tuberculosis (specially in sub-Saharan Africa), also Potential exposure to fungi is increased in specific geographic regions or climates
- Associated symptoms of fever and chills should raise the suspicion of infective etiologies
- Joint pain or swelling, rashes, dry eyes, dry mouth, or constitutional symptom for rheumatologic or autoimmune disease
- Symptoms of carcinomas from primary sources that commonly metastasize to the lung and cause respiratory symptoms

## PHYSICAL EXAMINATION

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### GENERAL APPEARANCE

- Patients can be acutely sick looking: in distress using accessory muscles of respiration
- Patient can also be chronically sick looking/emaciated: from chronic inflammatory process or from associated malnutrition
- The way the patient talks: Inability to complete a sentence in conversation is sign of severe impairment

### VITAL SIGN

- PR: elevated; if in pain, with fever, with dehydration
- RR: elevated or depressed
- Temperature: elevated in infectious processes, subnormal in some infectious diseases
- Oxygen saturation: patients may have hypoxemia

### RESPIRATORY SYSTEM

- **General:**
  - **Cyanosis:** in hypoxic respiratory disorders
    - results when  $>5$  g hemoglobin/dL is deoxygenated
  - **Clubbing:** in cystic fibrosis, IPF, lung abscess and lung cancer
- **Inspection**
  - Use of accessory muscle of respiration, chest movement, speech (can talk full sentence, only phrases, only words)
  - Chest deformity- barrel chest in COPD, kyphoscoliosis
- **Palpation**

- Tenderness (some ILD), subcutaneous air in barotrauma
- Tactile fremitus (not routinely done): helps to differentiate whether dullness is from effusion or consolidation
  - increases in consolidation while decreases in effusion
- Diaphragmatic excursion: hyperinflation as in COPD
- chest wall expansion: detect disorders of ventilation
- cardiac apex shift: detect mediastinal shifting
- **Percussion:** detect consolidation, pleural effusion or mass lesions
  - Dullness or stony dull→pleural effusion or mass
  - Hyperresonance→ COPD (hyperinflation), Pneumothorax
- **Auscultation:**
  - Breath sound:
    - Bronchial sound over large airway area(trachea) and
    - vesicular sound over the peripheral lung field
    - Emphysema: quiet chest with decreased breath sound
    - Pneumothorax or pleural effusion: absent breath sounds
  - Wheezes:
    - manifestation of airway obstruction as in
      - Asthma
      - Peribronchial edema in the setting of CHF,
      - other process that causes narrowing of small airways.
    - can be polyphonic, involving multiple different size airways (asthma) or
    - monophonic, involving one size airway (bronchogenic carcinoma)
  - Rhonchi: manifestation of obstruction of medium-sized airways, most often with secretions.
  - Stridor: high-pitched, focal inspiratory wheeze, usually heard over the neck as a manifestation of upper airway obstruction
  - Crackles/rales: are commonly sign of alveolar disease, present in:
    - Processes that fill the alveoli with fluid, including pulmonary edema (prominent at base) and pneumonia.
    - Diseases that result in fibrosis of the interstitium like IPF can also result in crackles (Velcro crackles)
  - Transmitted sound: Egophony, bronchophony, whispered pectoriloquy.

## OTHER SYSTEMS:

- Pedal edema:
  - if symmetric, suggest cor-pulmonale
  - if asymmetric, may be due to deep venous thrombosis and associated pulmonary embolism
- Jugular venous distention:
  - sign of volume overload associated with right heart failure/cor-pulmonale
- Pulsus paradoxus
  - an ominous sign in patient with obstructive lung disease, significant negative intrathoracic pressure required for ventilation and impending respiratory failure
- Joint and skin findings characteristics of rheumatologic disease
- Jaundice: some patients with lobar pneumonia

## DIAGNOSTIC EVALUATION

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### 1. IMAGING

#### Plain chest X-ray

- A postero-anterior (PA) film provides information on the lung fields, heart, mediastinum, vascular structures and thoracic cage
- A lateral film is used if pathology is suspected behind the heart shadow or deep in the diaphragmatic sulci
- Increased shadowing may represent
  - accumulation of fluid
  - lobar collapse or
  - consolidation
- Uncomplicated consolidation should not change the position of the mediastinum and the presence of an *air bronchogram* means that proximal bronchi are patent
- Collapse-implying obstruction of the lobar bronchus is accompanied by loss of volume and displacement of the mediastinum towards the affected side
- Suggestive of bronchiectasis
  - Presence of ring shadows (thickened bronchi seen end-on)
  - tramline shadows (thickened bronchi side-on) or
  - tubular shadows (bronchi filled with secretions)

- Presence of pleural fluid is suggested by a
  - dense basal shadow with meniscus sign
- In large *pulmonary embolism*, relative oligemia may cause a lung field to appear abnormally dark

#### HOW TO INTERPRET A CHEST X-RAY

Name, date, orientation: Films are posteroanterior (PA) unless marked AP to denote that they are anteroposterior

Lung fields: Equal translucency? Check horizontal fissure from right hilum to sixth rib at the anterior axillary line. Masses? Consolidation? Cavitation?

Lung apices: Check behind the clavicles. Masses? Consolidation? Cavitation?

Trachea: Central (midway between the clavicular heads)? Paratracheal mass? Goiter?

Heart: Normal shape? Cardiothoracic ratio (should be < 50% of the intrathoracic diameter)  
Retrocardiac mass?

Hila: Left should be higher than right Shape (should be concave laterally; if convex, consider mass or lymphadenopathy)? Density?

Diaphragm: Right should be higher than left. Anterior segment of the 6th rib should be visible above the diaphragm.

Costophrenic angles: Acute and well defined (pleural fluid or thickening, if not)?

Soft tissues: Breast shadows in females, chest wall for masses or subcutaneous emphysema

Bones: Ribs, vertebrae, scapulae and clavicles; any fracture visible at bone margins or lucency

## COMMON CHEST X-RAY ABNORMALITIES

### Pulmonary and pleural shadowing

- Consolidation: infection, infarction, inflammation and, rarely, Invasive mucinous adenocarcinoma (formerly called as bronchoalveolar carcinoma)
- Lobar collapse: mucus plugging, tumor, compression by lymph nodes
- Solitary nodule
- Multiple nodules: miliary tuberculosis (TB), dust inhalation, metastatic malignancy, healed varicella pneumonia, rheumatoid disease
- Ring shadows, tramlines and tubular shadows: bronchiectasis
- Cavitating lesions: tumor, abscess, infarct, pneumonia (*Staphylococcus/Klebsiella*), granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis)
- Reticular, nodular and reticulonodular shadows: diffuse parenchymal lung disease, infection
- Pleural abnormalities: fluid, plaques, tumor

### Increased translucency

- Bullae
- Pneumothorax
- Oligemia

### Hilar abnormalities

- Unilateral hilar enlargement: TB, lung cancer, lymphoma
- Bilateral hilar enlargement: sarcoid, lymphoma, TB, silicosis

### Other abnormalities

- Hiatus hernia
- Surgical emphysema

## COMPUTED TOMOGRAPHY (CT)

- Useful to delineate parenchymal processes, pleural disease, masses or nodules, mediastinal vascular structure, bony structures and large airways. If contrast is administered, the pulmonary vasculature can be assessed for determination of pulmonary emboli
- Cross-sectional formatting allows recognition of the axial distribution of the disease, while coronal reformation displays the craniocaudal distribution

- In cases of suspected lung cancer, CT is central to both diagnosis and staging, and facilitates percutaneous needle biopsy
- CT identifies the extent and appearance of pleural thickening and reliably differentiates pleural and pericardial fat from other pathologies
- High-resolution thin-section scanning provides detailed images of the pulmonary parenchyma and is useful in assessing diffuse parenchymal lung disease, identifying airway thickening, bronchiectasis and emphysema
- Prone imaging may be used to differentiate the gravity-induced posterobasal attenuation seen in supine scans
- CT pulmonary angiography (CTPA) is the investigation of choice in the diagnosis of pulmonary thromboembolism; it has replaced the radioisotope-based ventilation–perfusion scan, although the latter continues to provide useful information in the pre-operative assessment of patients being considered for lung resection and in the assessment of pulmonary hypertension
- CT may assist in identifying the cavitation of tuberculosis, fungal infection and other signs of infection (halo-air crescent)
- CT can be used to assess disease progression, thereby predicting prognosis, and in screening to detect the earliest signs of disease

### **POSITRON EMISSION TOMOGRAPHY (PET)**

- Enhances localization and characterization of metabolically active deposits helping differentiate between malignancy and benign pleural disease (scar)

### **MAGNETIC RESONANCE IMAGING (MRI)**

- For differentiation of benign from malignant pleural disease, and delineation of invasion of chest wall or diaphragm by tumor

### **ULTRASOUND**

- Transthoracic-ultrasound:
  - To assess the pleural space
  - Distinguish pleural fluid from pleural thickening
  - identify a pneumothorax
  - Used to guide pleural aspiration, biopsy and intercostal chest drain insertion safely
- Guide needle biopsy of superficial lymph node or chest wall masses
- Provides useful information on the shape and movement of the diaphragm

## 2. ENDOSCOPIC EXAMINATION

### Laryngoscopy

- Fibrotic laryngoscope: for direct inspection of larynx in cases of suspected vocal cord dysfunction
- Left-sided lung tumors may involve the left recurrent laryngeal nerve, paralyzing the left vocal cord and leading to a hoarse voice and a ‘bovine’ cough

### Bronchoscopy

- Flexible bronchoscopy: usually performed under local anesthesia with/without sedation, used for inspection of trachea and the first 3–4 generations of bronchi
  - Abnormal tissue in the bronchial lumen or wall can be biopsied, and bronchial brushings, washings or aspirates can be taken for cytological or bacteriological examination
- Rigid bronchoscopy: requires general anesthesia and is reserved for specific situations

### Endobronchial ultrasound

- Allows directed needle aspiration from peribronchial nodes and is used increasingly to stage lung cancer, can also be used in conditions like tuberculosis of the mediastinal lymph nodes or sarcoidosis

### Thoracoscopy

- Involves insertion of an endoscope through the chest wall
- Facilitates biopsy under direct vision and is performed by surgeons
- The gold standard for the evaluation of pleural interface, characterization of complex pleural effusion, and identification of exudate and hemorrhage
- Analysis of superior sulcus tumors (enables more accurate staging)

## 3. IMMUNOLOGICAL AND SEROLOGICAL TESTS

- Diagnosis of asthma can be supported by demonstrating an elevated level of IgE
- Serum precipitins are antibodies that form visible lines of precipitated glycoprotein when they encounter their specific antigen in an agarose gel or on an acetate cellulose sheet
  - They identify a reaction to fungi such as *Aspergillus* or antigens involved in hypersensitivity pneumonitis, such as farmer’s lung
- The presence of pneumococcal antigen in sputum, blood or urine can be of diagnostic importance in pneumonia
- *Legionella* infection can be diagnosed by detection of the urinary antigen

- Detection of galactomannan, a component of the cell wall of *Aspergillus*, assist in the diagnosis of invasive aspergillosis
- Interferon-gamma release assays are useful in the detection of latent tuberculosis

#### 4. MICROBIOLOGICAL INVESTIGATIONS

- Sputum, pleural fluid, throat swabs, blood, bronchial washings and aspirates can be examined for bacteria, fungi and viruses
- Nucleic acid amplification tests (NAATs) identify common respiratory viruses (influenza, adenovirus and RSV)
  - currently adopted as the first-line investigation for identification of tuberculosis (GeneXpert) and rapid identification of drug resistance

#### Cytology and histopathology

- Cytological examination of exfoliated cells in pleural fluid, bronchial brushings and washings, of fine needle aspirates from lymph nodes or pulmonary lesions, can support a diagnosis of malignancy
- Histopathology allows identification of infective agents such as *Mycobacterium tuberculosis*, *Pneumocystis jirovecii* or fungi

#### 5. RESPIRATORY FUNCTION TESTING

- Used to aid diagnosis, quantify functional impairment, and monitor treatment or progression of disease

#### Spirometry

- The initial pulmonary function test obtained
- An effort-dependent test used to assess for obstructive pathophysiology as in asthma, COPD, and bronchiectasis
- Patients are asked to breathe in fully, then blow out as hard and fast as they can into a peak flow meter or a spirometer over 6 seconds
- FEV1 is the volume exhaled in the first second, and FVC is the total volume exhaled
- If FEV1/FVC ratio is < 70%, spirometry should be repeated following inhaled short-acting  $\beta_2$ -adrenoceptor agonist; an increase of > 12% and > 200 mL in FEV1 or FVC indicates significant reversibility
- A large improvement in FEV1 (> 400 mL) and variability in peak flow over time are features of asthma
- A plateau of the inspiratory and expiratory curves suggests large-airway obstruction in extrathoracic and intrathoracic locations, respectively

- Flow volume loop: forced inspiratory and expiratory maneuvers
  - Useful for detection of airway obstruction located in the pharynx, larynx, or trachea (upper airways)
- Spirometry with symmetric decreases in FEV1 and FVC warrants further testing, including measurement of lung volumes and the diffusion capacity of the lung for carbon monoxide (DLCO)

### Lung volumes

- Spirometry can measure only the volume of gas that can be exhaled; but not the gas remaining in the lung
- All the gas in the lungs can be measured by rebreathing an inert non-absorbed gas (usually helium)
- Spirometry test can report four volume and four capacities
  - *Tidal volume/TV*: amount of air inhaled or exhaled during normal quiet breath
  - *Inspiratory reserve volume/IRV*: amount of air inhaled with maximum effort after quite inhalation
  - *Expiratory reserve volume/ERV*: amount of air that can be exhaled with maximum effort after quite exhalation
  - *Residual volume/RV*: amount of air remaining in the lung after maximum unit of air that can be inhaled after quite exhalation= TV + IRV exhalation
- The above volumes are used to calculate the following lung capacities
  - *Inspiratory capacities/IC*: the maximum amount of inspiration
  - *Functional residual capacity/FRC*: amount of air remaining in the lung after a quite exhalation= ERV + RV
  - *Vital capacity/VC*: amount of air that can be exhaled with maximum effort after a maximum inhalation= ERV + TV + IRV
  - *Total lung capacity/TLC*: RV + ERV + TV + IRV
- A total lung capacity <80% of the patient's predicted value defines restrictive pathophysiology
- Restriction can result from parenchymal disease, neuromuscular weakness, chest wall or pleural diseases
- Restriction with impaired gas exchange, as indicated by a decreased DLCO, suggests parenchymal lung disease
- Additional testing, such as measurements of maximal inspiratory and expiratory pressures, can help diagnose neuromuscular weakness

### Diffusing capacity for carbon monoxide (DLCO)

- Quick, safe, and useful in the evaluation of both restrictive and obstructive disease
- In the setting of restrictive disease, the diffusing capacity helps distinguish between intrinsic lung disease, in which DLCO is usually reduced, from other causes of restriction, in which DLCO is usually normal
- In the setting of obstructive disease, the DLCO helps distinguish between emphysema and other causes of chronic airway obstruction
  - Normal spirometry, normal lung volumes, and a low DLCO should prompt further evaluation for pulmonary vascular disease

### Arterial blood gas testing

- The measurement of hydrogen ion concentration,  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , and derived bicarbonate concentration in an arterial blood sample
- Pulse oximeters with finger/ear probes measure the difference in absorbance of light by oxygenated and deoxygenated blood and calculate the percentage of hemoglobin that is oxygenated
- essential for assessing the degree and type of respiratory failure and measuring acid–base status
- Allows measurement of arterial  $\text{PO}_2$  and the calculation of an alveolar gas and arterial blood oxygen tension difference ( $[\text{A}-\text{a}] \text{DO}_2$ )
  - Patients with diseases that cause ventilation-perfusion mismatch or shunt physiology have an increased  $(\text{A}-\text{a}) \text{DO}_2$  at rest
- Also allows the measurement of arterial  $\text{PCO}_2$ 
  - Hypercarbia can accompany disorders of ventilation, as seen in severe airway obstruction (COPD) or progressive restrictive physiology

## INFECTIOUS DISEASE OF RESPIRATORY SYSTEM

### URTI

#### COMMON COLD

- Most common cause of acute coughs
- Commonly caused by viruses (adenovirus, rhinovirus, influenza and Para influenza viruses, corona virus, RSV, coxsackievirus).

#### History

- Sore throat, runny nose, headache, muscle ache, fatigue and fever.

Diagnosis: clinical

Management: self-limited and lasts for no longer than 2 weeks, hence supportive!

## PNEUMONIA

It is Inflammation of the lung parenchyma

#### Classification

- Etiologic
  - Infectious, aspiration, inhalational
- Anatomic
  - Lobar, Bronchial, interstitial
- Place of acquisition
  - Community acquired pneumonia (CAP)
  - Nosocomial pneumonia: can be
    - Hospital acquired pneumonia
    - Ventilator associated pneumonia
    - Health care associated pneumonia

### COMMUNITY ACQUIRED PNEUMONIA (CAP)

- Commonly caused by bacteria;
  - Typical (*S. pneumoniae*, *H. influenzae*, *S. aurous*, *K. pneumoniae* and *P. aeruginosa*)
  - Atypical (*M. pneumoniae*, *C. pneumoniae*, and *Legionella*) but can also be caused by viruses, fungi, and protozoa.
- Classic (lobar pneumococcal) pneumonia: evolves through a series of pathologic changes or phases:
  - Edema
  - Red hepatization
  - Gray hepatization, and

- Resolution

### CLINICAL RULES FOR SEVERITY

1. **Pneumonia severity index/PSI:** stratified patient into five classes for risk of death from all causes within 30 days of presentation

#### Predictor variables:

- Demographic conditions
  - Age > 50 years
- Co morbid conditions
  - Neoplastic disease
  - Heart failure
  - Cerebrovascular disease
  - Renal disease
  - Liver disease
- Physical examination findings
  - Altered mental status
  - Pulse  $\geq 125$ /minute
  - Respiratory rate  $\geq 30$ /minute
  - SBP <90 mm Hg
  - Temp.  $<35^{\circ}\text{C}$  or  $\geq 40^{\circ}\text{C}$

Risk of death within one month and options for management		
class 1	0.1%	outpatient treatment
class 2	0.6%	
class 3	2.8%	admitted for observation
class 4	8.2%	
class 5	29.2%	in patient treatment

#### 2. CURB-65 score: commonly used:

- Confusion (based upon mental test or new disorientation to person, place, or time)
- Urea (blood urea nitrogen)  $>7$  mmol/L (20 mg/dL)
- Respiratory rate  $\geq 30$  breaths/minute
- Blood pressure [BP] (systolic  $<90$  mmHg or diastolic  $\leq 60$  mmHg)
- Age  $\geq 65$  years

Score	Risk of death within 30 days	options of management
Score 0	1.5%	outpatient treatment
Score of 1 or 2	-	should be hospitalized unless the score is entirely or in part attributable to an age of $\geq 65$ year
scores of $\geq 3$	22%	require ICU admission

### HOSPITAL ACQUIRED PNEUMONIA (HAP)

Occur after 48 hours of admission in either ICU or non-ICU patient (but not in intubated ICU patient as VAP), or within 7 days after discharge from hospital.

The following points differentiate HAP from VAP:

- MDR pathogens are not common, which allows mono therapy
- Better underlying host immunity
- Anaerobes are more common (increased risk of macro aspiration and decreased O<sub>2</sub> tension in lower lung)

### VENTILATOR ASSOCIATED PNEUMONIA (VAP)

Common complication in patient requiring mechanical ventilation and endo-tracheal intubation. Etiologic agents include both

- Non-MDR (*S. pneumonia*, *H. influenza*, *S. aures*) and
- MDR (*P. aeruginosa*, MRSA) bacterial pathogens

### HEALTH CARE ASSOCIATED PNEUMONIA

New classification used for patients presenting as outpatients and found to be infected with MDR pathogens (MRSA, MDR/PDR Gram-ve bacilli like *P.aeruginosa*). Responsible factors include:

- Earlier transfer of patients out of acute-care hospitals to their homes
- Increased use of outpatient IV antibiotic therapy
- Widespread use of potent oral antibiotics
- Extensive healthcare contact: -residence in a nursing home, attendance at hemodialysis clinic, IV therapy, wound care

### ASPIRATION PNEUMONIA

From abnormal entry of fluid, particulate substances, or endogenous secretions which leads to a compromise in the usual defense mechanism and inoculation of deleterious content to the lower airways.

- Can be classified as:
  - Chemical pneumonitis: from aspiration of substances that are toxic to the lower airways
    - Treatment: immediate tracheal suction to clear fluids and particulate matter that may cause obstruction, support pulmonary function
  - BACTERIAL INFECTION: infection caused by aspiration of bacteria that normally reside in the upper airways or stomach, primarily anaerobes and streptococci
    - Treatment: clindamycin 600 mg IV TID then 300 mg PO QID for 7-10 days

## APPROACH

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### HISTORY

- Symptoms: Cough- productive or non-productive (can be mucoid, purulent, blood tinged if productive) with HGF, chills/sweating, SOB, pleuritic chest pain, fatigue, headache, myalgia/arthritis, nausea, vomiting, diarrhea
- Risk factors:
  - Risk factors for CAP include
    - Alcoholism or drug overdose
    - Asthma
    - Institutionalization
    - Age of  $\geq 70$  years
    - Dementia
    - Seizure disorders
    - Heart failure
    - Cerebrovascular disease
    - Tobacco smoking
    - COPD, and
    - immunosuppressive conditions like malignancy, chemotherapy, steroid use, HIV infection
  - CA-MRSA pneumonia is more likely in patients with skin colonization or infection with CA-MRSA
  - Enterobacteriaceae tend to infect patients who have recently been hospitalized and/or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure
  - *P. aeruginosa* is a particular problem in patients with severe structural lung disease, such as bronchiectasis, cystic fibrosis, or severe COPD

- Risk factors for Legionella infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise

## PHYSICAL EXAMINATION

Vital signs: tachypnea, tachycardia, raised temperature, hypotension

Chest examination

- Inspection: respiratory distress; use of accessory muscle of neck, IC/SC retraction, pain
- Palpation: increased (consolidation) or decreased (effusion) tactile fremitus
- Percussion: stony dullness-pleural fluid, relative dullness-consolidation
- Auscultation: decreased breath sound, Crackles, bronchial breath sounds, pleural friction rub, wheezing (viral pneumonia)

Others: evidence of septic shock and organ failure:

- Hypothermia
- Hypotension
- Cool/clammy skin
- Metabolic acidosis
- Convulsion
- Mental status change

## INVESTIGATIONS

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- CBC- leukocytosis or leukopenia (poor prognostic feature)
- CXR: -infiltrates (consolidation), complications (effusion, multi lobular disease), pneumothorax
- Gram stain and culture of sputum
- The main purpose of the sputum Gram's stain is to ensure that a sample is suitable for culture. To be adequate for culture, a sputum sample must have >25 neutrophils and <10 squamous epithelial cells per low-power field. Even in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%
- Blood culture: Only 5–14% of cultures of blood are positive
- urine antigen test (legionella, pneumococcus)

## DIAGNOSIS

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- **Clinical diagnosis:** History + Physical examination finding + CXR finding
- **Etiologic diagnosis:** sputum stain and culture, blood culture, urinary antigen test, PCR, serology, biomarkers.

## MANAGEMENT

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### Non pharmacologic/Supportive care

- Bed rest
- Frequent vital sign monitoring to follow treatment response and detection of complications
- Fluid and nutrition replacement
- Oxygen if SPO<sub>2</sub> <94%

### Pharmacologic/antibiotics

- For outpatient with uncomplicated pneumonia, no significant comorbidities, no use of antibiotics within the last three months, low prevalence of macrolide-resistant strains, we can use one of the following oral regimens:
  - Amoxicillin 500 mg PO TID for 7 day
  - Azithromycin 500 mg on day one then 250 mg /day for 4 days; 500 mg/day for three days
  - Clarithromycin 1000 mg PO once daily for five days or until afebrile for 48 to 72 hours
  - Doxycycline 100 mg twice a day for 7 to 10 days
- The presence of comorbidities, use of antibiotics within the prior three months, increased risk of resistant pathogens, we can use one of the following oral regimens:
  - A respiratory fluoroquinolone ( gemifloxacin 320 mg daily, levofloxacin 750 mg daily, moxifloxacin 400 mg daily) for a minimum of five days
  - Combination therapy:
    - Beta-lactam effective against S. pneumoniae (high-dose amoxicillin 1 g TID/amoxicillin-clavulanate 2 g BID) or cefuroxime 500 mg BID PLUS
    - Either a macrolide ( azithromycin 500 mg on day one then 250 mg/day for 4 days or clarithromycin 250 mg BID or doxycycline 100 mg BID
- For inpatient
  - Respiratory floroquinolons or ceftriaxone plus azithromycin/claritromycin/doxycycline

## COMPLICATIONS

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- Exacerbation of co-morbid illness
- Complicated pleural effusion
- Lung abscess

- Metastatic infection
- Respiratory failure
- Shock and multi organ failure
- Coagulopathy

## COMPLICATED PLEURAL EFFUSION AND EMPYEMA

**Complicated parapneumonic effusion:** occurs when there is invasion of the pleural space by bacteria but pleural fluid culture and gram stain are negative due to rapid clearance of the Bacteria

**Empyema:** refers to invasion of the pleural space by significant number of bacteria resulting in pus and/or positive gram stain or culture from pleural fluid

**Uncomplicated pleural effusion:** refers to a sterile exudative pleural effusion which results from the movement of pulmonary interstitial fluid to the pleural space

- The following features are among indications for surgical drainage of pleural effusion
  - The presence of Gross Pus in the pleural space
  - Positive Gram Stain or Culture of the pleural fluid
  - Pleural fluid Glucose < 3.3 mmol/L (<60 mg/dL)
  - Pleural fluid PH < 7.20 or LDH > 100 U/dl
  - Loculated Pleural Fluid, massive effusion

NB: we can use the abbreviation 3GPL for easy recall

## INVESTIGATIONS

- Pleural fluid cell count with differential, LDH, Protein, glucose, gram stain, culture and AFB
- Chest ultrasound-useful for suspected loculated pleural effusion
- Chest CT scans-if chest X-ray and ultrasound are not conclusive

## TREATMENT

- Empyema and complicated parapneumonic effusion require prompt chest tube drainage plus antibiotic treatment
  - Empiric therapy that would cover anaerobic organisms: clindamycin, beta-lactam plus beta-lactamase inhibitors (amoxicillin-clavulanate, ampicillin-sulbactam), and carbapenems
  - Antibiotic therapy until there is radiographic resolution of fluid (for two to four weeks following defervescence)
- Multi loculated pleural effusions require thoracoscopic or open surgical drainage and debridement

- Uncomplicated parapneumonic effusion requires proper antibiotic treatment alone as for Pneumonia ceftriaxone plus metronidazole

## **ACUTE BRONCHITIS**

Inflammation of mucous membrane of the bronchi which is generally self-limited.

### **HISTORY**

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- Symptoms: cough, sore throat, SOB, LGF, runny nose, coryza, malaise and fatigue, wheezing, chest pain
  - The cough is dry initially which later becomes productive and it lasts longer (5 days to 3 weeks) which differentiate it from common cold

### **PHYSICAL EXAMINATION**

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- Wheezing-bronchospasm- evidenced by ↓ FEV1
- Rhonchi on auscultation-often clears after coughing up
- Bronchial hyperreactivity demonstrated with provocative test

### **INVESTIGATION**

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- CXR: may reveal bronchial wall thickening, also to rule out pneumonia and other cause of cough
- Culture: to rule out pertussis
- PFT: to rule out emphysema, asthma

### **DIAGNOSIS**

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clinical-from history and by ruling out others differentials

### **MANAGEMENT**

---

Supportive

- NSAID to treat sore throat and fever
- Antibiotics for bacterial etiology

## PERTUSSIS

- Caused by *B. pertussis* which produce the following virulence factors:-
  - Pertussis toxin-has mitogenic activity, affects circulation of lymphocytes, and serves as adhesion for bacterial binding to respiratory ciliated cells.
  - Tracheal cytotoxin-which causes respiratory epithelial damage
  - Adenylate cyclase toxin-which impairs host immune-cell function
  - Dermonecrotic toxin-which may contribute to respiratory mucosal damage
  - LPS

## CLINICAL MANIFESTATION

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### SYMPTOMS

Pertussis case definition: cough of 14 days with post-tussive vomiting

- Initial catarrhal stage-cold like symptom
- Paroxysmal whooping cough after 1-2 week of cold like symptom which can persist for 4 weeks or longer
- Complications: exhaustion, tussive syncope, conjunctivitis, hernias, dehydration, airway infection

### INVESTIGATIONS

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- Culture (nasopharyngeal secretion, blood)- identification of the organism
- PCR- identification of the organism

### DIAGNOSIS

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- The first 2 weeks- identification of the pathogen by culture of nasopharyngeal secretion
- The first 4 weeks- PCR
- Late phase- serology; these results are interpreted in the context of the clinical presentation

### MANAGEMENT

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- Supportive care: to decrease complication
- Antibiotics: eradicate bacteria from nasopharynx; alter the clinical course if given early in catarrhal stage
- Infection control: case isolation, antibiotic prophylaxis for contact person (with <6-month infant)

## SINUSITIS

Inflammation of Para nasal sinuses due to infection, allergy, or autoimmune problems.

Can be classified based on:

- Duration of illness: acute vs chronic
- Etiology: infectious vs noninfectious
- Pathogen type: viral, bacterial, or fungal

### CLINICAL MANIFESTATION:

Symptoms: cough, sneezing, fever, nasal congestion, facial pain or pressure, headache, thick/purulent/discolored nasal discharge, tooth pain

- **Complications:** soft tissue swelling and pitting edema over the frontal bone, orbital swelling/cellulitis, proptosis, ptosis, decreased extra ocular movement

### DIAGNOSIS:

- Clinical: The three cardinal symptoms (Purulent Nasal Discharge, Nasal Obstruction, and Facial Pain) and symptom duration (prolonged)
- CT or Radiography of sinus
- Biopsy specimen

### MANAGEMENT:

- Oral and topical decongestants, nasal saline lavage
- Glucocorticoids
- Antibiotics
- Surgical intervention

Complications: Meningitis, Epidural Abscess, and Cerebral Abscess

## CHRONIC OBSTRUCTIVE DISEASES

### ASTHMA

**DEFINITION:** It is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment.

Asthma is a heterogeneous disease with several phenotypes recognized, but thus far these do not correspond well to specific pathogenic mechanisms

**Asthma can be classified in to 4 types**

- Intermittent,
- Mild persistent,
- Moderate persistent
- Severe persistent

**There are two main categories of severe asthma**

- Type-2 inflammation
- Non-Type-2 inflammation.

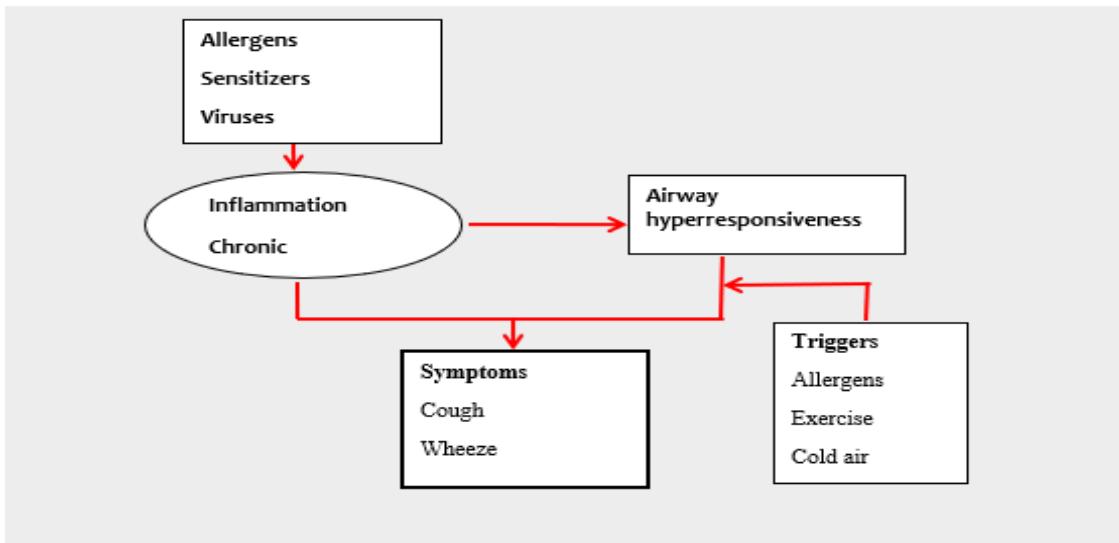
Comparison of the two major types of Asthma		
Features	Allergic (Atopic)	Non-Allergic (idiosyncratic)
Age of onset	Early in life	Late in life
Family or personal history of allergy: rhinitis, urticarial eczema	Present	Absent
Skin test with intradermal injection of allergens	Positive wheal - and - flare skin test	Negative skin test
Serum IgE level	Elevated	Normal
Response to inhalation (Provocative test)	positive	Negative

**Note:** Many patients have disease that doesn't fit into either of the 2 categories, but instead fall into a mixed group with some features from each group. In general asthma which has its onset early in life tends to have strong allergic component, whereas asthma that develops late in life tends to be nonallergic or to have mixed etiology.

Risk Factors and Triggers involved in Asthma	
Endogenous Factors	Environmental Factors
<ul style="list-style-type: none"> <li>Genetic predisposition</li> <li>Atopy is the single most important risk factor for asthma</li> <li>Airway hyperresponsiveness</li> <li>Gender</li> <li>Ethnicity</li> <li>Obesity</li> <li>Early viral infection</li> </ul>	<ul style="list-style-type: none"> <li>Indoor allergens</li> <li>Outdoor allergens</li> <li>Occupational sensitizers</li> <li>Passive smoking</li> <li>Respiratory infections</li> <li>Air pollution (diesel particulates, nitrogen oxides)</li> <li>Diet</li> <li>Dampness and mold exposure</li> <li>Acetaminophen (paracetamol)</li> </ul>
Triggers	
<ul style="list-style-type: none"> <li>Allergens</li> <li>Upper respiratory tract viral infections</li> <li>Exercise and hyperventilation</li> <li>Cold air</li> <li>Sulfur dioxide and irritant gases</li> <li>Drugs (<math>\beta</math>-blockers, aspirin)</li> <li>Stress</li> <li>Irritants (household sprays, paint fume)</li> </ul>	

## PATHOPHYSIOLOGY

- Associated with chronic inflammation in the respiratory mucosa from the trachea to terminal bronchioles with a predominance in the bronchi
- The pattern of airway inflammation in asthma is associated with airway hyper-responsiveness (AHR), which is correlated with variable airflow obstruction
- Inflammatory cells like mast cells, macrophages, dendritic cells Eosinophil, T-lymphocytes, neutrophils and inflammatory mediators like cytokines, Chemokines, Nitric oxide, and Proinflammatory transcription factors are involved in the inflammatory process.
- The following diagram shows the pathophysiology of Asthma



## APPROACH TO PATIENT

### HISTORY

- Symptoms
  - Prodromal symptoms (may precede an attack)
    - Itching under the chin,
    - Discomfort between the scapulae, or
    - Inexplicable fear (impending doom)
  - Episodic or chronic symptoms of airflow obstruction:
    - Dyspnea
    - Cough, dry or productive (typically tenacious and difficult to expectorate)
    - Wheezing, Chest tightness
  - The frequency of asthma symptoms is highly variable.
  - May be worse at night and patients typically awake in the early morning hours
  - Some patients have infrequent, brief attacks of asthma and others may suffer nearly continuous symptoms
  - May occur spontaneously or may be precipitated or exacerbated by many different triggers

### PHYSICAL FINDINGS

- Some physical findings increase the probability of asthma:
  - Nasal mucosal swelling
  - increased nasal secretions, and
  - nasal polyps are often seen in patients with allergic asthma

- Eczema, atopic dermatitis, or other manifestations of allergic skin disorders may also be present
- Chest examination
  - Rhonchi throughout the chest, hyperinflation – hyperresonant chest
  - There may be no abnormal physical findings when asthma is under control or between exacerbations in patients with mild asthma
  - During severe asthma exacerbations, airflow may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sounds with prolonged expiration.

## DIAGNOSIS

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### CLINICAL

- **Episodic asthma:**
  - Paroxysms of wheeze, dyspnea and cough, asymptomatic between attacks
- **Acute severe asthma:**
  - Upright position, use accessory respiratory muscles, cannot complete sentences in one breath
  - tachypnea > 30/min, tachycardia > 110/min, pulsus paradoxus
  - PEF < 50% of predicted or best
  - Chest hyperresonance, prolonged expiration, breath sounds decreased, inspiratory and expiratory rhonchi
- **Life-threatening features:**
  - PEF < 33% of predicted or best, PaO<sub>2</sub> < 60, PCO<sub>2</sub> normal or increased, acidosis (low pH)
  - Silent chest, cyanosis, bradycardia, hypotension, feeble respiratory effort, exhaustion, confusion, coma
- **Chronic asthma:**
  - Dyspnea on exertion, wheeze, chest tightness and cough on daily basis, usually at night and early morning
  - Intercurrent acute severe asthma (exacerbations) and productive cough (mucoid sputum), recurrent respiratory infection, expiratory rhonchi throughout and accentuated on forced expiration.

### PHYSIOLOGIC

- Lung Function Tests: variable airflow obstruction with reversibility by means of FEV<sub>1</sub> and PEF measurement (spirometer and peak flow meter)
  - FEV<sub>1</sub> < 80% of predicted – PEF < 80% of predicted.

- Reversibility: A good bronchodilator response is a >12% and 200-mL increase in FEV<sub>1</sub> 15 min after an inhaled short-acting β<sub>2</sub>-agonist (SABA; such as inhaled albuterol 400 µg) or in some patients a 2–4-week trial of oral corticosteroids (OCS) (prednisone or prednisolone 30–40 mg daily)
- Diurnal peak flow variation: Normal variation: Morning PEF 15% lower than evening PEF, with asthma this variation is > 15% (morning dipping)
- Provocation studies: Airway hyperresponsiveness
  - Not usually done
  - Exercise: A 15% drop in FEV<sub>1</sub> post exercise indicates exercise induced asthma.
  - Methacholine challenge: 20% reduction in FEV<sub>1</sub> at Methacholine concentrations < 8mg/ml indicates bronchial hyperactivity

### IMMUNOLOGIC

- Skin prick wheal and flare response
  - inhalant allergens are positive in allergic asthma and negative in intrinsic asthma
  - are not helpful in diagnosis
- IgE and RAST
- Eosinophil cationic protein (ECP)
- Peripheral blood and sputum eosinophilia

### RADIOLOGY

- Chest X-Ray
  - may be normal between attacks.
  - With attacks hyperinflation may be found.
  - In complicated asthma segmental lobar collapse (mucous plugs) and pneumothorax can occur

### CLASSIFICATION OF SEVERITY

Severity class	Clinical Features Before Treatment		
	Symptoms	Nocturnal symptoms	FEV <sub>1</sub> or PEF
STEP 1 Mild Intermittent	≤ 2 time a week Asymptomatic and normal PEF between attacks	≤ 2 times a month	>80% predicted Variability < 20%
STEP 2 Mild Persistent	> 2 time a week but < 1 time a day	> 2 times a month	>80% predicted Variability 20 - 30%
STEP 3 Moderate Persistent	Daily Attacks affect activity	> 1 time a week	60 - 80% predicted Variability > 30%
STEP 4 Severe Persistent	Continuous Limited physical activity	Frequent	<60% predicted Variability > 30%

The presence of one feature of severity is sufficient to place patient in that category

## MANAGEMENT PRINCIPLE

### COMPONENT OF MANAGEMENT

- Routine monitoring of symptoms and lung function
- Patient education to create a partnership between clinician and patient
- Controlling environmental factors (triggers) and comorbid conditions that contribute to asthma severity

### AIMS OF ASTHMA THERAPY

- Minimize chronic symptoms
- Minimize exacerbations
- Decrease No emergency visits
- Minimize use of a required  $\beta_2$ -agonist
- Improve limitations on activities, including exercise
- peak expiratory flow circadian variation <20%, Near normal PEF

### PHARMACOLOGIC THERAPY

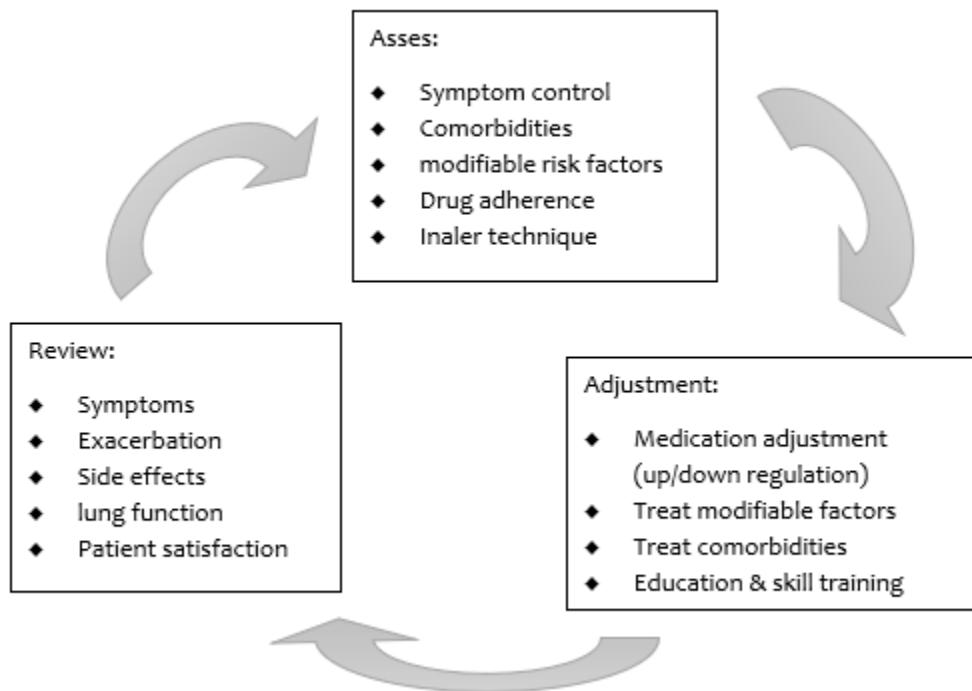
is guided by disease severity and treatment components include:

- **Bronchodilators**
  - Includes Beta Agonists, Anticholinergics
  - Act primarily on airway smooth muscle to reverse the bronchoconstriction
  - Gives rapid relief of symptoms
  - Has little or no effect on the underlying inflammatory process i.e. are not sufficient to control asthma
- **Glucocorticoids**
  - ICS are by far the most effective controllers for asthma
    - ICS reduce the numbers and activation inflammatory cell in the airways
  - Intravenous Corticosteroids (hydrocortisone, methylprednisolone) are used for acute severe asthma
  - OCS (usually prednisone or prednisolone 30–45 mg once daily for 5–10 days) is used to treat acute exacerbations of asthma

#### DIFFERENCE BETWEEN PREDNISONE AND PREDNISOLONE

- Prednisone is a prodrug which needs to be converted to prednisolone in the liver
- So, in people with severe liver disease, prednisolone is preferred
- Mode of action, dose, side effect and indications are the same for both
- Cost wise prednisone is cheaper than prednisolone

- **Antileukotrienes**
  - less effective than ICS in controlling asthma and have less effect on airway inflammation
  - useful as an add-on therapy in some patients not controlled with low doses of ICS
- **Anti-IgE Omalizumab:** neutralizes circulating IgE
- **Anti-IL-5 Antibodies:** markedly reduce blood and tissue eosinophils and reduce exacerbations
- **Oxygen**
- Generally, asthma treatment is adjusted in continuous cycle of assessment and review of patient response in both symptom response and future risk of exacerbation, and of patient preference



- Step up if symptom remain uncontrolled despite good adherence and technique, no persistent allergen exposure, no comorbidity
- Step down once asthma control has been achieved and maintained for about 3 month
- There are two tracks used (GINA 2021)
  - Track 1: the reliever is as needed low dose ICS-formoterol
    - there is reduced risk of severe exacerbation compared with SABA reliever regimen

- When patient at any treatment step has asthma symptoms, they use low dose ICS-formoterol as reliever
- Step 3-5 patients use ICS-formoterol as daily controller= maintenance and reliever therapy “MART”
- Track 2: the reliever is as needed SABA
  - Patient in step 1 take SABA + low dose ICS as reliever
  - Patient in step 2-5; SABA alone as reliever and ICS containing controller therapy

### Step wise treatment of chronic asthma (controller therapy) (track 1)

				Very severe persistent↓
		Moderate persistent↓	Severe persistent↓	Add-on LAMA± anti-IgE, anti-IL5/5R, anti-IL4/R Consider high dose ICS-formeterol
Mild intermittent↓	Mild persistent↓	Maintainance low dose ICS-formeterol	Maintainance medium dose ICS-formeterol	
As needed low dose ICS-formeterol	As needed low dose ICS-formeterol			

### ACUTE SEVERE ASTHMA

- Increasing chest tightness, wheezing, and dyspnea that are often not or poorly relieved by their usual reliever inhaler
- Patients may be breathless and cyanotic
- Examination usually shows increased ventilation, hyperinflation, and tachycardia
- Marked fall in spirometric values and PEF
- Arterial blood gases show hypoxemia, and PCO<sub>2</sub> is usually low due to hyperventilation

## MANAGEMENT

- High concentration of oxygen should be given by face mask to achieve oxygen saturation of >90%.
- The mainstay of treatment are high doses of SABA given either by nebulizer or via a MDI with a spacer
- In severely ill patients with impending respiratory failure, IV beta<sub>2</sub>-agonists ± nebulized anticholinergic can be given
- if refractory to inhaled therapies, a slow infusion of *aminophylline* may be effective
- *Magnesium sulfate* given intravenously or by nebulizer is effective when added to inhaled beta<sub>2</sub>-agonists
- For patients with respiratory failure, it is necessary to *intubate* and institute ventilation
  - These patients may benefit from a *general anesthetic*, such as halothane, if they have not responded to conventional bronchodilators
  - Sedatives should never be given as they may depress ventilation

## SPECIAL CONSIDERATIONS

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### REFRACTORY ASTHMA

- Small proportion of patients (~5%) are difficult to control despite maximal inhaled therapy, some of which will require maintenance treatment with OCS
- There are two major patterns of difficult asthma:
  - some patients have persistent symptoms and poor lung function, despite appropriate therapy
  - others may have normal or near normal lung function but intermittent, severe life-threatening exacerbations
- The most common reason for poor control of asthma is poor adherence with medication, particularly ICS
- exposure to high levels of allergens, Severe rhinosinusitis, upper airway disease, Drugs such as beta-adrenergic blockers, aspirin, and other cyclooxygenase (COX) inhibitors may make asthma more difficult to control

**CORTICOSTEROID-RESISTANT ASTHMA:** failure to respond to a high dose of oral prednisolone (40 mg once daily over 2 weeks)

**REDUCED RESPONSIVENESS TO CORTICOSTEROIDS:** control of asthma requires OCS (corticosteroid-dependent asthma)

**BRITTLE ASTHMA:** chaotic variations in lung function despite taking appropriate therapy.

- **Type 1 brittle asthma:** persistent pattern of variability and may require OCS or, at times, continuous infusion of beta<sub>2</sub>-agonists
- **Type 2 brittle asthma:** generally normal or near-normal lung function but precipitous, unpredictable falls in lung function that may result in death
  - difficult to manage as they do not respond well to corticosteroids and inhaled bronchodilators
  - The most effective therapy is subcutaneous epinephrine
- Treatment of refractory Asthma
  - Check adherence and the correct use of inhalers
  - Identify and eliminate any underlying triggers
  - Low doses of theophylline (has withdrawal effect)

### ASTHMA IN THE ELDERLY

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- side effects of therapy are a problem, including muscle tremor with beta<sub>2</sub>-agonists and more systemic side effects with ICS
- Comorbidities are frequent and interactions with drugs like beta<sub>2</sub>-blockers, COX inhibitors, and agents affecting theophylline metabolism need to be considered
- COPD is more likely in elderly patients and may coexist with asthma
- Pregnancy
- one-third of asthmatic patients who are pregnant improve during the course of a pregnancy one-third deteriorate, and one-third are unchanged
- Poor control may have adverse effects on fetal development.
- Adherence may be a problem as there is often concern about the effects of antiasthma medications on fetal development
- The drugs that have been used in asthma including SABA, ICS, and theophylline are safe and non-teratogenic

NB: there is evidence that Cigarette smoking interferes with the anti-inflammatory actions of corticosteroids by reducing HDAC2; necessitating higher doses for asthma control

- LABA and theophylline appear to overcome some of the steroid resistance; so, ICS-LABA combination therapy and low dose theophylline should be used

## ASTHMA-COPD OVERLAP (ACO)

- Although asthma and COPD are distinct syndromes with different clinical presentations and underlying inflammatory mechanisms;
  - some patients with asthma have features of COPD (for example, asthmatics who smoke and severe asthmatics with irreversible airflow limitation) and
  - Some patients with COPD have features of asthma with more reversibility and increased airway and blood eosinophils.
- This may represent the coincidence of two common diseases, or these may be distinct phenotypes
- ACO patients tend to have more symptoms and exacerbations than either of the two
- They may benefit from triple therapy with ICS, LABA, and LAMA.

## HOW TO USE A METERED-DOSE INHALER

- Remove the cap and shake the inhaler
- Breathe out gently and place the mouthpiece into the mouth
- Incline the head backwards to minimize oropharyngeal deposition
- Simultaneously, begin a slow deep inspiration, depress the canister and continue to inhale over 5 seconds
- Hold the breath for 10 seconds
- You should clean your mouth with clean water (gurgling) after use,  
If the inhaler is ICS



### RECOMMENDATION

- We highly recommend you to watch videos on proper use of MDI and DPI from YouTube and teach your patients, as more than 80% of patients fail to use these inhalers appropriately.

- The role of environmental factors (e.g. animal dander, dust, airborne molds, and pollens) in acute exacerbations is clear. Allergens that can be controlled by avoidance should be eliminated.
- Nonspecific exacerbating factors (e.g. cigarette smoke, odors, irritant fumes, and change in temperature, atmospheric pressure, and humidity) should also be investigated and avoided if possible

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

**DEFINITION:** COPD is defined as a disease state characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible.

It includes:

- **Emphysema:** is an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement
- **Chronic bronchitis:** is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough (eg, bronchiectasis) have been excluded
- **Small airway disease (those airways <2mm):** is a condition in which small bronchioles are narrowed and reduced in number.

## APPROACH TO PATIENT

### HISTORY:

- Exertional dyspnea, cough, and sputum production
- Many patients have such symptoms for months or years before seeking medical attention
- Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for patients with COPD
- Activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated [e.g. Pushing a shopping cart or walking on a treadmill]
- Worsening dyspnea on exertion is the principal feature of advanced COPD

### In COPD exacerbation:

- Dyspnea increases
- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character

### RISK FACTORS

- Cigarette Smoking
  - Calculated as:

$$\text{No. of cigarette smoked} \times \text{years of smoking}/20$$

- The effects of cigarette smoking on pulmonary function appear to depend on
  - The intensity of smoking exposure

- Timing of smoking exposure during growth
- The baseline lung function of the individual
- Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production there is also smooth-muscle hypertrophy and bronchial hyperreactivity leading to airflow limitation
- Genetic factors likely contribute to the level of pulmonary function achieved during growth and to the rate of decline in response to smoking and potentially to other environmental factors as well
- Airway Responsiveness
- Respiratory Infections (are important causes of COPD exacerbations)
- Occupational Exposures
  - exposure to dust and fumes at work
  - coal mining, gold mining, and cotton textile dust
  - household smoke for firewood (in our country)
- Ambient Air Pollution
  - Common in urban than in the rural areas
  - smoke produced by biomass combustion
- Passive, or Second-Hand, Smoking Exposure
- Genetic  $\alpha_1$  Antitrypsin Deficiency

## PHYSICAL FINDINGS

- Early stages of COPD
  - Normal physical examination
  - Current smokers - signs of active smoking (an odor of smoke or nicotine staining of fingernails)
- Severe disease
  - prolonged expiratory phase and expiratory wheezing
  - signs of hyperinflation (**a barrel chest** and enlarged lung volumes with poor diaphragmatic excursion)
  - use of accessory muscles of respiration, sitting in the characteristic "tripod"
- Advanced disease
  - systemic wasting - significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue

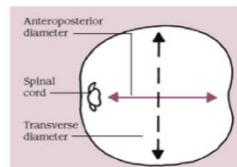
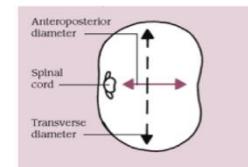
### Recognizing barrel chest

In a normal adult chest, the ratio of anteroposterior to transverse (or lateral) diameter is 1:2. In patients with barrel chest, this ratio approaches 1:1 as the anteroposterior diameter enlarges.

NORMAL CHEST



BARREL CHEST



- Independent poor prognostic factor in COPD
- paradoxical inward movement of the rib cage with inspiration (*Hoover's sign*)
- Signs of overt right heart failure (termed *cor-pulmonale*)
- Conjunctival hyperemia (secondary polycythemia)
- Clubbing of the digits is not a sign of COPD
- Traditionally emphysema and chronic bronchitis are differentiated as:
  - Patients with predominant emphysema ("pink puffers")
    - are thin and noncyanotic at rest and
    - have prominent use of accessory muscles
  - Patients with chronic bronchitis ("blue bloaters")
    - are more likely to be heavy and cyanotic

NB: current evidence demonstrates that most patients have elements of both chronic bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

## CLASSIFICATION

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### GOLD (Global Initiative for Chronic Obstructive Lung Disease) staging system

GOLD Criteria for Severity of Airflow Obstruction in COPD			
GOLD STAGE	SEVERITY	SYMPTOMS	SPIROMETRY
0	At risk	chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	FEV1/FVC <0.7 and FEV1 ≥80% predicted
II	Moderate	With or without chronic cough or sputum production	FEV1/FVC <0.7 and FEV1 ≥50% but <80% predicted
III	Severe	With or without chronic cough or sputum production	FEV1/FVC <0.7 and FEV1 ≥30% but <50% predicted
IV	Very severe	With or without chronic cough or sputum production	FEV1/FVC <0.7 and FEV1 <30% predicted

## COPD SEVERITY GROUP

COPD severity categories are based on respiratory symptoms (mMRC or CAT scales) and annual frequency of COPD exacerbations.

- Respiratory symptoms
  - mMRC—Modified Medical Research Council Dyspnea Scale:

The Modified Medical Research Council (mMRC) Dyspnea Scale		
GRADE OF DYSPNEA	DESCRIPTION	
0	Not troubled by breathlessness, except with strenuous exercise	
1	Shortness of breath walking on level ground or with walking up a slight hill	
2	Walks slower than people of similar age on level ground due to breathlessness, or has to stop to rest when walking at own pace on level ground	
3	Stops to rest after walking 100 m or after walking a few minutes on level ground	
4	Too breathless to leave the house, or breathless with activities of daily living (e.g., dressing/ undressing)	

- **CAT—COPD ASSESSMENT TEST.**

- An 8-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea on one flight of stairs, limitation in home activities, confidence in leaving the home, sleep and energy.
- Range of total score is 0–40

- **Annual frequency of COPD exacerbations**

- Low risk: A history of zero or one exacerbation in the past 12 months and GOLD 1 or 2 spirometric level
- High risk: two or more exacerbations or a hospitalized exacerbation or GOLD 3 or 4 spirometric level

COPD severity group		
Group	Symptoms	Risk (Exacerbation history)
Group A Low symptoms Low risk	mMRC grade 0 to 1 or CAT score <10	0 to 1 exacerbation per year and no prior hospitalization for exacerbation
Group B High symptoms Low risk	mMRC grade ≥2 or CAT score ≥10	0 to 1 exacerbation per year and no prior hospitalization for exacerbation
Group C Low symptoms High risk	mMRC grade 0 to 1 or CAT score <10	≥2 exacerbations per year or ≥1 hospitalization for exacerbation
Group D High symptoms, High risk	mMRC grade ≥2 or CAT score ≥10	≥2 exacerbations per year or ≥1 hospitalization for exacerbation

### BODE index for COPD survival prediction

- BODE stands for Body mass index, airflow Obstruction, Dyspnea and Exercise capacity
  - online calculators:
- Body mass index
  - >21 (0 point)
  - <21 (1 point)
- FEV1 % predicted after Bronchodilator
  - >65% (0 point)
  - 50-64% (1 point)
  - 36-49% (2 point)
  - <35% (3 point)
- MMRC dyspnea scale
  - MMRC 0: Dyspneic on strenuous exercise (0 points)
  - MMRC 1: Dyspneic on walking a slight hill (0 points)
  - MMRC 2: Dyspneic on walking level ground; must stop occasionally due to breathlessness (1 point)
  - MMRC 3: Must stop for breathlessness after walking 100 yards or after a few minutes (2 points)
  - MMRC 4: Cannot leave house; breathless on dressing/undressing (3 points)
- 6-minute walk distance
  - >350 meters (0 point)
  - 250-349 meters (1 point)
  - 150-249 meters (2 point)
  - <149 meters (3 point)

Approximate 4 Year Survival Interpretation

0-2 Points:	80%
3-4 Points:	67%
5-6 Points:	57%
7-10 Points:	18%

## INVESTIGATION

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- **Arterial blood gases (ABG) and oximetry**
    - Resting or exertional hypoxemia
    - alveolar ventilation and acid-base status by measuring arterial  $\text{PCO}_2$  and PH (ABG)
  - **Hematocrit** – Secondary polycythemia
  - **Pulmonary function testing**
    - Reduction in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC
    - lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity, and residual volume
  - **Chest X-Ray**
    - Sensitivity of 50%
    - Obvious bullae, paucity of parenchymal markings, or hyperlucency emphysema.
    - Increased lung volumes and flattening of the diaphragm ☐ hyperinflation
    - When advanced COPD leads to pulmonary hypertension and cor pulmonale, prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space may be seen.
  - **Chest computed tomography (CT)**
    - is the current definitive test for establishing the presence or absence of emphysema, the pattern of emphysema, and the presence of significant disease involving medium and large airways.
    - It also enables the discovery of coexisting interstitial lung disease and bronchiectasis, which are common complications in COPD.
    - can help determine the possible value of surgical therapy
  - **$\alpha_1$  AT deficiency testing**
  - **ECG**
    - Show typical changes in a patient with cor pulmonale secondary to advanced COPD (p-pulmonale, right axis deviation, partial right bundle block, dominant R wave in lead V<sub>1</sub>)
  - **Echocardiography** – right ventricular hypertrophy
- Diagnosis
- COPD is suspected in patient with chronic productive cough and/or exertional dyspnea of uncertain etiology, or whose physical examination reveals evidence of prolonged forced expiration
  - Pulmonary function tests (spirometric testing) are done at specialized hospitals to determine the type of pulmonary obstruction

- The pattern of physiologic abnormality in each patient depends to some extent on the relative severity of intrinsic bronchial disease and emphysema
  - In patients with severe emphysema, resting hypoxemia is usually mild (no or less cyanosis).
  - In patients with chronic bronchitis, severe hypoxemia may be noted relatively early

## **MANAGEMENT PRINCIPLES**

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### **Stable Phase COPD**

- The two main goals of therapy are
  - To provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, improve health status) and
  - Reduce future risk (prevent disease progression, prevent and treat exacerbations, and reduce mortality)

### **Pharmacologic**

- Smoking Cessation
  - Middle aged smokers experienced a significant improvement
  - Combining pharmacotherapies like Nicotine replacement therapy (gum, patch, inhaler, nasal spray), Bupropion, Varenicline

### **General principle**

- Pharmacologic therapy should be initiated with non-pharmacologic therapy
- For all COPD patient Short acting bronchodilators be used as needed for relief

### **Bronchodilator**

- are the primary treatment for almost all patients with COPD
- used for symptomatic benefit and to reduce exacerbation
- Short-acting bronchodilators(SABA,SAMA)improves symptoms with acute improvement in FEV1 while Long-acting bronchodilators (LABA, LAMA) provide symptomatic benefit and reduce exacerbations
- Group A
  - Bronchodilators, either short acting or long acting
  - Continued if benefit is documented
- Group B
  - Long acting (regular bases) plus short acting (as needed)
  - In this group selection of either LABA or LAMA is based on
    - Patients need

- Comorbidities and
- adverse effects
- Dual bronchodilators could be considered in severe breathlessness
- Group C
  - Use LAMA as initial treatment
  - In comparison to LABA, LAMA have a greater effect in reducing exacerbation (by around 17%)
- Group D
  - Dual bronchodilators are recommended
  - LAMA plus LABA are recommended when CAT  $\geq 20$
  - Selection of LAMA-LABA therapy over LABA-ICS is based on
    - Evidence of improved lung function
    - Better control of mild exacerbation
    - Fewer episodes of pneumonia (and other ICS adverse effect)
  - LABA-ICS maybe first choice
    - Blood eosinophil count  $\geq 300$  cell/ $\mu$ l
    - COPD with history of Asthma

### Glucocorticoids

- ICS
  - The main role is reducing exacerbation
  - Modestly slows progression of respiratory symptoms
  - has little impact on lung function and mortality
  - indicated in patients with
    - Frequent exacerbations  $\geq 2$  per year
    - Hospitalization with 1 exacerbation
    - Peripheral eosinophilia of  $> 300$
  - Considered in patients with features of asthma, benefit increases with eosinophil count  $> 100$
  - Are never used alone in COPD
- OCS: chronic use of oral glucocorticoids is associated with side effects, including
  - Osteoporosis
  - Weight gain
  - Cataracts
  - Glucose intolerance
  - Increased risk of infection
- Theophylline and PDE4 Inhibitor improves airflow and reduce exacerbation frequency

### Oxygen:

- The only pharmacologic therapy demonstrated to unequivocally decrease mortality rates
- Mortality benefit is proportional to number of hours' oxygen is used / day
- Indications
  - Resting hypoxemia ≤88%, confirmed twice per week for three weeks
  - Signs of pulmonary arterial hypertension, right heart failure or erythrocytosis (hct >55%), ≤89%

### Antibiotics:

- Indicated for patients with history of exacerbation in the past 6 months
- Azithromycin
  - Reduce frequency of exacerbation
  - Most effective in older patient and milder GOLD stages
  - Little benefit on current smokers

Others - α1AT augmentation therapy

### Non-pharmacologic

- General Medical Care
- Pulmonary Rehabilitation
- Lung Volume Reduction Surgery (LVRS)
- Lung Transplantation
- Vaccination: pneumococcal, influenza, bordetella pertussis

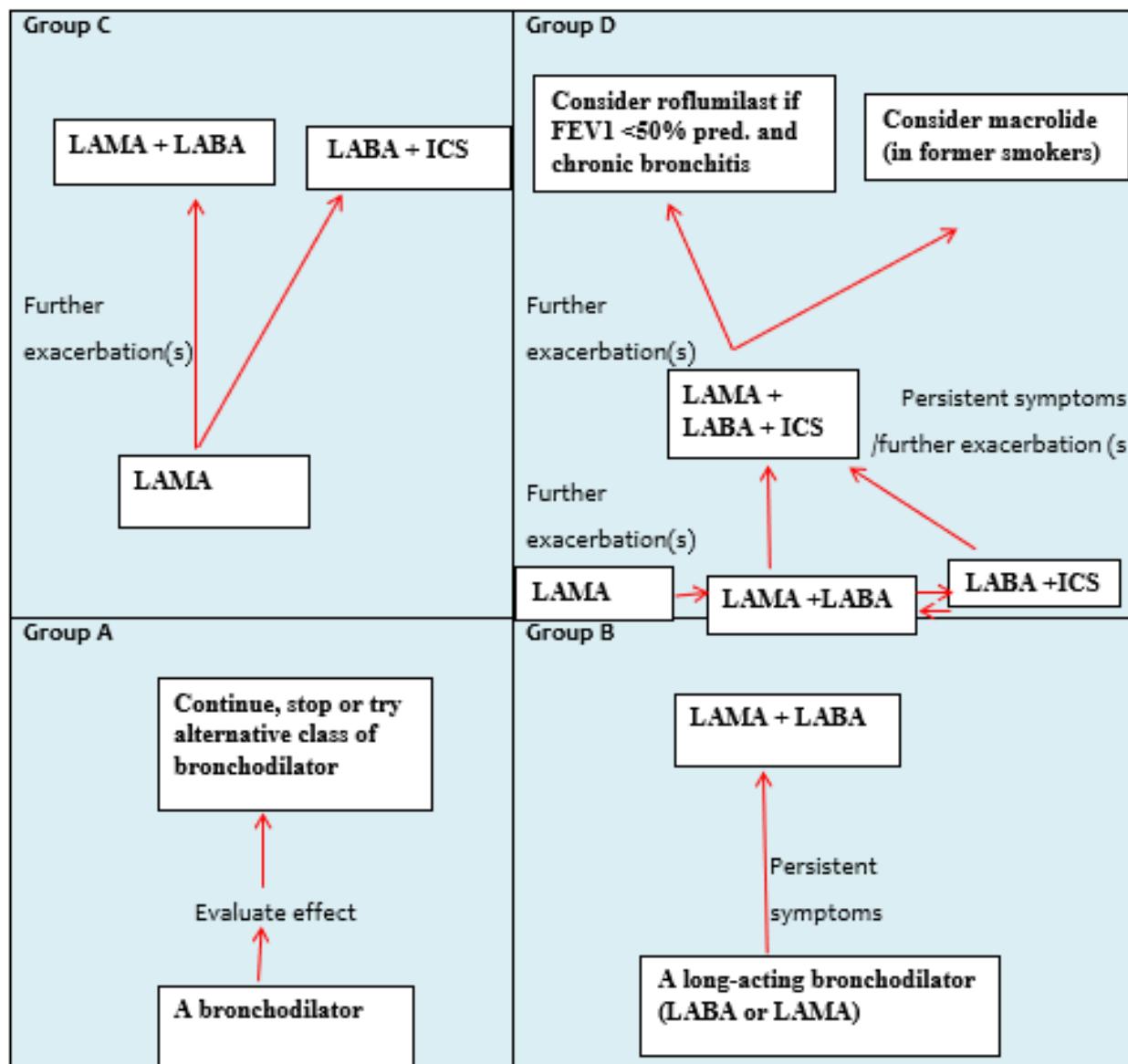


### Three interventions that improves survival are

1. Smoking cessation
2. Oxygen therapy in chronically hypoxic patient
3. Lung volume reduction surgery in selected patient with emphysema

### Follow up pharmacological management principle

1. Review
  - Symptoms (dyspnea) and exacerbation
2. Assess
  - Inhaler technique and adherence, non-pharmacological approach
3. Adjust
  - Escalate or de-escalate drugs, switch inhaler devices or molecules



## EXACERBATIONS OF COPD

- Exacerbations are episodic acute worsening of respiratory symptoms:
  - either worsening of SOB or increased sputum production or sputum purulence
- Frequency of exacerbations increases as airflow obstruction worsens
- Bacterial infection/superinfection is involved in >50% of exacerbations
- Viral respiratory infections are present in one-third of COPD exacerbations and
- Minority of cases (20–35%) has no specific precipitant
- The severity of the exacerbation and severity of preexisting COPD should be assessed

### COPD exacerbation can be classified into 4 categories based on severity

- Mild: can be managed at home with SABAs only
- Moderate: can be managed as outpatient with SABAs + antibiotics+ steroids
- Severe: without respiratory failure: can be treated in the wards with SABAs + antibiotics+ steroids
- Severe with respiratory failure: Needs ICU admission for Respiratory support (Noninvasive or invasive ventilation)

**NB:**

- **mild exacerbation**= only one of the symptoms of exacerbation (excluding sputum purulence)
- **Moderate exacerbation**= two of the symptoms of exacerbation
- **Severe exacerbation**= all the three symptoms

### Antibiotics:

- Bacteria frequently implicated in COPD exacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*
- *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are found in 5–10% of exacerbations
- The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above pathogens as well as the patient's clinical condition
- Patients with moderate or severe exacerbations are usually treated with antibiotics, even in the absence of data implicating a specific pathogen
- *Pseudomonas* should be covered in patient with the following risk factors:
  - Recent hospitalization ( $\geq 2$  days' duration during the past 90 days)
  - Frequent administration of antibiotics ( $\geq 4$  courses within the past year)
  - Severe COPD (FEV<sub>1</sub> <50 percent of predicted)
  - Isolation of *Pseudomonas aeruginosa* during a previous exacerbation
  - Systemic glucocorticoid use

### Glucocorticoids

- The use of systemic glucocorticoids
  - Reduces the length of stay
  - Hastens recovery, and
  - Reduces the chance of subsequent exacerbation or relapse
- Current recommendations suggest 30–40 mg of oral prednisolone or its equivalent typically for a period of 5–10 days in outpatients

### Oxygen Supplementation

- Should be supplied to maintain oxygen saturation 90-92%

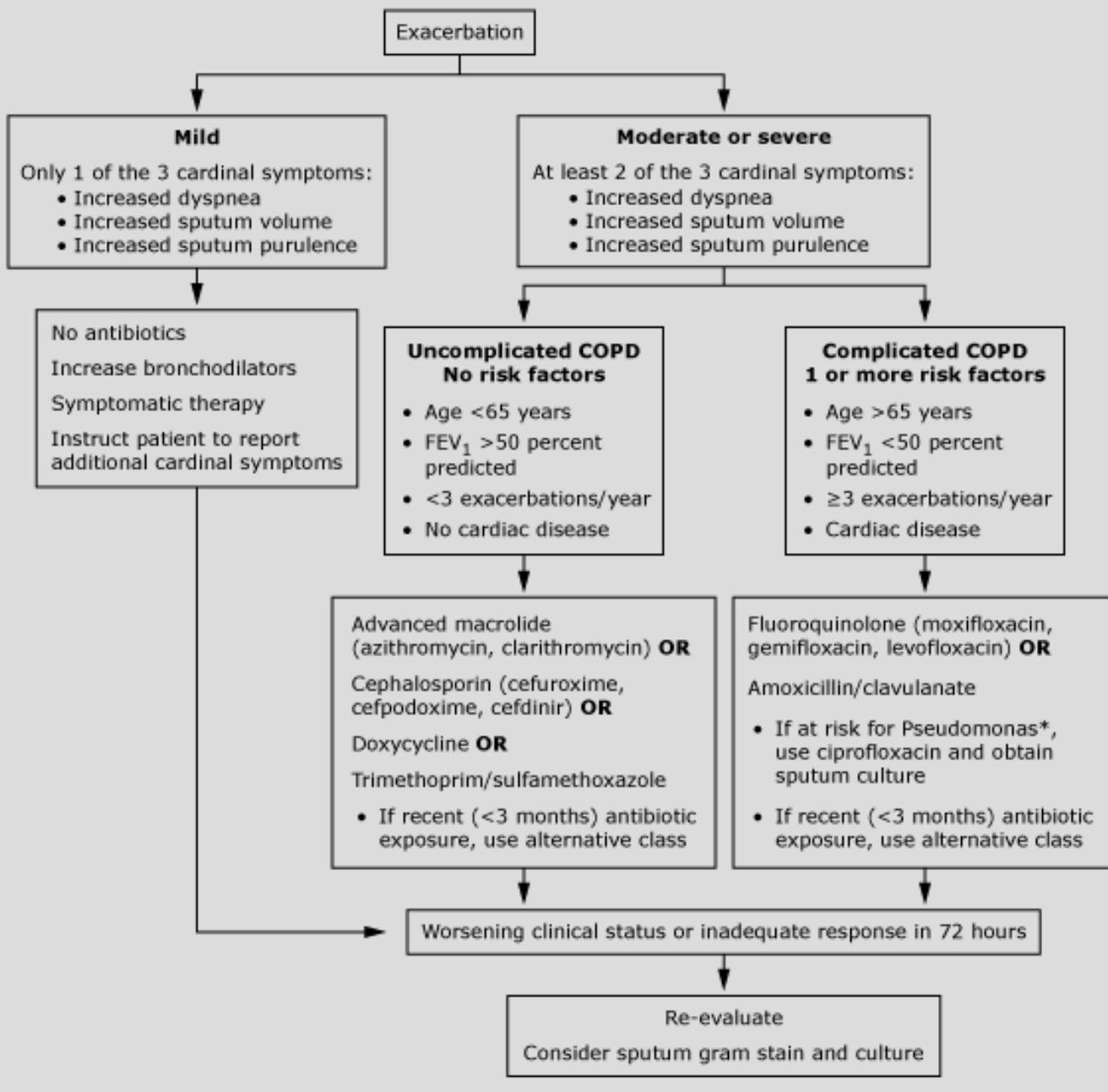
## INDICATIONS FOR ICU ADMISSION

- Severe dyspnea that responds inadequately to initial therapy
- Change mental status
- Worsening of hypoxemia  $\text{PaO}_2 < 40 \text{ mmHg}$  and/ or respiratory acidosis ( $\text{PH} < 7.25$ ) despite supplemental O<sub>2</sub> and noninvasive ventilation
- Hemodynamic instability-need for vasopressor
- Need for invasive mechanical ventilation

### Mechanical Ventilatory Support

- Noninvasive mechanical ventilation: is needed in patients with at least one of the following
  - Respiratory acidosis/respiratory failure ( $\text{PaCO}_2 > 45 \text{ mmHg}$  and arterial  $\text{PH} < 7.35$ )
  - Increased dyspnea, respiratory muscle fatigue, increased work of breathing
  - Persistent hypoxemia despite oxygen supplement
- Invasive (conventional) mechanical ventilation is indicated for:
  - Severe respiratory distress despite initial therapy
  - Life-threatening hypoxemia, severe hypercarbia and/or acidosis
  - Markedly impaired mental status
  - Respiratory or cardiac arrest
  - Hemodynamic instability not responding to fluid or vasoactive
  - Unable to remove respiratory secretions, massive aspiration and persistent vomiting
  - Ventricular supraventricular arrhythmia

## Outpatient management of acute exacerbations of COPD



## BRONCHIECTASIS

Is irreversible airway dilation. The pattern can be

- Focal (obstruction) or
- Diffuse (infection, immunodeficiency, genetic problem, autoimmune)

### ETIOLOGY:

- idiopathic in more than 50% of adults despite aggressive investigations, but generally the etiologies are classified as follow
- Congenital syndromes
  - Cystic fibrosis
  - Immotile Cilia Syndrome, e.g. Kartagener's Syndrome
  - Alpha-1 antitrypsin deficiency
  - Primary Hypogamma-globulinemia
- Acquired
  - Post infection
  - Airway obstruction
  - Traction

**N.B** The major factors that contribute to the development of bronchiectasis are loss of muco-ciliary clearance system and infection

History: symptoms

- Persistent productive cough with ongoing production of: - thick, tenacious, offensive, postural and purulent sputum
- SOB, pleuritic chest pain, wheezing, hemoptysis, fever, weakness and weight loss

**N.B** Acute exacerbations are characterized by changes in the nature of sputum production, with increased volume and purulence

### PHYSICAL FINDINGS:

Respiratory System Examination

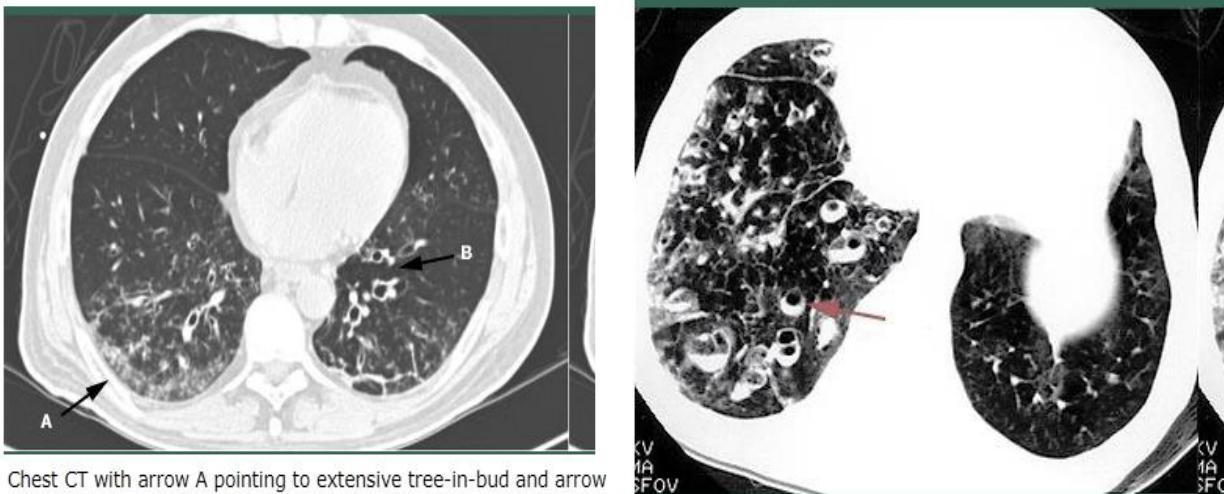
- General: digital clubbing, cyanosis
- Auscultation: crackles and wheezing

Investigation

- CXR- “tram tracks” indicating dilated airways
- Chest CT-is diagnostic work up. Findings include; -
  - Airway dilation detected as parallel “tram tracks” or as the “signet-ring sign”
  - Lack of bronchial tapering

- bronchial wall thickening in dilated airways
- Inspissated secretions/ "tree-in-bud" pattern/or cysts emanating from the bronchial wall
- Gram stain and culture (of sputum or BAL)- infectious etiologies
- Laboratory tests;
  - CBC (shows infection)
  - Immunoglobulin and HIV test (immune compromization)
  - Alpha<sub>1</sub> antitrypsin
  - Sweat chloride level (cystic fibrosis)
  - Rheumatoid factors (autoimmune causes)

#### Tree-in-bud



## DIAGNOSIS

- Persistent chronic cough and sputum production + consistent radiographic features and Chest CT for confirming the diagnosis.

## MANAGEMENT

- Antibiotics: - targeting the causative or presumptive pathogen (with *H. influenza* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations.
  - usually for a minimum of 7–10 days and perhaps for as long as 14 days
- Bronchial hygiene: -used to enhance secretion clearance by:-
  - Hydration and mucolytic administration

- Aerosolization of bronchodilators and hyperosmolar agents (e.g. hypertonic saline).
- Chest physiotherapy (postural drainage, traditional mechanical chest percussion or use of devices such as a high-frequency chest wall oscillation vest).
- Pulmonary rehabilitation and a regular exercise
- The mucolytic dornase (DNase) is recommended in CF-related bronchiectasis
- Anti-inflammatory therapy: - oral/systemic glucocorticoids
  - may be important in certain etiologies, such as ABPA, or of noninfectious bronchiectasis like an autoimmune conditions(e.g., rheumatoid arthritis or Sjögren's syndrome)
- Surgical: -focal resection
  - lung transplantation [in advanced cases]

## **COMPLICATIONS**

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- Acute exacerbation (commonest)
- Recurrent pneumonia
- Suppurative complications
  - Empyema, Lung abscess, Brain abscess
- Massive hemoptysis- injury to superficial mucosal vessels
- Respiratory failure
- Cor-pulmonale

## RESTRICTIVE LUNG DISEASE

### INTERSTITIAL LUNG DISEASE (ILD)

**DEFINITION:** large number of conditions that affect the lung parenchyma with varying degrees of inflammation and fibrosis.

#### CLASSIFICATION:

- Idiopathic interstitial pneumonia
  - Idiopathic Pulmonary Fibrosis
  - Nonspecific interstitial pneumonia
  - Smoking related ILD
  - Cryptogenic organizing pneumonia
  - Respiratory Bronchiolitis associated ILD
  - Desquamative Interstitial Pneumonitis
  - Acute Interstitial Pneumonia
  - Lymphocytic Interstitial Pneumonia
- ILD of known cause
  - Systemic sclerosis
  - Rheumatoid arthritis
  - Dermatomyositis/polymyositis
  - Granulomatous ILD
  - Granulomatous vasculitis

#### HISTOPATHOLOGIC PATTERNS

- A granulomatous pattern
  - Sarcoidosis
  - HP
- A pattern in which inflammation and fibrosis predominate
  - Usual Interstitial Pneumonia (UIP)
  - Nonspecific Interstitial Pneumonia
  - Respiratory Bronchiolitis
  - Organizing Pneumonia [Bronchiolitis obliterans with organizing pneumonia (BOOP) pattern]
  - Diffuse Alveolar Damage (Acute or Organizing)
  - Desquamative Interstitial Pneumonia
  - Lymphocytic Interstitial Pneumonia
- Development of irreversible scarring (Fibrosis) of Alveolar Walls, Airways, or Vasculature is the most feared outcome in all of these conditions

## OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASES

- Disease caused by environmental agents and their interaction with other factors (smoking, genetic risk).
- History of environmental exposure is uncovered through inquiry of specific work practices including
  - Questions about the specific contaminants involved
  - The presence of visible dusts, chemical odors, ventilation of workspaces
  - The use of respiratory protective equipment
  - Whether co-workers have similar complaints
  - Proximity to traffic or industrial facilities.
- Symptoms are indistinguishable from that of disease not caused by such agents, but
  - The temporal association of exposure at work and symptoms provide clues to occupation-related disease
  - 15–20% of the burden of adult asthma and COPD has been estimated to be due to occupational factors.

## HYPERSensitivity PNEUMONITIS

- Inflammatory disorder of the lung involving alveolar walls and terminal airways
- Induced by repeated inhalation of variety of organic agents in a susceptible host

### COMMON TYPES OF HP

- Farmer's lung
- Bird fancier's lung
- Chemical worker's lung

**HISTORY:** The presentation can be

- **Acute**
  - symptoms occur 6 to 8 h after exposure to the antigen and usually clear within a few days if no further exposure to antigen
  - symptoms include-cough, fever, chills, malaise, and dyspnea
- **Subacute:**
  - Appears insidiously over a period of weeks
  - Marked by cough and dyspnea
  - May progress to cyanosis and severe dyspnea
  - May persist after an acute presentation if there is continued exposure to antigen but disappears over weeks to months on removal of the antigen
- **Chronic:**
  - Continuous low-level antigen exposure or repeated episodes

- With subtler symptoms
- Symptoms include cough, weight loss, malaise, and gradual increase in dyspnea

### Offending agents

- Antigens derived from fungal, bacterial, mycobacterial, bird-derived, and chemical sources
- Individuals at particular risk include farmers, bird owners, industrial workers, and hot tub users

### PHYSICAL EXAMINATION

- Respiratory system
  - General: - digital clubbing
  - Auscultation: -Inspiratory crackles

### INVESTIGATIONS

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#### Laboratory work up

- Elevation in ESR, CRP, RF, LDH, serum Immunoglobulin
- CBC-neutrophilia and lymphopenia but not Eosinophilia

**Serum precipitant:** IgG antibodies against specific antigens

### IMAGING

- CXR
  - Acute and subacute
    - poorly defined, patchy, or diffuse infiltrates with discrete, nodular infiltrates or
    - with air-space consolidation
  - Chronic
    - diffuse reticulonodular infiltrate
    - Honeycombing-advanced disease
- HRCT- diagnostic
  - Acute-often normal
  - Subacute-ground-glass airspace opacities and centrilobular nodules
  - Chronic-reticular changes and traction bronchiectasis, subpleural honeycombing which usually spare lung bases
- PFT: restrictive or obstructive abnormalities

Bronchoscopy-BAL-shows lymphocytosis and most HP have CD4+/CD8+ of <1

## DIAGNOSIS

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Six significant predictors of HP

1. Exposure to a known antigen
2. Positive predictive antibodies to the antigen
3. Recurrent episodes of symptoms
4. Inspiratory crackles
5. Symptoms developing 4–8 h after exposure, and
6. Weight loss

This diagnostic paradigm has a high predictive value in the diagnosis of HP, but the diagnosis of HP is established by:

- Consistent symptoms, physical findings, pulmonary function tests, and radiographic tests
- History of exposure to a recognized antigen
- Identification of an antibody to that antigen
- Lung biopsy may be needed in some circumstances

## MANAGEMENT

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- Acute HP: removal of offending antigen
- Subacute and chronic:
  - Removal of offending antigen
  - Glucocorticoids
  - Lung transplantation if extensive lung fibrosis

## COMPLICATION

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- Progressive worsening may result in
  - Dependence on supplemental oxygen
  - Pulmonary hypertension
  - Respiratory failure

## OTHER PULMONARY DISORDERS

### PULMONARY HYPERTENSION (PH)

Definition: Pulmonary hypertension (PH) is defined as an elevated mean pulmonary arterial pressure  $\geq 25$  mmHg at rest. PH has several etiologies and can be a progressive, fatal disease, if untreated.

#### CLASSIFICATION

The World Health Organization (WHO) has classified PH based upon etiology into the five groups

##### **Group-1 Pulmonary arterial hypertension (PAH)**

- Idiopathic PAH and Heritable
- Drug- and toxin-induced
- Connective tissue diseases
- HIV infection
- Portal hypertension
- Congenital heart diseases
- Schistosomiasis

##### **Group-2 Pulmonary hypertension owing to left heart disease**

- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular heart disease
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

##### **Group-3 Pulmonary hypertension owing to lung diseases and/or hypoxia**

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

##### **Group-4: pulmonary hypertension due to chronic thromboembolic pulmonary hypertension (CTEPH)**

### Group-5 Pulmonary hypertension with unclear multifactorial mechanisms (miscellaneous)

- Hematologic disorders: chronic hemolytic anemia (e.g., sickle cell disease), myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.

### INVESTIGATIONS

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- Echo with bubble study-important initial screening test for determining specific causes
- Cardiopulmonary exercise test
  - identify true physiologic limitation
  - differentiate between cardiac and pulmonary causes of dyspnea
- HRCT
  - Enlarged pulmonary arteries
  - peripheral pruning of the small vessels
  - enlarged right ventricle and atrium
  - signs of venous congestion
    - Centrilobular ground glass infiltrate
    - thickened septal lines
- Right heart catheterization-gold standard
- CT- critical for distinguishing co-morbid interstitial lung disease or emphysema.
- CT angiograms
  - evaluate acute thromboembolic disease
  - Ventilation-perfusion (V/Q) scanning – for qualifying patients for surgical intervention
- PFT
  - isolated reduction in DLCO is the classic finding in PAH
  - suggest restrictive or obstructive lung diseases as cause of PH
- BNP and NT-proBNP
  - correlate with right ventricular dysfunction
  - hemodynamic severity, and
  - functional status in PAH

## DIAGNOSIS

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- Clinical signs and symptoms
- Right heart catheterization (RHC) for definitive diagnosis
- Etiologic diagnosis: Chest imaging and lung function tests are essential because lung disease is an important cause of PH

## MANAGEMENT

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- Pharmacologic: prostacyclin, prostacyclin analogues and agonists, NO pathway enhancers, endothelin receptor antagonists, calcium channel blockers

## RESPIRATORY FAILURE

- Impaired oxygen uptake with or without hypercapnia
- The diagnosis of respiratory failure requires an arterial blood gas analysis
  - **Type I:** Hypoxemic respiratory failure: respiratory failure with hypoxemia and normal or low levels of CO<sub>2</sub> in the blood at rest.
    - It occurs with alveolar flooding and subsequent intrapulmonary shunt physiology as a consequence of pulmonary edema, lung injury, pneumonia, or alveolar hemorrhage.
    - Type I respiratory failure occurs in clinical settings such as sepsis, gastric aspiration, pneumonia, near-drowning, multiple blood transfusions, and pancreatitis, i.e. It is caused by:
      - Ventilation-perfusion inequality
      - Impaired diffusion (decreased surface, thickening of the alveolocapillary membrane)
      - Right-left shunt
    - Type I respiratory failure may not respond to O<sub>2</sub> supplement
    - Pulmonary edema can occur due to elevated pulmonary microvascular pressures as in heart failure or due to intravascular volume overload/ARDS
  - **Type II/Hypoxic Hypercarbic Respiratory Failure:** occur as a consequence of alveolar hypoventilation that results from the inability to eliminate carbon dioxide effectively. It can be caused due to:
    - Impaired central nervous system (CNS) drive to breathe from drug overdose, brainstem injury, sleep-disordered breathing, and severe hypothyroidism
    - Impaired strength with failure of neuromuscular function in the respiratory system as seen in myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, myopathy, electrolyte derangement
    - Increased load on the respiratory system;

- Resistive loads (bronchospasm)
  - Loads due reduced lung compliance (alveolar edema, atelectasis, intrinsic positive end-expiratory pressure [auto-PEEP])
  - loads due to reduced chest wall compliance (pneumothorax, pleural effusion, abdominal distention), and
  - loads due to increased minute ventilation requirements (pulmonary embolus with increased dead-space fraction, sepsis)
  - The mainstays of therapy for type II respiratory failure are directed at reversing the underlying cause(s) of ventilatory failure
- NB: type II RF can be corrected with O<sub>2</sub> supplement
- **Respiratory Failure Type III:** results from lung atelectasis, commonly in the perioperative period from residual anesthesia effects, post-operative pains, and abnormal abdominal mechanics i.e. is also called perioperative respiratory failure
    - Can be treated by frequent changes in position, chest physiotherapy, upright positioning, and control of incisional and/or abdominal pain
  - **Respiratory Failure Type IV-Shock:** result from hyperperfusion of respiratory muscle in patients in shock.
    - Patients in shock often experience respiratory distress due to pulmonary edema, lactic acidosis, and anemia, in which up to 40% of cardiac output may be distributed to the respiratory muscles (<5% normally)
    - Intubation and mechanical ventilation can allow redistribution of the cardiac output away from the respiratory muscles and back to vital organs while the shock is treated

## LUNG ABSCESS

Lung abscess represents necrosis and cavitation of the lung following microbial infection. Can be single or multiple but usually are marked by a single dominant cavity >2 cm in diameter

Classification

### PRIMARY LUNG ABSCESS (80%)

- occur in the absence of an underlying pulmonary or systemic condition
- major risk factor is aspiration; colonization of the gingival crevices by anaerobic bacteria or microaerophilic streptococci is important in the disease process
- The dependent segments (posterior upper lobes and superior lower lobes) are the most common locations (right lung)
- the microbiology is polymicrobial; primarily anaerobic organisms and microaerophilic streptococci

- Pneumonitis develops initially (exacerbated in part by tissue damage caused by gastric acid); then, over 7–14 days, the anaerobic bacteria produce parenchymal necrosis and cavitation
- When no pathogen is isolated from a primary lung abscess (40% of cases), the abscess is termed a nonspecific lung abscess
- A putrid lung abscess refers to cases with foul-smelling breath, sputum, or empyema; that are diagnostic of an anaerobic lung abscess

## SECONDARY LUNG ABSCESS

- arise in the setting of underlying conditions like post obstructive process (bronchial foreign body or tumor) or a systemic process
- pathogenesis depends on the predisposing factor, e.g. obstructing lesion prevents clearance of oropharyngeal secretions, leading to abscess development
- The location of secondary abscesses may vary with the underlying cause
- Microbiology: broad bacterial spectrum, but infection by *P. aeruginosa* and other G-negative rods is most common
- significant incidence of fungal infections among immunosuppressed patients
- Since we had wide array of unusual organisms, it is of special importance to obtain culture material in order to target therapy
- Lung abscesses also arise from septic emboli, either in tricuspid valve endocarditis or in Lemierre's syndrome

NB: Necrotizing Pneumonia or Lung Gangrene refers to multiple small pulmonary abscesses in contiguous areas of the lung, usually resulting from a more virulent infection.

## CAUSES OF LUNG ABSCESS

- Post pneumonia- commonly
- Aspiration
- Post traumatic- infected hematoma
- Septic pulmonary embolism
- Amoebic lung abscess
- Malignant lung abscess

## CLINICAL MANIFESTATION

### HISTORY

- Initially similar to pneumonia; fevers, cough, sputum production, chest pain
- chronic and indolent presentation: night sweats, fatigue, position dependent foul-smelling sputum (production of short-chain fatty acids by anaerobes), symptom of anemia

**P/E:** fevers, poor dentition, and/or gingival disease, signs of consolidation on lung examination, digital clubbing

## INVESTIGATIONS

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- Blood picture: increase in white cell count
- Sputum examination: culture and drug sensitivity test
- Chest X-ray: thick-walled cavity with an air-fluid level
- CT: possible underlying cause of lung abscess, such as malignancy, and differentiate peripheral lung abscess from pleural space infection like empyema
- Bronchoscopy: foreign body or endo-bronchial tumor causing bronchial obstruction

## DIAGNOSIS

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Clinical; history +physical finding + imaging

## MANAGEMENT:

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### 1. Non pharmacologic:

- Chest physiotherapy and postural drainage
- Surgery in selected cases
- Treatment of underlying disease

### 2. Pharmacologic:

- Empiric antibiotic therapy

**For primary lung abscesses:** recommended regimens are

1. Clindamycin 600 mg IV TID; then, with the disappearance of fever and clinical improvement, 300 mg PO four times daily

2. IV-administered amoxicillin-clavulanate, followed by orally administered amoxicillin-clavulanate once the patient's condition is stable

3. Combination of penicillins/cephalosporins with metronidazole is another alternative

- it can take up to 7 days for patients receiving appropriate therapy to defervesce
- Rx is continued until imaging demonstrates that the abscess has cleared or regressed to small scar (weekly/biweekly CXR needed)
- if patient fails to improve (10–20%), an underlying predisposing cause for secondary lung abscess should be ruled out
- An abscess >6–8 cm is less likely to respond to antibiotic therapy; require surgical resection and percutaneous drainage

### Secondary lung abscesses

- Treatment regimens and courses vary depending on the immune state of the host and the identified pathogen
- treatment is directed towards the underlying condition predisposing the patient to lung abscess

### COMPLICATIONS

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- persistent cystic changes like pneumatoceles, bronchiectasis, extension to the pleural space with development of empyema, life-threatening hemoptysis, and massive aspiration of lung abscess contents

## LUNG CANCER

Refers to malignancies that originate in the airways or pulmonary parenchyma and it is the leading cause of cancer-related death.

### CLASSIFICATION

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Around 90% of all lung cancers are classified as either SCLC or NSCLC and others 5%. This distinction is essential for staging, treatment, and prognosis.

- **Small Cell Lung Cancer (SCLC)**
  - Strongly associated with smoking
  - Poorly differentiated neuroendocrine tumor
  - produce paraneoplastic syndromes like
    - SIADH
    - Cushing syndromes
    - Neurologic (Eaton-Lambert syndrome and retinal blindness)
  - Tends to occur as a central mass
- **Non-small Cell Lung Cancer (NSCLC) histology including**
  - Adenocarcinoma
    - Most common in women and adults <40 years of age
    - Also, most common in non-smokers
    - Often occur in more peripheral lung locations
  - Squamous Cell Carcinoma
    - Associated with smoking
    - tend to occur centrally
  - Large Cell Carcinoma
    - poorly differentiated carcinomas of the lung
    - tends to occur peripherally

**Others:** Undifferentiated Carcinomas, Carcinoids, Bronchial Gland Tumors (adenoid cystic carcinomas, mucoepidermoid tumors)

N.B They produce paraneoplastic syndromes like:

- Hypercalcemia
- Hypertrophic primary osteoarthropathy
- Leukocytosis

## HISTORY

- Cough, hemoptysis, chest pain, SOB, wheezing, stridor, weight loss, fever, weakness
- metastatic symptoms
  - Constitutional: weight loss >10lb
  - Musculoskeletal: pain
  - Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental

## PHYSICAL EXAMINATION

**RS:** clubbing

Clinical findings suggestive of metastatic disease

- Lymphadenopathy (>1 cm)
- Hoarseness, superior vena cava syndrome
- Bone tenderness
- Hepatomegaly (>13 cm)
- Focal neurologic signs, papilledema, soft tissue mass

## INVESTIGATION

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- Routine laboratory tests
    - CBC-Hematocrit
    - Elevated alkaline phosphatase, GGT, SGOT, and calcium levels
  - Imaging- non-calcified nodule
  - metastatic work up-if any compliant (metastatic symptoms)
  - sputum cytology, lung biopsy

## DIAGNOSIS

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Clinical Manifestation, imaging, lung biopsy- confirmatory

## MANAGEMENT

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- NSCLC:
  - Surgical-for stage I
  - Surgery followed by adjuvant chemotherapy for stage II- III
  - systemic therapy or palliative treatment for stage IV

- SCLC: already disseminated at presentation, only systemic chemotherapy

**RISK FACTORS:**

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- Smoking-primary cause
- second hand smoking
- radiation therapy
- environmental toxins
- age (40-80)
- dietary factors
- occupational exposure
- pulmonary fibrosis, genetic factor

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## CHAPTER THREE

# Diseases of cardiovascular system

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Introduction  
Heart Failure  
Ischemic heart disease  
Valvular heart disease  
Hypertensive heart disease  
Cardiomyopathies  
Pericardial disease

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### INTRODUCTION TO CARDIOVASCULAR DISEASE

#### THE MAGNITUDE OF THE PROBLEM

- Cardiovascular diseases are most prevalent in industrialized nations and are rapidly growing problem in developing nations.
- Despite improvement in the treatment and interventions, cardiovascular diseases remain the most common causes of death
  - Responsible for **35% of all deaths**, almost 1 million deaths each year
  - Approximately **one-fourth of these deaths are sudden**
- In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population due to atherosclerosis risk factors:
  - The growing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome which play prominent roles **in women than in men**
- The percentage of all deaths secondary to cardiovascular disease is higher among **women (43%) than among men (37%) because:**
  - The absolute number of deaths due to cardiovascular disease has declined over the past decades in men, but this number has actually risen in women.
  - The development of coronary atherosclerosis risk factors is more common in women.
- **CAD** is more frequently associated with dysfunction of the coronary microcirculation in women

#### FAMILY HISTORY

- It is important to illicit family history because; familial clustering is common in many forms of heart disease.

- Mendelian transmission of single-gene defects (monogenic) may occur, as in
  - Hypertrophic cardiomyopathy,
  - Marfan's syndrome, and
  - Sudden death associated with a prolonged QT syndrome.
- Genetic disorders that are caused by the combination of more than one gene (polygenic disorders) include
  - Premature coronary disease
  - Essential hypertension
  - type 2 diabetes mellitus, and
  - hyperlipidemia (the most important risk factors for CAD)
- Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders, as well.
- Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to
  - Familial dietary or behavior patterns, such as excessive ingestion of **salt or calories and cigarette smoking.**

### CARDIAC SYMPTOMS

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- The symptoms caused by heart disease result most commonly from
  - **Myocardial ischemia** - manifest most frequently as chest discomfort
  - **Disturbance of the contraction and/or relaxation of the myocardium** - commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle which results in abnormal fluid accumulation, with peripheral edema or pulmonary congestion and dyspnea
  - **Obstruction to blood flow**, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure
  - **Abnormal cardiac rhythm or rate**, often develop abruptly and may disappear as rapidly as they develop, the resulting symptoms and signs
    - palpitations, dyspnea, hypotension, and syncope
- Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions as well.
- Thus, **dyspnea** is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety.
- Similarly, **chest discomfort** may result from a variety of noncardiac and cardiac causes other than myocardial ischemia.
- **dyspnea and/or chest discomfort** that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern is rarely observed in such patients,

therefore, it is important to question the patient carefully about the relation of symptoms to exertion.

- **Edema**, may occur with primary renal disease and in hepatic cirrhosis.
- **Syncope** occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well.
- Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination, supplemented by noninvasive testing using electrocardiography at rest and during exercise, echocardiography, roentgenography, and other forms of myocardial imaging.
- Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as
  - a heart murmur,
  - elevated arterial pressure, or
  - an abnormality of the electrocardiogram (ECG) or imaging test.
- It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients.
- Since the first clinical manifestation of CAD may be catastrophic—*sudden cardiac death, acute myocardial infarction, or stroke in previous asymptomatic persons*—it is mandatory to identify those at high risk of such events and institute further testing and preventive measures.

## ASSESSMENT OF THE PATIENT WITH A HEART MURMUR

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- The cause of a heart murmur can often be readily elucidated from a systematic evaluation of its major attributes: timing, duration, intensity, quality, frequency, configuration, location, and radiation when considered in the light of the history, general physical examination, and other features of the cardiac examination.
- The majority of heart murmurs are midsystolic and soft (grades I–II/VI).
- When such a murmur occurs in an asymptomatic child or young adult without other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required.
- By contrast, two-dimensional and Doppler echocardiography are indicated in patients with loud systolic murmurs (grades ≥III/VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs.

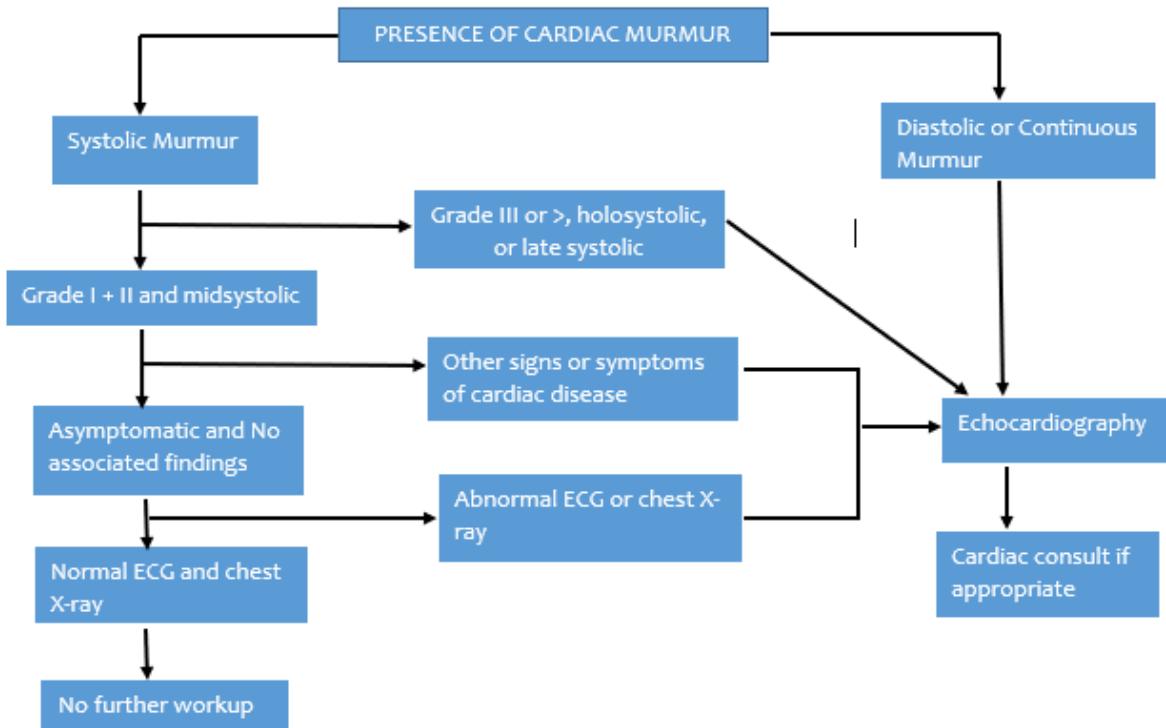


Figure: Approach to the evaluation of a heart murmur

## ASSESSMENT OF FUNCTIONAL IMPAIRMENT

- When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the level of activity and the rate at which it is performed before symptoms develop.
  - Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground.
  - In addition, the degree of customary physical activity at work and during recreation should be considered. The development of two flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person.
- The history should include a detailed consideration of the patient's therapeutic regimen. For example,
  - The persistence or development of edema, breathlessness, and other

manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure is far graver than are similar manifestations in the absence of treatment.

- Similarly, the presence of angina pectoris despite treatment with optimal doses of multiple antianginal drugs is more serious than it is in a patient on no therapy.
- 3. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier that he or she cannot carry out at present.

## NATURAL HISTORY

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- Cardiovascular disorders often present acutely, as in a previously asymptomatic person who develops an acute myocardial infarction, or a previously asymptomatic patient with hypertrophic cardiomyopathy or with a prolonged QT interval whose first clinical manifestation is syncope or even sudden death.
- However, the alert physician may recognize the patient at risk for these complications long before they occur and often can take measures to prevent their occurrence.
  - For example, a patient with acute myocardial infarction will often have had risk factors for atherosclerosis for many years
  - Had these risk factors been recognized, their elimination or reduction might have delayed or even prevented the infarction.
- Similarly, a patient with hypertrophic cardiomyopathy may have had a heart murmur for years and a family history of this disorder
  - These findings could have led to an echocardiographic examination, recognition of the condition, and appropriate therapy long before the occurrence of a serious acute manifestation.
- Patients with valvular heart disease or idiopathic dilated cardiomyopathy, by contrast, may have a prolonged course of gradually increasing dyspnea and other manifestations of chronic heart failure that is punctuated by episodes of acute deterioration only late in the course of the disease.
- Understanding the natural history of various cardiac disorders is essential for applying appropriate diagnostic and therapeutic measures to each stage of the condition, as well as for providing the patient and family with the likely prognosis

## INVESTIGATION OF CARDIOVASCULAR DISEASE

### ELECTROCARDIOGRAM (ECG)

- Although an ECG usually should be recorded in patients with known or suspected heart disease, with the exception of the identification of arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute myocardial infarction, it generally does not establish a specific diagnosis.
- The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations.
- In general, electrocardiographic changes should be interpreted in the context of other abnormal cardiovascular findings.

### CARDIAC BIOMARKERS

- Several biomarkers are available that can be measured in peripheral blood to assess myocardial dysfunction and ischaemia.
- **Brain natriuretic peptide**
  - BNP is a peptide hormone of 32 amino acids with diuretic properties.
  - It is secreted by the LV as a 108-amino acid prohormone, which is cleaved to produce active BNP, and an inactive 76-amino acid N-terminal fragment (NT-proBNP).
  - Circulating levels are elevated in conditions associated with LV systolic dysfunction.
  - Generally, NT-proBNP is measured in preference to BNP since it has a longer half-life.
  - Measurements of NT-proBNP are indicated for the diagnosis of LV dysfunction and to assess prognosis and response to therapy in patients with heart failure
- **Cardiac troponins**
  - Troponin I and troponin T are structural cardiac muscle proteins that are released during myocyte damage and necrosis, and represent the cornerstone of the diagnosis of acute myocardial infarction (MI).
  - However, modern assays are extremely sensitive and can detect very low levels of myocardial damage, so that elevated plasma troponin concentrations are seen in other acute conditions, such as pulmonary embolus, septic shock and acute pulmonary oedema.
  - The diagnosis of MI therefore relies on the patient's clinical presentation

### CHEST X-RAY

- This is useful for determining
  - The size and shape of the heart
    - An estimate of overall heart size can be made by comparing the maximum width of the cardiac outline with the maximum internal transverse diameter of the thoracic cavity.
    - ‘Cardiomegaly’ is the term used to describe an enlarged cardiac silhouette where the ‘cardiothoracic ratio’ is  $> 0.5$ .
      - It can be caused by chamber dilatation, especially left ventricular dilatation, or by a pericardial effusion.
      - It is not a sensitive indicator of left ventricular systolic dysfunction since the cardiothoracic ratio is normal in many affected patients.
  - The state of the pulmonary blood vessels, lung fields and pleura.
    - Pulmonary edema in patients with heart failure
    - An increase in pulmonary blood flow (‘pulmonary plethora’) in those with left-to-right shunt.
    - Pleural effusions may also occur in heart failure.
    - Lung infections which may be heart failure precipitant
  - Most information is given by a postero-anterior (PA) projection taken in full inspiration.
  - Anteroposterior (AP) projections are convenient when patient movement is restricted but result in magnification of the cardiac shadow.
  - Artefactual cardiomegaly may be due to a mediastinal mass or pectus excavatum, and cannot be reliably assessed from an AP film.
  - Lateral or oblique projections may be useful for detecting pericardial calcification in patients with constrictive pericarditis or a calcified thoracic aortic aneurysm, as these abnormalities may be obscured by the spine on the PA view.

### ECHOCARDIOGRAPHY (ECHO)

- Commonly indicated for
  - Assessment of cardiac function
  - Assessment of chambers size
  - Diagnosis and quantification of severity of valve disease
  - Identification of vegetations in endocarditis
  - Estimation of Left ventricular wall thickness and ejection fraction
  - Identification of structural heart disease in atrial fibrillation, cardiomyopathies or congenital heart disease
  - Detection of pericardial effusion

- Identification of structural heart disease or intracardiac thrombus in systemic embolism

### **COMPUTED TOMOGRAPHIC (CT) IMAGING**

- This is useful for imaging the cardiac chambers, great vessels, pericardium, and mediastinal structures and masses.
- Contrast scans are very useful for imaging the aorta in suspected aortic dissection, and the pulmonary arteries and branches in suspected pulmonary embolism.
- Multidetector scanning allows non-invasive imaging of the epicardial coronary arteries with a spatial resolution approaching that of conventional coronary arteriography.
- Coronary artery bypass grafts are also well seen, and in some centres, multidetector scanning is routinely used to assess graft patency.
- It is likely that CT will supplant invasive coronary angiography for the initial elective assessment of patients with suspected coronary artery disease.
- Some centres use cardiac CT scans for quantification of coronary artery calcification, which may serve as an index of cardiovascular risk.

### **MAGNETIC RESONANCE IMAGING (MRI)**

- MRI provides better differentiation of soft tissue structures than CT but is poor at demonstrating calcification.
- MRI scans can be ‘gated’ to the ECG, allowing the scanner to produce moving images of the heart and mediastinal structures throughout the cardiac cycle.
- MRI is very useful for imaging the aorta, including suspected dissection, and can define the anatomy of the heart and great vessels in patients with congenital heart disease.
- It is also useful for detecting infiltrative conditions affecting the heart.
- Physiological data can be obtained from the signal returned from moving blood that allows quantification of blood flow across regurgitant or stenotic valves.
- It is also possible to analyse regional wall motion in patients with suspected coronary disease or cardiomyopathy.
- The RV is difficult to assess using echocardiography because of its retrosternal position but is readily visualised with MRI.
- MRI can also be employed to assess myocardial perfusion and viability.
- When a contrast agent such as gadolinium is injected, areas of myocardial hypoperfusion can be identified with better spatial resolution than nuclear medicine techniques.
- Later redistribution of this contrast, so-called delayed enhancement, can be used to identify myocardial scarring and fibrosis.

- This can help in selecting patients for revascularisation procedures, or in identifying those with myocardial infiltration such as that seen with sarcoid heart disease and right ventricular dysplasia.

## DIAGNOSIS

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- As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the systematic consideration of the following:
  1. **The underlying etiology.**
    - Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
  2. **The anatomic abnormalities.**
    - Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?
  3. **The physiologic disturbances.**
    - Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
  4. **Functional disability.**
    - How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability.
- One example may serve to illustrate the importance of establishing a complete diagnosis.
- In a patient who presents with exertional chest discomfort,
  - The identification of myocardial ischemia as the etiology is of great clinical importance.
  - However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, for example, coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play contributory roles.
  - Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.
- The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination.

- Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests:
  - 1) ECG,
  - 2) Noninvasive imaging examinations (chest X-ray, echocardiogram, radionuclide imaging, computed tomographic imaging, positron emission tomography, and magnetic resonance imaging),
  - 3) Blood tests to assess risk (e.g., lipid determinations, C-reactive protein) or cardiac function (e.g., brain natriuretic peptide [BNP]),
  - 4) occasionally specialized invasive examinations (i.e., cardiac catheterization and coronary arteriography), and
  - 5) genetic tests to identify monogenic cardiac diseases (e.g., hypertrophic cardiomyopathy, Marfan's syndrome, and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death).
- These tests are becoming more widely available

## PITFALLS IN CARDIOVASCULAR MEDICINE

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- Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences.
- **Examples include the following:**
  1. Failure by the noncardiologist to recognize important cardiac manifestations of systemic illnesses.
    - For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke.
    - A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.
  2. Failure by the cardiologist to recognize underlying systemic disorders in patients with heart disease.
    - For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure.
    - A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.

3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system.
  - Cardiac catheterization and coronary arteriography provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD.
  - Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to supplement, not supplant, a careful examination carried out with clinical and noninvasive techniques.
  - A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's complaint of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.
  - Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities.
  - Therefore, they should be carried out only if the results can be expected to modify the patient's management.

## DISEASE PREVENTION AND MANAGEMENT

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- The prevention of heart disease, especially of CAD, is one of the most important tasks of primary health care givers as well as cardiologists.
- Prevention begins with
  - 1) **Risk assessment** followed by
  - 2) **Attention to lifestyle**, such as achieving optimal weight, physical activity, and smoking cessation, and then
  - 3) **Aggressive treatment** of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus.
- After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available.
- Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:
  - 1) In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and not be asked to return at intervals for repeated examinations.
    - If there is no evidence of disease, such continued attention may lead to the

patient's developing inappropriate concern about the possibility of heart disease.

- 2) If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease, a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.
- 3) Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6 to 12 months, by clinical and noninvasive examinations.
  - Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment.
- 4) In patients with CAD, available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization).
  - The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization.
  - Instead, these interventions should be limited to patients with CAD whose angina has not responded adequately to medical treatment or in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

## HEART FAILURE

### DEFINITION

- **Heart failure** is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. Elevated jugular venous pressure, pulmonary crackles, and peripheral edema).
- It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.
- Identification of the etiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF as the specific pathology can determine subsequent treatment.
- Most commonly, HF is due to myocardial dysfunction: either systolic, diastolic, or both.
- However, pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause or contribute to HF.

### EPIDEMIOLOGY AND NATURAL HISTORY

- **Incidence and prevalence**
  - In developed countries, the age-adjusted incidence of HF may be falling, presumably reflecting better management of CV disease, but due to ageing, the overall incidence is increasing.
  - Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults.
  - The prevalence of HF appears to be 1-2% of adults. As studies only usually include recognized/diagnosed HF cases, the true prevalence is likely to be higher.
  - The prevalence increases with age: from around 1% for those aged <55 years to >10% in those aged 70 years or over.
  - It is generally believed that, of those with HF, about 50% have HFrEF and 50% have HFpEF/HFmrEF, mainly based on studies in hospitalized patients.

### ETIOLOGY

- The most common causes (as well as some key investigations) of HF are shown in Table below
- The etiology of HF varies according to geography. In Western-type and developed countries, coronary artery disease (60–75% of cases of HF) and hypertension are predominant factors.
- Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD.

- Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.
  - With regard to ischaemic etiology, HFmrEF resembles HFrEF, with a higher frequency of underlying CAD compared to those with HFpEF.

## NATURAL HISTORY AND PROGNOSIS

**Table: Selected Causes of Heart Failure**

<b>Heart Failure with Reduced Ejection Fraction</b>	
Coronary artery disease	Nonischemic cardiomyopathy
Myocardial infarction	Infiltrative disorders
Myocardial ischemia	Familial disorders
	Tachycardia induced
Valvular heart disease	Toxic cardiomyopathy
Aortic stenosis or regurgitation	Chemotherapy, immunotherapy
Mitral or tricuspid regurgitation	Drugs such as hydroxychloroquine
	Alcohol, cocaine
Congenital heart disease	Chronic lung/pulmonary vascular disease
Intracardiac shunts	Cor pulmonale
Repaired defects	Pulmonary arterial hypertension
Systemic right ventricular failure	
Infectious	Autoimmune disease
Chagas	Giant cell myocarditis
HIV	Lupus myocarditis
<b>Heart Failure with Preserved Ejection Fraction</b>	
Hypertension	Coronary artery disease
Valvular heart disease	Restrictive cardiomyopathy
Aortic stenosis	Amyloidosis
Mitral stenosis	Sarcoidosis
	Hemochromatosis
	Glycogen storage disease
Hypertrophic cardiomyopathy	Radiation therapy
Constrictive pericarditis	Aging
Myocarditis	Endomyocardial fibroelastosis
Obesity	
<b>High-Output Heart Failure</b>	
Thyroid toxicosis	Arteriovenous shunt
Obesity	Cirrhosis
Anemia	Vitamin B deficiency (beriberi)
Chronic lung disease	Myeloproliferative disorder

- The prognosis of patients with HF has improved considerably since the publication of the first treatment trials a few decades ago. However, it remains poor, and quality of life (QOL) is also markedly reduced.
- The improvement in prognosis has been confined to those with HFrEF.
- Mortality rates are higher in observational studies than in clinical trials.

- In the Olmsted County cohort, 1-year and 5-year mortality rates after diagnosis, for all types of HF patients, were 20% and 53%, respectively, between 2000 and 2010.
- A study combining the Framingham Heart Study (FHS) and Cardiovascular Health Study (CHS) cohorts reported a 67% mortality rate within 5 years following diagnosis.
- Despite receiving less evidence-based treatment, women have a better survival than men.
- Overall prognosis is better in HFmrEF compared to HFrEF. Of note, transition in ejection fraction over time is common, and patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or transition to a higher ejection fraction category.
- HFpEF is generally considered to confer a better survival than HFrEF, but most observational studies show that this difference is negligible. In contrast, the large MAGGIC meta-analysis concluded that the adjusted mortality risk for patients with HFpEF was considerably lower than in patients with HFrEF.
- The risk of HF hospitalization is 1.5 times higher in patients with diabetes compared to controls. AF, a higher body mass index (BMI), and higher glycated haemoglobin (HbA1c), as well as a low estimated glomerular filtration rate (eGFR) are strong predictors of HF hospitalizations.
- Due to population growth, ageing, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future, perhaps by as much as 50% in the next 25 years.

## APPROACH TO PATIENT WITH HEART FAILURE

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### HISTORY

- Dyspnea with exertion (early) or at rest (late)
- Orthopnea
  - Dyspnea when recumbent; relief with sitting upright or use of several pillows
- Nocturnal cough
- Paroxysmal nocturnal dyspnea (PND)
  - In patients with severe heart failure, fluid shifts from the interstitial tissues of the peripheries into the circulation within 1–2 hours of lying down.
  - Pulmonary oedema supervenes, causing the patient to wake and sit upright, profoundly breathless.
  - Coughing and wheezing often persist even with sitting upright.
  - Cardiac asthma: nocturnal dyspnea, wheezing and cough due to bronchospasm
- **CHEYNE-STOKES RESPIRATION** a.k.a periodic respiration or cyclic respiration

- present in 40% of patients with advanced HF and usually is associated with low cardiac output.
- Occurs in severe left ventricular failure.
- caused by an increased sensitivity of the respiratory center to arterial  $\text{PCO}_2$  and a lengthy circulatory time.
- There is an apneic phase (when  $\text{PO}_2$  falls and  $\text{PCO}_2$  rises) which stimulate the respiratory center, resulting in hyperventilation and hypocapnia, followed by recurrence of apnea.
- The condition can also occur in diffuse cerebral atherosclerosis, stroke or head injury, and may be exaggerated by sleep, barbiturates and opiates.
- Fatigue and weakness
- Abdominal symptoms - may be related to edema of the bowel wall and/or a congested liver
  - Anorexia
  - Nausea
  - Early satiety associating with abdominal pain and fullness
- Cerebral symptoms
  - Altered mental status due to reduced cerebral perfusion
    - Confusion
    - Disorientation
    - Difficulty concentrating
    - Impaired memory
    - Headache
    - Insomnia
    - Anxiety
- Nocturia

## RISK FACTORS

Table: Risk factors for the development of heart failure and potential corrective actions	
Risk factors for heart failure	Preventive strategies
Sedentary habit	Regular physical activity
Cigarette smoking	Cigarette smoking cessation
Obesity	Physical activity and healthy diet
Excessive alcohol intake	General population: no/light alcohol intake is beneficial Patients with alcohol-induced CMP should abstain from alcohol
Influenza	Influenza vaccination
Microbes (e.g. Trypanosoma cruzi, Streptococci)	Early diagnosis, specific antimicrobial therapy for either prevention and/or treatment
Cardiotoxic drugs (e.g., anthracyclines)	Cardiac function and side effect monitoring, dose adaptation, change of chemotherapy
Chest radiation	Cardiac function and side effect monitoring, dose adaptation
Hypertension	Lifestyle changes, antihypertensive therapy
Dyslipidaemia	Healthy diet, statins
Diabetes mellitus	Physical activity and healthy diet, SGLT2 inhibitors
CAD	Lifestyle changes, statin therapy

CAD= coronary artery disease; CMP = cardiomyopathy; SGLT2 = sodium-glucose co-transporter 2.

## PHYSICAL FINDINGS

### General appearance

- The patient appears to be in no distress at rest except for feeling uncomfortable when lying flat for more than a few minutes – mild or moderate severe
- The patient sit upright, may have labored breathing, and may not be able to finish a sentence because of shortness of breath – more severe

### Vital signs

- Blood pressure
  - Systolic blood pressure may be normal or high in early HF, but it generally is reduced in advanced HF because of severe LV dysfunction.
  - The pulse pressure may be diminished, reflecting a reduction in stroke volume.
- Pulse rate
- Sinus tachycardia is a nonspecific sign caused by increased adrenergic activity.
- Respiratory rate - tachypnea

### Respiratory system

- Pulmonary crackles (rales or crepitations) result from the transudation of fluid from the intravascular space into the alveoli.
- In patients with pulmonary edema, rales may be heard widely over both lung fields and may be accompanied by expiratory wheezing (cardiac asthma).
- Pleural effusions – absent air entry and dullness
  - often bilateral in HF, when they are unilateral, they occur more frequently in the right pleural space.

### **Cardiovascular system**

- Venous examination
  - Raised Jugular venous pressure (when >3cm from angle of Louis or >8cm from right atrium)
  - Jugular venous distention
- Precordium
  - Cardiomegaly
    - PMI - usually is displaced below the fifth intercostal space and/or lateral to the midclavicular line.
    - The impulse is palpable over two interspaces
  - S3 gallop is audible and palpable at the apex
    - in patients with volume overload who have tachycardia and tachypnea, and it often signifies severe hemodynamic compromise.
  - S4 is not a specific indicator of HF but is usually present in patients with diastolic dysfunction.
  - The murmurs of mitral and tricuspid regurgitation are frequently present in patients with advanced HF.

### **Abdominal examination and Extremities**

- Hepatomegaly - tender and may pulsate during systole if tricuspid regurgitation is present.
- Ascites, a late sign, occurs as a consequence of increased pressure in the hepatic veins and the veins draining the peritoneum.
- Jaundice, also a late finding in HF, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin.
- Peripheral edema
  - usually symmetric and dependent
  - occurs predominantly in the ankles and the pretibial region in ambulatory patients.

- May be found in the sacral area and the scrotum in bedridden patients.
- Long-standing edema may be associated with indurated and pigmented skin.

### CARDIAC CACHEXIA

- There may be marked weight loss and cachexia – in severe chronic HF
- Although the mechanism is not entirely understood, it is probably multifactorial.
- Augurs a poor overall prognosis.

### PRECIPITATING FACTORS

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Are relatively acute disturbances that place an additional load on a myocardium that is chronically and excessively burned. Patient become symptomatic in the presence of these factors, including: Mnemonic (**HEART FAILES**)

**H:** Systemic Hypertension

**E:** Infective Endocarditis

**A:** Anemia

**R:** Rheumatic fever and myocarditis

**T:** Thyrotoxicosis and pregnancy

**F:** Fever (Infections)

**A:** Arrhythmia

**I:** Myocardial Infarction

**L:** Lung infection (pneumonia)

**E:** Pulmonary Embolism

**S:** Stress (Emotional, physical, environmental, dietary, fluid excess)

### INVESTIGATION

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#### ROUTINE LABORATORY TESTING

##### CBC

- Infection - precipitating factor
- Anemia - precipitating factor

##### Urinalysis

- Albuminuria
- High specific gravity
- Low sodium level

##### Renal function

- Prerenal azotemia

### Electrolytes

- Hypokalemia from thiazide diuretics
- Hyperkalemia from potassium-retaining diuretics
- Dilutional hyponatremia in late HF

### Liver function testing

- Hepatic enzymes; frequently elevated
- Elevated direct and indirect bilirubin level (late finding)

### In selected patients

- Random blood sugar or fasting serum glucose (DM)
- Fasting lipid panel (dyslipidemia)
- Thyroid-stimulating hormone level (thyroid abnormalities)

## DIAGNOSTIC

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### ELECTROCARDIOGRAM (ECG)

- Assess cardiac rhythm and rate
- Determine the presence of LV hypertrophy or a prior MI (presence or absence of Q-waves)
- RV hypertrophy
- PR prolongation
- Peaked(hyper)or flattened/ inverted(hypokalemia) T-wave
- Determine QRS width to ascertain whether the patient may benefit from resynchronization therapy
- A normal ECG virtually excludes LV systolic dysfunction.

### CHEST RADIOGRAPHY

- To detect cardiomegaly and pulmonary congestion
- To detect lung infection which can be precipitant

### 2-DIMENSIONAL ECHOCARDIOGRAPHY WITH DOPPLER FLOW

- Assess LV size and function
- Determine the presence or absence of valvular and/or regional wall motion abnormalities (indicative of a prior MI).
- Determine the presence of left atrial dilation and LV hypertrophy
- Assess valvular lesion
- Assess Ejection fraction
- invaluable in assessing RV size and pulmonary pressure

### MAGNETIC RESONANCE IMAGING (MRI)

- now the gold standard for assessing LV mass and volumes.
- analysis of cardiac anatomy and function
- assessing LV structure and determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, hemochromatosis).

#### BNP MEASUREMENT

- **>200 pg/mL supports diagnosis**
- <40 pg/mL rarely seen in HF
- Useful in diagnosis, prognosis, and monitoring therapy
- Helps in differentiating between cardiac and pulmonary causes of dyspnea

#### MANAGEMENT PRINCIPLE

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- Supportive care
  - Head of bed elevation
  - Salt restriction
- Oxygen therapy for patient with **SpO<sub>2</sub><90**
- Identify and treat the precipitating factors
- Control the congestive state
- Improve myocardial performance & Prevention of deterioration of myocardial function (slowing progression of heart failure)
- Treat the underlying cause

#### TERMINOLOGY

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- **Heart failure with preserved, mildly reduced, and reduced ejection fraction**
  - Traditionally, HF has been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction (LVEF).
  - The rationale behind this relates to the original treatment trials in HF that demonstrated substantially improved outcomes in patients with LVEF  $\leq 40\%$ . We have decided on the following classification of HF:
    - Reduced LVEF is defined as  $\leq 40\%$ , i.e. those with a significant reduction in LV systolic function. This is designated as HFrEF.
    - Patients with a LVEF between 41% and 49% have mildly reduced LV systolic function, i.e. HFmrEF. Retrospective analyses from randomized clinical trials in HFrEF or HFpEF that have included patients with ejection fractions in the 40-50% range suggest that they may benefit from similar therapies to those with LVEF  $\leq 40\%$ . This supports the renaming of HFmrEF from ‘heart failure with mid-range ejection fraction’ to ‘heart failure with mildly reduced ejection fraction’.
    - Those with symptoms and signs of HF, with evidence of structural and/or

functional cardiac abnormalities and/or raised natriuretic peptides (NPs), and with an LVEF  $\geq 50\%$ , have HFpEF.

- Patients with non-CV disease, e.g. anemia, pulmonary, renal, thyroid, or hepatic disease may have symptoms and signs very similar to those of HF, but in the absence of cardiac dysfunction, they do not fulfil the criteria for HF. However, these pathologies can coexist with HF and exacerbate the HF syndrome.

**Table: Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1 Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	2 LVEF $\leq 40\%$	LVEF 41-49% <sup>b</sup>	LVEF $\geq 50\%$
	3 --	--	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides <sup>c</sup>

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

<sup>a</sup>Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

<sup>b</sup>For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

<sup>c</sup>For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

- **Right ventricular dysfunction**

- Heart failure can also be a result of right ventricular (RV) dysfunction.
  - RV mechanics and function are altered in the setting of either pressure or volume overload.
  - Although the main etiology of chronic RV failure is LV dysfunction-induced pulmonary hypertension, there are a number of other causes of RV dysfunction [e.g. MI, arrhythmogenic right ventricular cardiomyopathy (ARVC), or valve disease].
  - The diagnosis is determined by a quantitative assessment of global RV function,

most commonly by echocardiography, using at least one of the following measurements:

- fractional area change (FAC);
- tricuspid annular plane systolic excursion (TAPSE); and
- Doppler tissue imaging-derived systolic S' velocity of the tricuspid annulus.

- **Other common terminology used in heart failure**

- Heart failure is usually divided into two presentations: chronic heart failure (CHF) and acute heart failure (AHF).
- CHF describes those who have had an established diagnosis of HF or who have a more gradual onset of symptoms.
- If CHF deteriorates, either suddenly or slowly, the episode may be described as 'decompensated' HF. This can result in a hospital admission or treatment with intravenous (i.v.) diuretic therapy in the outpatient setting. In addition, HF can present more acutely.
- Some individuals with HF may recover completely [e.g. those due to alcohol-induced cardiomyopathy (CMP), viral myocarditis, Takotsubo syndrome, peripartum cardiomyopathy (PPCM), or tachycardiomyopathy].
- Other patients with LV systolic dysfunction may show a substantial or even complete recovery of LV systolic function after receiving drug and device therapy.

- **Terminology related to the symptomatic severity and stages of heart failure**

- The simplest terminology used to describe the severity of HF is the New York Heart Association (NYHA) functional classification. However, this relies solely on symptoms and there are many other better prognostic indicators in HF.
- Importantly, patients with mild symptoms may still have a high risk of hospitalization and death.
- Predicting outcome is particularly important in advanced HF to guide selection of cardiac transplantation and device therapies.

**Table: New York Heart Association functional classification based on severity of symptoms and physical activity**

<b>Class I</b>	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
<b>Class II</b>	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
<b>Class III</b>	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue, or palpitations
<b>Class IV</b>	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

- The ACC/AHA stages of HF emphasize the development and progression of disease, and advanced stages and progression are associated with reduced survival.
- Therapeutic interventions in each stage aim to modify risk factors (stage A), treat risk and structural heart disease to prevent HF (stage B), and reduce symptoms, morbidity, and mortality (stages C and D).

**Table: America heart association (AHA) staging system**

<b>Stage A: At Risk for HF</b>	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (e.g., patients with hypertension, atherosclerotic CVD, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy).
<b>Stage B: Pre-HF</b>	<p>No symptoms or signs of HF and evidence of 1 of the following:</p> <ul style="list-style-type: none"> <li>Structural heart disease* <ul style="list-style-type: none"> <li>Reduced left or right ventricular systolic function</li> <li>Reduced ejection fraction, reduced strain</li> <li>Ventricular hypertrophy</li> <li>Chamber enlargement</li> <li>Wall motion abnormalities</li> <li>Valvular heart disease</li> </ul> </li> <li>Evidence for increased filling pressures* <ul style="list-style-type: none"> <li>By invasive hemodynamic measurements</li> <li>By noninvasive imaging suggesting elevated filling pressures (e.g., Doppler echocardiography)</li> </ul> </li> <li>Patients with risk factors and <ul style="list-style-type: none"> <li>Increased levels of BNP*</li> <li>Persistently elevated cardiac troponin in the absence of competing diagnoses resulting in such biomarker elevations such as acute coronary syndrome, CKD, pulmonary embolus, or myopericarditis</li> </ul> </li> </ul>
<b>Stage C:</b>	Structural heart disease with current or previous symptoms of HF.

Symptomatic HF	
Stage D: Advanced HF	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT.

\*For thresholds of cardiac structural, functional changes, elevated filling pressures, and biomarker elevations. BNP indicates B-type natriuretic peptide; CKD, chronic kidney disease; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.

## HEART FAILURE CLASSIFICATION

- Based on patient presentation, we can classify heart failure as
  - I. Acute heart failure
  - II. Chronic heart failure
  - III. Advanced heart failure

### ACUTE HEART FAILURE (AHF)

#### DEFINITION

- AHF can be defined as the new onset or recurrence of symptoms and signs of HF requiring urgent or emergent therapy and resulting in unscheduled care or hospitalization.
- An important source of confusion with this proposed definition is the word “acute”—although this suggests a sudden onset of symptoms, many patients may have a more sub-acute course, with gradual worsening of symptoms that ultimately reaches a level of severity sufficient to seek unscheduled medical care.

#### EPIDEMIOLOGY AND PROGNOSIS

- AHF refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit.
- Patients with AHF require urgent evaluation with subsequent initiation or intensification of treatment, including i.v. therapies or procedures.
- AHF is a leading cause of hospitalizations in subjects aged >65 years and is associated with high mortality and rehospitalization rates.
- In-hospital mortality ranges from 4% to 10%. Post-discharge 1-year mortality can be 25-30% with up to more than 45% deaths or readmission rates.
- AHF may be the first manifestation of HF (new onset) or, more frequently, be due to an acute decompensation of chronic HF.
- Compared to patients with acutely decompensated CHF, those with new onset HF may

have a higher in-hospital mortality but have lower post-discharge mortality and rehospitalization rates. Specific extrinsic factors may precipitate, but not cause, AHF in patients with pre-existing cardiac dysfunction.

- Clinical severity and in-hospital trajectory are determined by the complex interplay between precipitants, the underlying cardiac substrate, and the patient's comorbidities.

## **CLINICAL PRESENTATIONS**

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- Four major clinical presentations can be described with possible overlaps between them.
- Clinical presentations are mainly based on the presence of signs of congestion and/or peripheral hypoperfusion and require different treatments.

### **ACUTELY DECOMPENSATED HEART FAILURE**

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- Acutely decompensated heart failure (ADHF) is the most common form of AHF, accounting for 50-70% of presentations usually occurs in patients with history of HF and previous cardiac dysfunction across the spectrum of LVEF and may include RV dysfunction.
- Distinct from the acute pulmonary edema phenotype, it has a more gradual onset, and the main alteration is progressive fluid retention responsible for systemic congestion. Sometimes, congestion is associated with hypoperfusion.
- The objectives of treatment are identification of precipitants, decongestion, and in rare instances, correction of hypoperfusion.
- Factors commonly precipitating HF hospitalization with Acute Decompensated HF are
  - acute coronary syndrome (ACS)
  - Uncontrolled hypertension
  - Atrial fibrillation and other arrhythmias
  - Additional cardiac disease (e.g., endocarditis)
  - Acute infections (e.g., pneumonia, urinary tract)
  - Nonadherence with medication regimen or dietary intake
  - Anemia
  - Hyper- or hypothyroidism
  - Medications that increase sodium retention (e.g., NSAID)
  - Medications with negative inotropic effect (e.g., verapamil)

**Table: Common Presenting Symptoms and Signs of Decompensated Heart Failure**

SYMPTOMS	SIGNS
<b>Predominantly related to volume overload</b>	
Dyspnea (exertional, paroxysmal nocturnal dyspnea, orthopnea, or at rest); cough; wheezing	Rales, pleural effusion
Foot and leg discomfort	Peripheral edema (legs, sacral)
Abdominal discomfort/bloating; early satiety or anorexia	Ascites/increased abdominal girth; right upper quadrant pain or discomfort; hepatomegaly/splenomegaly; scleral icterus
	Increased weight
	Elevated jugular venous pressure, abdominojugular reflux
	Increasing S <sub>3</sub> , accentuated P <sub>2</sub>
<b>Predominantly related to Hypoperfusion</b>	
Fatigue	Cool extremities
Altered mental status, daytime drowsiness, confusion, or difficulty concentrating	Pallor, dusky skin discoloration, Hypotension
Dizziness, pre- syncope, or syncope	Pulse pressure (narrow)/proportional pulse pressure (low)
	Pulsus alternans
<b>Other signs and symptoms of AHF</b>	
Depression	Orthostatic hypotension (hypovolemia)
Sleep disturbances	S <sub>4</sub>
Palpitations	Systolic and diastolic cardiac murmurs

### ACUTE PULMONARY OEDEMA

- Acute pulmonary oedema is related to lung congestion.
- Clinical criteria for acute pulmonary oedema diagnosis include dyspnoea with orthopnoea, respiratory failure (hypoxaemia-hypercapnia), tachypnoea >25 breaths/min, and increased work of breathing.
- Three therapies should be commenced, if indicated.
  - **First**, oxygen, given as continuous positive airway pressure, non-invasive positive pressure-ventilation and/or high-flow nasal cannula, should be started.
  - **Second**, i.v. diuretics should be administered, and
  - **Third**, i.v. vasodilators may be given if systolic BP (SBP) is high, to reduce LV afterload.

- In a few cases of advanced HF, acute pulmonary oedema may be associated with low cardiac output and, in this case, inotropes, vasopressors, and/or MCS are indicated to restore organ perfusion.

### ISOLATED RIGHT VENTRICULAR FAILURE

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- RV failure is associated with increased RV and atrial pressure and systemic congestion.
- RV failure may also impair LV filling, and ultimately reduce systemic cardiac output, through ventricular interdependence.
- Diuretics are often the first option of therapy for venous congestion.
- Noradrenaline and/or inotropes are indicated for low cardiac output and hemodynamic instability.
- Inotropes reducing cardiac filling pressures may be preferred (i.e. levosimendan, phosphodiesterase type III inhibitors).
- Since inotropic agents may aggravate arterial hypotension, they may be combined with norepinephrine if needed.

### CARDIOGENIC SHOCK

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- Cardiogenic shock is a syndrome due to primary cardiac dysfunction resulting in an inadequate cardiac output, comprising a life-threatening state of tissue hypoperfusion, which can result in multiorgan failure and death.
- Cardiac insult causing severe impairment of cardiac performance may be acute, as a result of the acute loss of myocardial tissue (acute MI, myocarditis) or may be progressive as seen in patients with chronic decompensated HF who may experience a decline in disease stability as a result of the natural progression of advanced HF and/or specific precipitants.
- Diagnosis of cardiogenic shock mandates the presence of clinical signs of hypoperfusion, such as cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure.
- In addition, biochemical manifestations of hypoperfusion, elevated serum creatinine, metabolic acidosis and elevated serum lactate are present and reflect tissue hypoxia and alterations of cellular metabolism leading to organ dysfunction.
- Of note, hypoperfusion is not always accompanied by hypotension, as BP may be preserved by compensatory vasoconstriction (with/without pressor agents), albeit at the cost of impaired tissue perfusion and oxygenation
- Management of cardiogenic shock should start as early as possible.
- Early identification and treatment of the underlying cause, concomitant with hemodynamic stabilization and management of organ dysfunction, are key components of its management

**Table: Clinical presentations of acute heart failure**

	Acutely decompensated heart failure	Acute pulmonary edema	Isolated right ventricular failure	Cardiogenic shock
<b>Main mechanisms</b>	LV dysfunction Sodium and water renal retention	Increased afterload and/or predominant LV diastolic dysfunction Valvular heart disease	RV dysfunction and/or precapillary pulmonary hypertension	Severe cardiac dysfunction
<b>Main cause of symptoms</b>	Fluid accumulation, increased intraventricular pressure	Fluid redistribution to the lungs and acute respiratory failure	Increased central venous pressure and often systemic hypoperfusion	Systemic hypoperfusion
<b>Onset</b>	Gradual (days)	Rapid (hours)	Gradual or rapid	Gradual or rapid
<b>Main haemodynamic abnormalities</b>	Increased LVEDP and PCWP <sup>a</sup> Low or normal cardiac output Normal to low SBP	Increased LVEDP and PCWP <sup>a</sup> Normal cardiac output Normal to high SBP	Increased RVEDP Low cardiac output Low SBP	Increased LVEDP and PCWP <sup>a</sup> Low cardiac output Low SBP
<b>Main clinical presentations</b>	Wet and warm OR Wet and cold	Wet and warm <sup>b</sup>	Wet and cold	Wet and cold
<b>Main treatment</b>	Diuretics Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Diuretics Vasodilators <sup>b</sup>	Diuretics for peripheral congestion Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Inotropic agents/vasopressors Short-term MCS RRT

LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; RV = right ventricular;

RVEDP = right ventricular end-diastolic pressure; RRT = renal replacement therapy; SBP = systolic blood pressure.

<sup>a</sup>May be normal with low cardiac output.

<sup>b</sup>Wet and cold profile with need of inotropes and/or vasopressors may rarely occur.

## DIAGNOSIS

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- The diagnostic workup of AHF starts at the time of the first medical contact, and is continued throughout the initial patient pathway, aiming to identify the clinical presentation and to diagnose and manage any potentially reversible causes/precipitants/coexisting life-threatening conditions in a timely manner.
- In addition to clinical signs and symptoms, diagnostic workup includes **ECG** and **echocardiography**, if possible.
- Additional investigations, i.e. chest X-ray and lung ultrasound may be used to confirm AHF diagnosis, especially when NP testing is not available.
- **Plasma NP levels** (BNP or NT-proBNP or MRproANP) should be measured if the diagnosis is uncertain and a point-of-care assay is available.
  - Normal concentrations of NPs make the diagnosis of AHF unlikely.
  - Cut-offs for acute HF are: BNP <100pg/mL, NT-proBNP <300 pg/mL and MR-proANP <120 pg/mL.
  - Low concentrations can be detected in some patients with advanced decompensated end-stage HF, obesity, flash pulmonary oedema or right sided AHF.
  - Higher levels can be found in the patients with concomitant AF and/or reduced renal function.
- Among other laboratory tests, troponin is useful for the detection of acute coronary syndrome (ACS) although elevated levels are detected in the vast majority of patients with AHF.
- **Blood urea nitrogen or urea, serum creatinine, electrolytes** (sodium, potassium, chloride), and **antigen carbohydrate** may help tailor treatment.
- Detection of abnormal **liver function** identifies patients with a poor prognosis.
- Since both hypothyroidism and hyperthyroidism may precipitate AHF, **thyroid-stimulating hormone (TSH)** should be assessed in those with newly diagnosed AHF.
- **Arterial blood gas analysis** should be performed when a precise measurement of O<sub>2</sub> and CO<sub>2</sub> partial pressure is needed (i.e. patients with respiratory distress).
- **Lactate and pH levels** should be measured in patients with cardiogenic shock.
- **D-dimer** should be measured when acute pulmonary embolism is suspected.
- **Procalcitonin** may be used for the diagnosis of pneumonia and antibiotic therapy may have an indication when plasma levels are >0.2 lg/L. However, no impact of a strategy based on routine procalcitonin measurements on outcomes was shown in a prospective, controlled, trial.
- **Pulse oximetry** should be measured routinely at the time of first presentation of patients with AHF and continuous monitoring may be needed in the first hours or days.

## MANAGEMENT

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- **General aspects**
  - Management can be subdivided in three stages (pre-hospital, in-hospital, and pre-discharge), having different goals and requiring different approaches.
- **Pre-hospital phase**
  - In the pre-hospital setting, AHF patients should benefit from noninvasive monitoring, including pulse oximetry, BP, heart rate respiratory rate, and a continuous ECG, instituted within minutes of patient contact and in the ambulance if possible.
  - Oxygen therapy may be given based on clinical judgment unless oxygen saturation is <90% in which case it should be administered.
  - In patients with respiratory distress, respiratory rate >25 breaths/min, oxygen saturation <90%, non-invasive ventilation should be initiated.
  - Prehospital management should not delay the rapid transfer of AHF patients to the most appropriate medical setting.
- **In-hospital management**
  - Diagnostic workup and appropriate pharmacological and nonpharmacological treatment must be started promptly and in parallel.
  - AHF patients are triaged to the appropriate level of care according to the degree of haemodynamic instability and severity of the critical illness.
  - Disposition decisions are important components of the initial phase of management.
  - The type and intensity of in-hospital monitoring depends on clinical severity, settings of care and in-hospital course.
  - As AHF is a heterogeneous condition, management may differ according to the main clinical presentation.
  - Management starts with the search for specific causes of AHF. These include
    - Acute coronary syndrome,
    - Hypertensive emergency,
    - rapid arrhythmias or severe bradycardia/conduction disturbance,
    - acute mechanical causes such as acute valve regurgitation or acute pulmonary embolism,
    - Infection, including myocarditis, and
    - Tamponade.
  - After exclusion of these conditions, which need to be treated/corrected urgently, management of AHF differs according to the clinical presentations

- **Pre-discharge phase**
  - Details on this phase are shown in Pre-discharge assessment and post-discharge section below.
- **Oxygen therapy and/or ventilatory support**
  - In AHF, oxygen should not be used routinely in non-hypoxemic patients, as it causes vasoconstriction and a reduction in cardiac output.
  - Oxygen therapy is recommended in patients with AHF and SpO<sub>2</sub> <90% or PaO<sub>2</sub> <60 mmHg to correct hypoxemia.
  - In chronic obstructive pulmonary disease (COPD), hyper-oxygenation may increase ventilation perfusion mismatch, suppress ventilation and lead to hypercapnia. During oxygen therapy, acid-base balance and SpO<sub>2</sub> should be monitored.
  - Non-invasive positive pressure ventilation, either continuous positive airway pressure and pressure support, improves respiratory failure, increases oxygenation and pH, and decreases the partial pressure of carbon dioxide (pCO<sub>2</sub>) and work of breathing.
  - Noninvasive positive pressure ventilation should be started as soon as possible in patients with respiratory distress (respiratory rate >25 breaths/min, SpO<sub>2</sub> <90%) to improve gas exchange and reduce the rate of endotracheal intubation.
  - The fraction of inspired oxygen (FiO<sub>2</sub>) should be increased up to 100%, if necessary, according to oxygen saturation level.
  - Blood pressure should be monitored regularly during non-invasive positive pressure ventilation.
  - The increase in intrathoracic pressure with non-invasive positive pressure ventilation decreases venous return and right and left ventricular preload. It may also decrease cardiac output and BP and should therefore be used with caution in patients with reduced preload reserve and hypotension.
  - The increase in pulmonary vascular resistance and RV afterload may also be detrimental in RV dysfunction.
  - Intubation is recommended for progressive respiratory failure in spite of oxygen administration or non-invasive ventilation.
- **Diuretics**
  - Intravenous diuretics are the cornerstone of AHF treatment.
  - They increase renal excretion of salt and water and are indicated for the treatment of fluid overload and congestion in the vast majority of AHF patients.
  - **Loop diuretics** are commonly used due to their rapid onset of action and efficacy.
  - It may be appropriate when starting i.v. diuretic treatment, to use low doses, to

assess the diuretic response and increase the dose when that is insufficient.

- Diuretic treatment should be started with an initial i.v. dose of furosemide, or equivalent dose of bumetanide or torasemide, corresponding to 1-2 times the daily oral dose taken by the patient before admission.
- If the patient was not on oral diuretics, a starting dose of 20-40 mg of furosemide, or a bolus of 10-20 mg i.v. torasemide, can be used.
- Furosemide can be given as 2-3 daily boluses or as a continuous infusion.
- Daily single bolus administrations are discouraged because of the possibility of post-dosing sodium retention.
- With continuous infusion, a loading dose may be used to achieve steady state earlier.
- Diuretic response should be evaluated shortly after start of diuretic therapy and may be assessed by performing a spot urine sodium content measurement after 2 or 6 h and/or by measuring the hourly urine output.
- A satisfactory diuretic response can be defined as a urine sodium content >50-70 mEq/L at 2 h and/or by a urine output >100-150mL/h during the first 6 h.
- If there is an insufficient diuretic response, the loop diuretic i.v. dose can be doubled, with a further assessment of diuretic response.
- If the diuretic response remains inadequate, e.g. <100 mL hourly diuresis despite doubling loop diuretic dose, concomitant administration of other diuretics acting at different sites, namely thiazides or metolazone or acetazolamide, may be considered. However, this combination requires careful monitoring of serum electrolytes and renal function.
- This strategy, based on early and frequent assessment of diuretic response, allows starting treatment with relatively low doses of loop diuretics, with frequent dose adjustments that may be less likely to cause dehydration and increase in serum creatinine.
- The loop diuretic dose should be progressively decreased when a significant negative fluid balance has been obtained. However, it should be pointed out that this algorithm's entirely based on expert opinion, to date.
- Transition to oral treatment should be commenced when the patient's clinical condition is stable.
- It is recommended that, after achievement of congestion relief, oral loop diuretics are continued at the lowest dose possible to avoid congestion.
- Care must also be taken to avoid patients being discharged from hospital with persistent congestion, as this is a major predictor of increased deaths and

rehospitalizations.

- Hence, care should be taken to achieve adequate decongestion and establish an appropriate long-term diuretic dose before discharge.

**Table: Therapeutic Approaches for Volume Management in Acute Heart Failure**

Severity of volume overload	Diuretic	Dose (mg)	Comments
<b>Moderate</b>	Furosemide, or	20–40 mg or up to 2.5 times oral dose	Intravenous administration preferable in symptomatic patients
	Bumetanide, or	0.5–1.0	Titrate dose according to clinical response
	Torsemide	10–20	Monitor Na <sup>+</sup> , K <sup>+</sup> , creatinine, BP
<b>Severe</b>	Furosemide, or	40–160 or 2.5 times oral dose 5–40 mg/hr infusion	Intravenously
	Bumetanide, or	1–4 / 0.5- 2 mg/hr infusion (max 2–4 mg/hr, limit 2–4 hr)	Bumetanide and torsemide have higher oral bioavailability than furosemide, but intravenous administration preferable in AHF
	Torsemide	20–100/ 5–20 mg/hr	
<b>Refractory to loop diuretics</b>	Ultrafiltration	200–500 mL/hr	Adjust ultrafiltration rate to clinical response, monitor for hypotension; consider hematocrit sensor
	Add HCTZ, or	25–50 twice daily	Combination with loop diuretic may be better than very high dose of loop diuretics alone
	Metolazone, or	2.5–10 once daily	Metolazone more potent if creatinine clearance <30mL/min
<b>In case of alkalosis</b>	Chlorothiazide, or	250–500 mg IV 500–1000 mg po	
	Spironolactone	25–50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K <sup>+</sup> , although may not be very potent
	Acetazolamide	0.5	Intravenously
<b>Refractory to loop diuretic and thiazides</b>	Add dopamine (renal vasodilation), or dobutamine or milrinone (inotropic agent)		
	Ultrafiltration, or hemodialysis if		

	coexisting renal failure		
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- **Vasodilators**

- Intravenous vasodilators, namely nitrates or nitroprusside, dilate venous and arterial vessels leading to a reduction in venous return to the heart, less congestion, lower afterload, increased stroke volume and consequent relief of symptoms.
- Nitrates act mainly on peripheral veins whereas nitroprusside is more a balanced arterial and venous dilator.
- Because of their mechanisms of action, i.v. vasodilators may be more effective than diuretics in those patients whose acute pulmonary oedema is caused by increased afterload and fluid redistribution to the lungs in the absence or with minimal fluid accumulation.
- However, two recent randomized trials comparing usual care with early intensive and sustained vasodilation failed to show a beneficial effect of i.v. vasodilators vs. high-dose diuretics. No recommendation favouring a regimen based on vasodilator treatment vs. usual care can thus be given, to date.
- Intravenous vasodilators may be considered to relieve AHF symptoms when SBP is >110 mmHg. They may be started at low doses and uptitrated to achieve clinical improvement and BP control.
- Nitrates are generally administered with an initial bolus followed by continuous infusion. However, they may also be given as repeated boluses.
- Nitroglycerine can be given as 1-2 mg boluses in severely hypertensive patients with acute pulmonary oedema.
- Care should be taken to avoid hypotension due to an excessive decrease in preload and afterload. For this reason, they should be used with extreme caution in patients with LVH and/or severe aortic stenosis.
- However, favorable effects were described in patients with LV systolic dysfunction and aortic stenosis when vasodilators were given with careful monitoring of haemodynamic parameters

- **Inotropes**

- Inotropes are still needed for treatment of patients with low cardiac output and hypotension (Table 9).
- They should be reserved for patients with LV systolic dysfunction, low cardiac output and low SBP (e.g. <90 mmHg) resulting in poor vital organ perfusion. However, they must be used with caution starting at low doses and uptitrating them with close monitoring.

- Inotropes, especially those with adrenergic mechanisms, can cause sinus tachycardia, increase ventricular rate in patients with AF, may induce myocardial ischaemia and arrhythmias, and increase mortality.
- Levosimendan or type-3-phosphodiesterase inhibitors may be preferred over dobutamine for patients on beta-blockers as they act through independent mechanisms.
- Excessive peripheral vasodilation and hypotension can be major limitations of type-3-phosphodiesterase inhibitors or levosimendan, especially when administered at high doses and/or when commenced with a bolus dose.
- **Vasopressors**
  - Vasopressors used for the treatment of AHF are reported in the table below.
  - Among drugs with a prominent peripheral arterial vasoconstrictor action, norepinephrine may be preferred in patients with severe hypotension.
  - The aim is to increase perfusion to the vital organs. However, this is at the expense of an increase in LV afterload.
  - Therefore, a combination of norepinephrine and inotropic agents may be considered, especially in patients with advanced HF and cardiogenic shock.
  - Some studies, though with limitations, support the use of norepinephrine as first choice, compared with dopamine or epinephrine.
  - Dopamine was compared with norepinephrine as a first-line vasopressor therapy in patients with shock and was associated with more arrhythmic events and with a greater mortality in patients with cardiogenic shock but not in those with hypovolemic or septic shock.

**Table: Inotropes and/or vasopressors used to treat acute heart failure**

Drug	Infusion rate
Dobutamine	2-20 microgram/kg/min (beta+)
Dopamine	3-5 microgram/kg/min; inotropic (beta+) >5 microgram/kg/min: inotropic (beta+), vasopressor (alpha+)
Milrinone	0.375-0.75 microgram/kg/min
Enoximone	5-20 microgram/kg/min
Levosimendan	0.1 microgram/kg/min, which can be decreased to 0.05 or increased to 0.2 microgram/kg/min
Norepinephrine	0.2-1.0 microgram/kg/min
Epinephrine	0.05-0.5 microgram/kg/min

- **Opiates**

- Opiates relieve dyspnoea and anxiety.
- They may be used as sedative agents during non-invasive positive pressure ventilation to improve patient adaptation.
- Dose-dependent side effects include nausea, hypotension, bradycardia, and respiratory depression.
- Retrospective analyses suggest that morphine administration is associated with a greater frequency of mechanical ventilation, prolonged hospitalization, more intensive care unit admissions, and increased mortality.
- Thus, routine use of opiates in AHF is not recommended although they may be considered in selected patients, particularly in case of severe/intractable pain or anxiety or in the setting of palliation.

- **Digoxin**

- Digoxin should be considered in patients with AF with a rapid ventricular rate (>110 b.p.m.) despite beta-blockers.
- It can be given in boluses of 0.25-0.5 mg i.v., if not used previously. However, in patients with comorbidities (i.e. CKD) or other factors affecting digoxin metabolism (including other drugs) and/or the elderly, the maintenance dose may be difficult to estimate theoretically and measurements of serum digoxin concentrations should be performed.
- Digitoxin is a potential alternative to digoxin and is currently being evaluated in a randomized placebo-controlled trial.

- **Thromboembolism prophylaxis**

- Thromboembolism prophylaxis with heparin (e.g. low-molecularweight heparin) or another anticoagulant is recommended, unless contraindicated or unnecessary (because of existing treatment with oral anticoagulants).

- **Pre-discharge assessment and post-discharge management planning**

- A significant proportion of patients with AHF are discharged with minimal or no weight loss and, more importantly, persistent congestion.
- Persistent congestion before discharge is associated with a higher risk of readmission and mortality.
- Treatment, including diuretic dose, should therefore be optimized in order to keep the patient free of congestion.
- In those admitted with ADHF, oral optimal medical therapy should be continued, except for possible dose reduction or withdrawal if there is haemodynamic instability (symptomatic hypotension), severely impaired renal function or

hyperkalaemia.

- Once haemodynamic stabilization is achieved with i.v. therapy, treatment should be optimized before discharge. Treatment optimization has three major aims.
  - **First**, to relieve congestion.
  - **Second**, to treat comorbidities, such as iron deficiency, that have an impact on post-discharge outcome.
  - **Third**, to initiate, or restart oral, optimal medical therapy with beneficial effects on outcome.
- Doses may be up titrated before discharge and/or in the early post discharge phase.
- Studies have shown that such optimization of medical treatment is associated with a lower risk of 30-day readmission, although prospective randomized trials have not been performed, to date.
- Retrospective analyses show that discontinuation or dose reduction of beta-blocker therapy during an AHF hospitalization is associated with worse outcomes.
- Initiation of ARNI in recently hospitalized stable patients with HFrEF, including those who are ACE-I/ARB naive, is safe and may be considered in this setting.
- Safety and better outcome have also been recently shown in a prospective randomized trial with sotagliflozin in diabetic patients hospitalized for HF, irrespective of their LVEF.
- It is recommended to have one follow-up visit within 1 to 2 weeks after discharge.
- Components of this follow-up visit should include:
  - Monitoring of signs and symptoms of HF,
  - Assessment of volume status, BP, heart rate, and
  - Laboratory measurements including renal function, electrolytes, and possibly NPs. Iron status and hepatic function should also be assessed when not done before discharge.
- Based on clinical evaluation and laboratory exams, further optimization and/or initiation of disease-modifying treatment for HFrEF should occur.
- Retrospective studies show that such an approach is associated with lower 30-day readmission rates although prospective randomized trials have not been performed, to date.

**Table:- Considerations Prior to Discharge after Acute Heart Failure Hospitalization**

<b>Recommended for all heart failure patients</b>
<ul style="list-style-type: none"> <li>• Exacerbating factors addressed</li> <li>• Near-optimal volume status observed</li> <li>• Transition from intravenous to oral diuretic successfully completed</li> <li>• Patient and family education completed, including clear discharge instructions</li> <li>• LVEF documented</li> <li>• Smoking cessation counseling initiated</li> <li>• Near-optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance Documented</li> <li>• Follow-up clinic visit scheduled, usually for 7–10 days</li> </ul>
<b>Should be considered for patients with advanced heart failure or recurrent admissions for heart failure</b>
<ul style="list-style-type: none"> <li>• Oral medication regimen stable for 24hr</li> <li>• No intravenous vasodilator or inotropic agent for 24hr</li> <li>• Ambulation before discharge to assess functional capacity after therapy</li> <li>• Plans for post- discharge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge)</li> <li>• Referral for disease management, if available</li> </ul>

ACE, Angiotensin- converting enzyme; LVEF, left ventricular ejection fraction.

Adapted from Heart Failure Society of America

## CHRONIC HEART FAILURE

### A) Key steps in the diagnosis of chronic heart failure

- The diagnosis of CHF requires the presence of symptoms and/or signs of HF and objective evidence of cardiac dysfunction.
- Typical symptoms include *breathlessness, fatigue, and ankle swelling* (Table 11). Symptoms and signs lack sufficient accuracy to be used alone to make the diagnosis of HF.
- The diagnosis of CHF is made more likely in patients with a history of
  - Myocardial Infarction,
  - Arterial hypertension,
  - CAD,
  - Diabetes mellitus,
  - Alcohol misuse,
  - Chronic kidney disease (CKD),

- Cardiotoxic chemotherapy, and
- in those with a family history of CMP or sudden death.
- The following diagnostic tests are recommended for the assessment of patients with suspected chronic HF:
  - **Electrocardiogram (ECG).**
    - A normal ECG makes the diagnosis of HF unlikely.
    - The ECG may reveal abnormalities such as AF, Q waves, LV hypertrophy (LVH), and a widened QRS complex that increase the likelihood of a diagnosis of HF and also may guide therapy.
  - **Measurement of NPs** are recommended, if available.
    - A plasma concentration of B-type natriuretic peptide (BNP) <35 pg/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) <125 pg/mL, or mid-regional pro-atrial natriuretic peptide (MR-proANP) <40 pmol/L make a diagnosis of HF unlikely.
  - **Echocardiography**
    - is recommended as the key investigation for the assessment of cardiac function.
    - Determination of the LVEF,
    - Provides information on other parameters such as
      - Chamber size,
      - Eccentric or concentric LVH,
      - Regional wall motion abnormalities (that may suggest underlying CAD, Takotsubo syndrome, or myocarditis),
      - RV function,
      - Pulmonary hypertension,
      - Valvular function, and
      - Markers of diastolic function.
  - **Chest X-ray**
    - Is recommended to investigate other potential causes of breathlessness (e.g. pulmonary disease) which may be precipitant of HF.
    - It may also provide supportive evidence of HF (e.g. pulmonary congestion or cardiomegaly).
  - Basic investigations such as **serum urea and electrolytes, creatinine, full blood count, liver and thyroid function tests** are recommended to differentiate HF from other conditions, to provide prognostic information, and to guide potential therapy.

**Table: Symptoms and signs typical of heart failure**

Symptoms	Signs
Typical	More specific
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	Less specific
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitation Dizziness Syncope Bendopnea <sup>a</sup>	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral edema (ankle, sacral, scrotal) Pulmonary crepitations Pleural effusion Tachycardia Irregular pulse Tachypnoea Cheyne-Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

<sup>a</sup>This symptom of advanced HF corresponds to shortness of breath when leaning forward.

## B) Heart failure with reduced ejection fraction

### a) The diagnosis of heart failure with reduced ejection fraction

- The diagnosis of HFrEF requires the presence of symptoms and/or signs of HF and a reduced ejection fraction (LVEF  $\leq 40\%$ ). This is most usually obtained by echocardiography.

**b) Pharmacological treatments for patients with heart failure with reduced ejection fraction**

- **Goals of pharmacotherapy for patients with heart failure with reduced ejection fraction**
  - Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy, and alongside non-pharmacological interventions.
  - There are three major goals of treatment for patients with HFrEF:
    1. Reduction in mortality,
    2. Prevention of recurrent hospitalizations due to worsening HF, and
    3. Improvement in clinical status, functional capacity, and QOL.
- **General principles of pharmacotherapy for heart failure with reduced ejection fraction**
  - Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with following drugs have been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF:
    - Angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI),
    - beta-blockers, and
    - mineralocorticoid receptor antagonists (MRA).
  - The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated.
  - They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). The guideline still recommends the use of ARNI as a replacement for ACE-I in suitable
  - Patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I.
  - Angiotensin-receptor blockers (ARBs) still have a role in those who are intolerant to ACE-I or ARNI.
  - The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to therapy with ACE-I/ARNI/betablocker/ MRA reduced the risk of CV death and worsening HF in patients with HFrEF.
  - Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not.

- Other drugs may be used for selected patients with HFrEF.
- **Drugs recommended in all patients with heart failure with reduced ejection fraction**
  - **Angiotensin-converting enzyme inhibitors**
    - ACE-Is were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF.
    - They have also been shown to improve symptoms.
    - They are recommended in all patients unless contraindicated or not tolerated.
    - They should be uptitrated to the maximum tolerated recommended doses
    - **Side Effects**
      - The majority of the adverse effects of ACEIs are related to suppression of the renin angiotensin system.
      - The decreases in blood pressure and mild azotemia often seen during the initiation of therapy are, in general, well tolerated and do not require a decrease in the dose of the ACEI.
      - However, if hypotension is accompanied by dizziness or if the renal dysfunction becomes severe, it may be necessary to decrease the dose of the diuretic if significant fluid retention is not present, or alternatively decrease the dose of the ACEI if significant fluid retention is present.
      - Potassium retention may also become problematic if the patient is receiving potassium supplements or a potassium- sparing diuretic.
      - Potassium retention that is not responsive to these measures may require a reduction in the dose of ACEI.
      - The side effects of ACEIs that are related to kinin potentiation include a nonproductive cough (10% to 15% of patients) and angioedema (1% of patients).
      - In patients who cannot tolerate ACEIs because of cough or angioedema, ARBs are the next recommended line of therapy.
      - Patients intolerant to ACEIs because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs.
      - The combination of hydralazine and an oral nitrate should be considered for these latter patients
- **Beta-blockers**
  - Beta-blockers have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACE-I and diuretic.
  - They also improve symptoms.
  - There is consensus that ACE-I and beta-blockers can be commenced together as

soon as the diagnosis of symptomatic HFrEF is established.

- There is no evidence favouring the initiation of a beta-blocker before an ACE-I and vice versa.
- Beta-blockers should be initiated in clinically stable, euvolaemic, patients at a low dose and gradually uptitrated to the maximum tolerated dose.
- In patients admitted with AHF, betablockers should be cautiously initiated in hospital, once the patient is haemodynamically stabilized.
- An individual patient data (IPD) meta-analysis of all major beta blocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF with AF. However, since this is a retrospective subgroup analysis, and because beta-blockers did not increase risk, the guideline committee decided not to make a separate recommendation according to heart rhythm.
- **Side Effects**
  - The adverse effects of beta- blockers are generally related to the predictable complications that arise from interfering with the adrenergic nervous system.
  - These reactions generally occur within several days of initiating therapy, and are generally responsive to adjusting concomitant medications, as described above.
  - Treatment with a beta- blocker can be accompanied by feelings of general fatigue or weakness.
  - In most instances, the increased fatigue spontaneously resolves within several weeks or months; however, in some patients, it may be severe enough to limit the dose of beta- blocker or require the withdrawal or reduction of treatment.
  - Therapy with beta- blockers can lead to bradycardia and/ or exacerbate heart block.
  - Moreover, beta- blockers (particularly those that block the  $\alpha_1$  receptor) can lead to vasodilatory side effects.
  - Accordingly, the dose of beta- blockers should be decreased if the heart rate decreases to less than 50 beats/min and/or second- or third- degree heart block develops, or symptomatic hypotension develops.
  - Continuation of beta- blocker treatment during an episode of acute decompensation is safe, although dose reduction may be necessary.

- Beta-blockers are not recommended for patients with asthma with active bronchospasm.
- **Mineralocorticoid receptor antagonists**
  - MRAs (spironolactone or eplerenone) are recommended, in addition to an ACE-I and a beta-blocker, in all patients with HFrEF to reduce mortality and the risk of HF hospitalization.
  - They also improve symptoms.
  - MRAs block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormones (e.g. Corticosteroid and androgen) receptors.
  - Eplerenone is more specific for aldosterone blockade and, therefore, causes less gynaecomastia.
  - Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium concentrations >5.0mmol/L.
  - **Side Effects**
    - The major problem with the use of aldosterone antagonists is the development of life-threatening hyperkalemia, which is more prone to occur in patients who are receiving potassium supplements, or who have underlying renal insufficiency.
    - Aldosterone antagonists are not recommended when the serum creatinine is greater than 2.5 mg/dL (or creatinine clearance is <30 mL/min) or serum potassium is greater than 5.5 mmol/L.
    - The development of worsening renal function should lead to consideration regarding stopping aldosterone antagonists because of the potential risk of hyperkalemia.
    - Painful gynecomastia may develop in 10% to 15% of patients who use spironolactone, in which case eplerenone may be substituted.
- **Angiotensin receptor-neprilysin inhibitor**
  - In the PARADIGM-HF trial, sacubitril/valsartan, an ARNI, was shown to be superior to enalapril in reducing hospitalizations for worsening HF, CV mortality, and all-cause mortality in patients with ambulatory HFrEF with LVEF  $\leq 40\%$  (changed to  $\leq 35\%$  during the study).
  - Patients in the trial had elevated plasma NP concentrations, an eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> and were able to tolerate enalapril and then sacubitril/valsartan during the run-in period.
  - Additional benefits of sacubitril/valsartan included an improvement in symptoms and QOL, a reduction in the incidence of diabetes requiring insulin

treatment, and a reduction in the decline in eGFR, as well as a reduced rate of hyperkalaemia.

- Additionally, the use of sacubitril/valsartan may allow a reduction in loop diuretic requirement.
- Symptomatic hypotension was reported more commonly in patients treated with sacubitril/valsartan as compared to enalapril, but despite developing hypotension, these patients also gained clinical benefits from sacubitril/valsartan therapy.
- Therefore, it is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment outlined above.
- Two studies have examined the use of ARNI in hospitalized patients, some of whom had not been previously treated with ACE-I. Initiation in this setting appears safe and reduces subsequent CV death or HF hospitalizations by 42% compared to enalapril.
- As such, initiation of sacubitril/valsartan in ACE-I naive (i.e. de novo) patients with HFrEF may be considered.
- Patients being commenced on sacubitril/valsartan should have an adequate blood pressure (BP), and an eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>.
- **Side Effects**
  - The use of an ARNI is associated with hypotension (approximately 14%), hyperkalemia (4%), cough (11%), and a very low- frequency incidence of angioedema.
  - Oral neprilysin inhibitors, used in combination with ACE inhibitors, can lead to angioedema; accordingly, the concomitant use of ACEIs and ARNIs is contraindicated.
  - For patients who are switching from ACEIs to sacubitril/valsartan, the ACEI should be withheld for at least 36 hours before initiating sacubitril/valsartan in order to minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition.
  - There are additional concerns about the effects of sacubitril/valsartan on the degradation of beta- amyloid peptide in the brain, which could theoretically accelerate amyloid deposition.
  - The optimal titration and tolerability of ARNIs, particularly with regard to blood pressure and the adjustment of concomitant HF medications, will require addition clinical experience.

- **Sodium-glucose co-transporter 2 inhibitors**
  - Significantly reduce worsening HF (hospitalization or an urgent visit resulting in i.v. therapy for HF) or CV death.
  - Moreover, dapagliflozin reduced all-cause mortality, alleviated HF symptoms, improved physical function and QOL in patients with symptomatic HFrEF.
  - Benefits were seen early after the initiation of dapagliflozin, and the absolute risk reduction was large.
  - Survival benefits were seen to the same extent in patients with HFrEF with and without diabetes, and across the whole spectrum of HbA1c values.
  - Reduce decline in eGFR in individuals receiving empagliflozin.
  - It was also associated with an improvement in QOL. Therefore, dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status.
  - The diuretic/natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.
  - The combined SGLT-1 and 2 inhibitor, sotagliflozin, has also been studied in patients with diabetes who were hospitalized with HF. The drug reduced CV death and hospitalization for HF.
  - Therapy with SGLT2 inhibitors may increase the risk of recurrent genital fungal infections.
  - A small reduction in eGFR following initiation is expected and is reversible and should not lead to premature discontinuation of the drug.
- **Other drugs recommended or to be considered in selected patients with heart failure with reduced ejection fraction**
  - **Diuretics**
    - Loop diuretics are recommended to reduce the signs and/or symptoms of congestion in patients with HFrEF.
    - One meta-analysis has shown that in patients with HFrEF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF compared with a placebo, and compared with an active control, diuretics improve exercise capacity.
    - Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically (sequential nephron blockade) and the combination may be used to treat diuretic resistance. However, adverse effects

are more likely, and these combinations should only be used with care.

- Of note, ARNI, MRAs, and SGLT2 inhibitors may also possess diuretic properties.
- The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest diuretic dose.
- In some euvoalaemic/hypovolaemic patients, the use of a diuretic drug might be reduced or discontinued.
- Patients should be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.
- **Angiotensin II type I receptor blockers**
  - The place of ARBs in the management of HFrEF has changed over the last few years.
  - They are now recommended for patients who cannot tolerate ACE-I or ARNI because of serious side effects.
  - Candesartan in the CHARM-Alternative study reduced CV deaths and HF hospitalizations in patients who were not receiving an ACE-I due to previous intolerance.
  - Valsartan, in addition to usual therapy, including ACE-I, reduced HF hospitalizations in the Val-HeFT trial.
  - However, no ARB has reduced all-cause mortality in any trial.
- **Side Effects**
  - Both ACEIs and ARBs have similar effects on blood pressure, renal function, and potassium.
  - Therefore, the problems of symptomatic hypotension, azotemia, and hyperkalemia will be similar for both of these agents.
  - Although less frequent than with ACEIs, angioedema has also been reported in some patients who receive ARBs.
  - In patients who are intolerant to ACEIs and ARBs, the combined use of hydralazine and isosorbide dinitrate (H-ISDN) may be considered as a therapeutic option in such patients
  - However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions.

▪ **Digoxin**

- Digoxin may be considered in patients with HFrEF in Sinus rhythm to reduce the risk of hospitalization, although its effect on those routinely treated with beta-blockers has not been tested.
- Digoxin may be useful for the treatment of patients with HFrEF and AF with rapid ventricular rate, when other therapeutic options cannot be pursued.
- Digoxin has a narrow therapeutic window and so levels should be checked aiming for a serum digoxin concentration <1.2 ng/mL.
- Caution should also be exercised when using it in females, the elderly, frail, hypokalaemic, and malnourished subjects.
- In patients with reduced renal function, digitoxin could be considered.
- Digitoxin use in HF and Sinus rhythm is currently being investigated.

**Table: Drugs Commonly Used for HFrEF**

Drug	Initial Daily Dose(s)	Target Doses(s)
<b>ACEi</b>		
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Fosinopril	5–10 mg once daily	40 mg once daily
Lisinopril	2.5–5 mg once daily	20–40 mg once daily
Perindopril	2 mg once daily	8–16 mg once daily
Quinapril	5 mg twice daily	20 mg twice daily
Ramipril	1.25–2.5 mg once daily	10 mg once daily
Trandolapril	1 mg once daily	4 mg once daily
<b>ARB</b>		
Candesartan	4–8 mg once daily	32 mg once daily
Losartan	25–50 mg once daily	50–150 mg once daily
Valsartan	20–40 mg once daily	160 mg twice daily
<b>ARNi</b>		
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily
<b>Beta blockers</b>		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25–50 mg twice daily

Carvedilol CR	10 mg once daily	80 mg once daily
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily
<b>Mineralocorticoid receptor antagonists</b>		
Spironolactone	12.5–25 mg once daily	25–50 mg once daily
Eplerenone	25 mg once daily	50 mg once daily
<b>SGLT2i</b>		
Dapagliflozin	10 mg once daily	10 mg once daily
Empagliflozin	10 mg once daily	10 mg once daily
<b>Isosorbide dinitrate and hydralazine</b>		
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses
<b>I<sub>f</sub> Channel inhibitor</b>		
Ivabradine	5 mg twice daily	7.5 mg twice daily
<b>Soluble guanylate cyclase stimulator</b>		
Vericiguat	2.5 mg once daily	10 mg once daily
Digoxin	0.125–0.25 mg daily (modified according to monogram)	Individualized variable dose to achieve serum digoxin concentration 0.5–<0.9 ng/mL

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NR, not reported; and SGLT2i, sodium glucose cotransporter 2 inhibitor

▪ **Anticoagulation and Antiplatelet therapy**

- Patients with HF have an increased risk for arterial or venous thromboembolic events.
- In clinical HF trials the rate of stroke ranges from 1.3% to 2.4%/yr.
- Depressed LV function is believed to promote relative stasis of blood in dilated cardiac chambers with increased risk of thrombus formation.
- Thromboembolism prophylaxis in patients with HF and AF should be individualized and based on an assessment of the risk of stroke versus the risk of bleeding on an anticoagulant.
- In general most patients with HFrEF will have an increased risk of stroke.
- The AHA/ACC/Heart Rhythm Society guidelines for AF recommend use of the **CHA<sub>2</sub>DS<sub>2</sub>-VASc score** to assess patient risk for adverse outcomes before initiating anticoagulation therapy
  - C: Cardiac failure,
  - H: history of Hypertension,
  - A: Age  $\geq 75$  (Doubled),
  - D: Diabetes,
  - S: previous Stroke or transient ischemic attack or thromboembolism (doubled),
  - V: Vascular disease,
  - A: Age 65 to 74 and
  - S: Sex category (Female).
- Regardless of whether patients receive rhythm or rate control, anticoagulation is recommended for patients with HF and AF for stroke prevention with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  (for men) and  $\geq 3$  (for women)
- A recent meta-analysis of clinical trials in patients with nonvalvular AF suggests that, when compared to warfarin, novel oral anticoagulants (NOACs) have a favorable risk-benefit profile, with significant reductions in stroke, don't need routine anticoagulation monitoring or dose adjustment, intracranial hemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding.
- Other studies have suggested comparable efficacy but fewer major bleeding events.
- On the basis of these studies, the ESC HF guidelines recommend NOACs, recognizing that their safety in older subjects and subjects with impaired renal function is not known.

- Anticoagulation is also recommended for all patients with a history of systemic or pulmonary emboli, including stroke or transient ischemic attack.
- Patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus should be treated with warfarin (goal INR 2.0 to 3.0) for the initial 3 months after MI unless there are contraindications.
- The question of whether HF patients who are in sinus rhythm should be treated with anticoagulants to reduce stroke was addressed in the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, which showed that treatment with warfarin as compared with aspirin did not reduce the composite outcome of time to ischemic stroke, intracerebral hemorrhage, or death from any cause.
- Although treatment with warfarin was associated with a significant reduction in the rate of ischemic stroke, this benefit was offset by a significant increase in the rate of major hemorrhage.
- Interestingly, the rates of intracerebral and intracranial hemorrhage did not differ significantly between the two treatment groups.
- Based on the results of the WARCEF trial, there is no compelling reason to use warfarin rather than aspirin in HF patients with a reduced LVEF who are in sinus rhythm.

**C) Heart failure with mildly reduced ejection fraction**

- **The diagnosis of heart failure with mildly reduced ejection fraction**
  - The diagnosis of HFmrEF requires the presence of symptoms and/or signs of HF, and a mildly reduced EF (41-49%)
  - The presence of elevated NPs (BNP  $\geq 35$  pg/mL or NT-proBNP  $\geq 125$  pg/mL) and other evidence of structural heart disease [e.g. increased left atrial (LA) size, LVH or echocardiographic measures of LV filling] make the diagnosis more likely but are not mandatory for diagnosis if there is certainty regarding the measurement of LVEF.
- **Clinical characteristics of patients with heart failure with mildly reduced ejection fraction**
  - There is a substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodelling, and outcomes among the LVEF categories in HF.
  - Patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, in that they are more commonly men, younger, and are more likely to have CAD (50-60%), and less likely to have AF and non-cardiac comorbidities.
  - However, ambulatory patients with HFmrEF have a lower mortality than those with HFrEF, more akin to those with HFpEF.

- Patients with HFmrEF may include patients whose LVEF has improved from  $\leq 40\%$  or declined from  $>50\%$ .
- **Treatments for patients with heart failure with mildly reduced ejection fraction**
  - As in other forms of HF, diuretics should be used to control congestion.
  - No substantial prospective randomized controlled trial has been performed exclusively in patients with HFmrEF.
- **Angiotensin-converting enzyme inhibitors**
  - There are no specific trials of ACE-I in patients with HFmrEF.
  - However, in patients with HFmrEF, many will also have CAD, hypertension, or post-MI LV systolic dysfunction and will, therefore, already be treated with ACE-I.
  - Therefore, ACE-I use may be considered in patients with HFmrEF.
- **Angiotensin receptor II type 1 receptor blockers**
  - There are no specific trials of ARBs in HFmrEF. However, a retrospective analysis showed that candesartan reduced the number of patients hospitalized for HF among those with HFmrEF (with similar trends for CV and all-cause mortality).
  - As for ACE-I, many with HFmrEF will already be on an ARB for other CV indications. Therefore, treatment with ARBs may be considered in patients with HFmrEF.
- **Beta-blockers**
  - There is no specific trial of beta-blockade in HFmrEF. An IPD meta analysis of landmark trials of beta-blockers suggested similar reductions in CV and all-cause mortality (of 50%) for patients in Sinus rhythm with HFrEF and HFmrEF.
  - Many patients with HFmrEF may have another CV indication, such as AF or angina, for a beta-blocker. Therefore, treatment with beta-blockers may be considered in patients with HFmrEF.
- **Mineralocorticoid receptor antagonists**
  - There is no specific trial of MRAs in HFmrEF. In a retrospective analysis of the TOPCAT trial in patients with an LVEF  $\geq 45\%$ , spironolactone reduced hospitalizations for HF in those with an LVEF  $<55\%$ .
  - There was a similar trend for CV but not all-cause mortality.
  - Treatment with an MRA may be considered in patients with HFmrEF.
- **Angiotensin receptor-neprilysin inhibitor**
  - There is no specific trial of ARNI in HFmrEF.
  - In the PARAGON-HF trial, which included patients with EF  $\geq 45\%$ , although the

trial missed its primary endpoint overall, a significant EF-by-treatment interaction was observed.

- Sacubitril/valsartan, compared with valsartan, reduced the likelihood of the primary composite outcome of CV death and total HF hospitalizations by 22% in those with an EF below or equal to the median of 57%.
- Further data are available from a combined analysis of the PARADIGM-HF and PARAGON-HF trials showing that sacubitril/valsartan, compared to other forms of RAAS blockade, has a beneficial effect, especially on hospitalizations for HF in those with HFmrEF.
- Treatment with an ARNI may be considered in patients with HFmrEF.

#### D) Heart failure with preserved ejection fraction

- **Clinical characteristics of patients with heart failure with preserved ejection fraction**
  - HFpEF differs from HFrEF and HFmrEF in that HFpEF patients are older and more often female.
  - AF, CKD, and non-CV comorbidities are more common in patients with HFpEF than in those with HFrEF.
  - There are numerous potential causes of HFpEF.
  - The pathophysiology of various HFpEF syndromes differs, and thus they require distinct therapies.
  - Red flags for the potential presence of CA include low normal BP in patients with a history of hypertension, intolerance to beta-blockers or ACE-I, history of bilateral carpal tunnel syndrome, low voltage on ECG and echocardiographic features such as thickening of the septum, posterior wall, or RV wall, enlarged atria, a small pericardial effusion, or valve thickening.
  - Furthermore, it is important to exclude other conditions that might mimic the HFpEF syndrome (e.g. lung disease, anemia, obesity, and deconditioning).
- **The diagnosis of heart failure with preserved ejection fraction**
  - The diagnosis should include the following:
    - Symptoms and signs of HF.
    - An LVEF  $\geq 50\%$ .\*
    - Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised NPs.
  - \*Of note, patients with a history of overtly reduced LVEF ( $\leq 40\%$ ), who later present with LVEF  $\geq 50\%$ , should be considered to have recovered HFrEF or ‘HF with improved LVEF’ (rather than HFpEF). Continued treatment for HFrEF is

recommended in these patients. It is not known whether starting HF therapy in patients with recovered LVEF is beneficial.

- Patients with HFpEF tend to have stable trajectory of LVEF over time. However, in those who develop a clinical indication for a repeat echo during follow-up, around one third have a decline in LVEF.
- The approach to the diagnosis should involve additional confirmatory tests in cases of diagnostic uncertainty, such as cardiopulmonary exercise testing (to confirm a reduction in exercise capacity and to help differentiate the cause of dyspnea), exercise stress testing, and invasive hemodynamic testing.
- If resting echocardiographic and laboratory markers are equivocal, a diastolic stress test is recommended.
- The confirmatory test for the diagnosis of HFpEF is invasive hemodynamic exercise testing.
- An invasively measured pulmonary capillary wedge pressure (PCWP) of  $\geq 15$  mmHg (at rest) or  $\geq 25$  mmHg (with exercise) or LV end-diastolic pressure  $\geq 16$  mmHg (at rest) is generally considered diagnostic.
- However, instead of an exercise PCWP cut-off, some have used an index of PCWP to cardiac output for the invasive diagnosis of HFpEF.
- Recognizing that invasive hemodynamic exercise testing is not available in many centers worldwide, and is associated with risks, its main use is limited to the research setting.
- In the absence of any disease-modifying treatments, the current guidelines do not mandate gold standard testing in every patient to make the diagnosis, but emphasize that the greater the number of objective non-invasive markers of raised LV filling pressures, the higher the probability of a diagnosis of HFpEF.
- **Treatment of heart failure with preserved ejection fraction**
  - To date, no treatment has been shown to convincingly reduce mortality and morbidity in patients with HFpEF, although improvements have been seen for some specific phenotypes of patients
  - In the absence of recommendations regarding disease-modifying therapies, treatment should be aimed at reducing symptoms of congestion with diuretics. Loop diuretics are preferred, although thiazide diuretics may be useful for managing hypertension.
  - Reducing body weight in obese patients and increasing exercise may further improve symptoms and exercise capacity and should therefore be considered in appropriate patients.
  - It is important to identify and treat the underlying risk factors, aetiology, and

coexisting comorbidities in HFpEF (e.g., hypertension, CAD, amyloidosis, AF, and valvular heart disease).

- Undoubtedly, treatment of some of the underlying phenotypes of the the HFpEF syndrome leads to improved outcomes.

**E) Follow-up of chronic heart failure**

- This is a relatively understudied area.
- Patients with HF, even if symptoms are well controlled and stable, require follow-up to ensure continued optimization of therapy, to detect asymptomatic progression of HF or its comorbidities and to discuss any new advances in care.
- Optimal medical therapy (OMT) should be reached within 3 to 6months.
- It recommended at intervals no longer than 6 months to check symptoms, heart rate and rhythm, BP, full blood count, electrolytes, and renal function.
- For patients recently discharged from hospital, or in those undergoing uptitration of medication, follow-up intervals should be more frequent.
- Whether such stable patients need to be followed-up by cardiologists is uncertain.
- Some studies suggest that follow-up in primary care may be appropriate.
- However, uptake of evidence-based interventions is poor in many settings and several studies suggest that care and follow-up provided by HF specialists, and use of quality improvement registries can lead to higher rates of optimal therapy and improved outcomes.
- An ECG should be done annually to detect QRS prolongation as such patients may become candidates for Cardiac resynchronization therapy (CRT). Furthermore, it may identify conduction disturbances and AF.
- Serial echocardiography is generally not necessary, although an echocardiogram should be repeated if there has been a deterioration in clinical status.
- An echocardiogram is also advised 3-6months after optimization of standard therapies for HFrEF to determine the need for addition of newer pharmacological agents and implanted devices.

**F) Patient education**

- Adequate patient self-care is essential in the effective management of HF and allows patients to understand what is beneficial, and to agree to self-monitoring and management plans.
- HF patients who report more effective self-care have a better QOL, lower readmission rates, and reduced mortality.
- Misunderstandings, misconceptions, and lack of knowledge all contribute to insufficient self-care and therefore patient education is vital.

- Improving patients' knowledge of their condition is fundamental for the development of self-care skills.

**Table: Patient education and self-care**

<b>Education topic</b>	<b>Goal for the patient and caregiver</b>	<b>Professional behavior and educational tools</b>
<b>Explanation about HF</b>	To understand the cause of their HF, symptoms and treatment choice	Provide tailored information.
<b>The HF trajectory</b>	To understand prognosis and the different possible phases in the HF trajectory. To make joint treatment decisions that recognize the patient's position on the HF trajectory.	Sensitively communicate information on prognosis at time of diagnosis, during decision making about treatment options, when there is a change in the clinical condition and whenever the patient requests.
<b>Medical treatment</b>		
<b>Medication</b>	To be able to make joint decisions about medication. To understand the indications, benefits, the need for longterm adherence to certain drugs, and the dosing and side effects of medication. To be able to recognize the common side effects of medication and know what actions to take.	Provide written and oral information on indication, benefits, dosing, effects and side effects. Discuss practical issues such as optimal time-schedule, what to do in case of a missed dose etc. Discuss possible barriers for medication taking. Advise on support aids such as dosette box, electronic reminders etc. when appropriate
<b>Self-care aspects</b>		
<b>Activity and exercise</b>	To undertake regular exercise and be physically active. To be able to adapt physical activity to symptom status and personal circumstances	Advise on exercise that recognizes physical and functional limitations, such as frailty, comorbidities. Refer to exercise programme or other activity modes. Discuss possible barriers, side-effects and opportunities.
<b>Fluids</b>	To avoid large volumes of fluid intake. A fluid restriction of 1.5-2 L/day may be considered in patients with severe HF/hyponatraemia to relieve symptoms and congestion. To avoid dehydration: where fluids are restricted, increase intake during periods of high heat/humidity and/or nausea/vomiting.	Provide information and discuss the advantages and disadvantages of fluid restriction. Advise to adapt fluid intake to weight, and in times of high heat and humidity, nausea/vomiting. Adjust advice during periods of acute decompensation and consider altering this advice towards end-of-life.
<b>Healthy diet</b>	To be able to prevent malnutrition and know how to eat healthily, avoiding excessive salt intake (>5 g/day) and maintaining a healthy body weight	Discuss current food intake, role of salt, role of micronutrients. Discuss the need for supplementing in case of nutrient deficiencies but there is no clear role for routine micronutrient supplementation. Discuss maintaining a healthy body weight.

<b>Alcohol</b>	To be able to abstain from or avoid excessive alcohol intake, especially for alcohol-induced CMP. To restrict alcohol according to CV prevention guidelines	Tailor alcohol advice to aetiology of HF; e.g. abstinence in alcoholic CMP. Inform and discuss alcohol intake according to CV prevention guidelines (2 units per day in men or 1 unit per day in women) <sup>a</sup> .
<b>Smoking and recreational drugs</b>	To be aware of the consequences for health of smoking and use of recreational drugs. Stop smoking (including e-cigarettes) and taking recreational drugs.	Inform, discuss and help in decision making. Refer for specialist advice for smoking cessation and drug withdrawal and replacement therapy. Consider referral for cognitive behavioural theory and psychological support if patient wishes to stop smoking or taking drugs.
<b>Symptom monitoring and symptom self management</b>	Monitor and recognize change in signs and symptoms. Being able to react adequately to change in signs and symptoms. Know how and when to contact a healthcare professional.	Provide individualized information to support self-management such as: In the case of increasing dyspnea or edema or a sudden unexpected weight gain of >2 kg in 3 days, patients may increase their diuretic dose and/or alert their healthcare team.

CMP = cardiomyopathy; CV = cardiovascular; HF = heart failure.

<sup>a</sup>1 unit is 10 mL of pure alcohol (e.g., 1 glass of wine, 1=2 pint of beer, 1 measure of spirit).

## ADVANCED HEART FAILURE

### EPIDEMIOLOGY, DIAGNOSIS, AND PROGNOSIS

- Many patients with HF progress into a phase of advanced HF, characterized by persistent symptoms despite maximal therapy.
- The prevalence of advanced HF is increasing due to the growing number of patients with HF, ageing of the population, and better treatment and survival of HF.
- Prognosis remains poor, with a 1-year mortality ranging from 25% to 75%.
- The updated HFA-ESC 2018 criteria for the definition of advanced HF are reported in Table 14.
- A severely reduced LVEF is common but not required for a diagnosis of advanced HF as it may develop in patients with HFpEF as well.
- In addition to the reported criteria, extra-cardiac organ dysfunction due to HF (e.g. cardiac cachexia, liver or kidney dysfunction) or type II pulmonary hypertension may be present, but are not required for the definition of advanced HF.
- Despite many prognostic parameters, predicting outcomes remains difficult and patients are often referred to advanced HF centers too late.
- Identifying warning signs in patients with non-advanced symptoms may allow early referral so that MCS and heart transplantation may be offered before the development of end-organ failure.

**Table: Criteria for definition of advanced heart failure**

All the following criteria must be present despite optimal medical treatment:
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by at least one of the following:
<ul style="list-style-type: none"> <li>• LVEF <math>\leq 30\%</math></li> <li>• Isolated RV failure (e.g., ARVC)</li> <li>• Non-operable severe valve abnormalities</li> <li>• Non-operable severe congenital abnormalities</li> <li>• Persistently high (or increasing) BNP or NT-proBNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF).</li> </ul>
3. Episodes of pulmonary or systemic congestion requiring high-dose i.v. diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWT distance (<300 m) or pVO <sub>2</sub> <12 mL/kg/min or <50% predicted value, estimated to be of cardiac origin.

6MWT = 6-minute walk test; ARVC = arrhythmogenic right ventricular cardiomyopathy; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pVO<sub>2</sub> = peak oxygen consumption; RV = right ventricular. Modified from

#### CLINICAL INDICATORS

- Repeated hospitalizations or emergency department visits for HF in the past 12 mo.
- Need for intravenous inotropic therapy.
- Persistent NYHA functional class III to IV symptoms despite therapy.
- Severely reduced exercise capacity (peak VO<sub>2</sub>, <14 mL/kg/min or <50% predicted, 6-min walk test distance <300 m, or inability to walk 1 block on level ground because of dyspnea or fatigue).
- Intolerance to RAAS inhibitor because of hypotension or worsening renal function.
- Intolerance to beta blockers as a result of worsening HF or hypotension.
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d or use of supplemental metolazone therapy.
- Refractory clinical congestion.
- Progressive deterioration in renal or hepatic function.
- Worsening right HF or secondary pulmonary hypertension.
- Frequent SBP  $\leq 90$  mm Hg.
- Cardiac cachexia.

- Persistent hyponatremia (serum sodium, <134 mEq/L).
- Refractory or recurrent ventricular arrhythmias; frequent implantable cardioverter-defibrillator (ICD) shocks.
- Increased predicted 1-year mortality (e.g., >20%) according to HF survival models.

## **CAUSES OF HEART FAILURE**

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### **MAJOR CAUSES OF HEART FAILURE**

- Ischemic heart disease
- Valvular heart disease
- Hypertensive heart disease
- Cardiomyopathies
- Pericardial disease
- Congenital heart disease - much more common disease in children

## ISCHEMIC HEART DISEASE

### INTRODUCTION

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**Ischemic heart disease (IHD)** is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium

It typically occurs when there is an imbalance between myocardial oxygen supply and demand.

The most common cause of myocardial ischemia is **atherosclerotic disease** of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery.

### CLASSIFICATION OF IHD

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- Chronic Coronary Artery Disease (CAD) / Stable Angina
- Acute Coronary Syndromes:
  - **STEMI** (Acute Myocardial Infarction (MI) with ST-segment elevation on their presenting electrocardiogram (ECG))
  - **Unstable Angina**
  - **NSTEMI** (Non-ST-segment Elevation MI)

### KILLIP CLASSIFICATION OF STEMI

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**Killip class I** - no signs of pulmonary or venous congestion (0-5% mortality rate)

**Killip class II** - moderate heart failure as evidenced by rales at the lung bases, S<sub>3</sub> gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion (10-20%),

**Killip class III** - severe heart failure, pulmonary edema (35-45%);

**Killip class IV** - shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and **oliguria** (MR=85-95%)

### PATHOPHYSIOLOGY

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Central to an understanding of the pathophysiology of myocardial ischemia is the concept of Myocardial Supply and Demand.

The major determinants of Myocardial Oxygen Demand (**MVO<sub>2</sub>**) are:

- Heart Rate,
- Myocardial Contractility, and
- Myocardial Wall Tension (Stress).

- Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole.
- Three sets of arteries contribute to about 75% of the total coronary resistance:
  - large epicardial arteries (Resistance 1 =  $R_1$ ),
  - pre-arteriolar vessels ( $R_2$ ), and
  - arteriolar and intramyocardial capillary vessels ( $R_3$ )
- In the absence of significant flow-limiting atherosclerotic obstructions,  $R_1$  is trivial; the major determinant of coronary resistance is found in  **$R_2$  and  $R_3$** .

### How does the heart maintain homeostasis?

- **Metabolic regulation**-the changing oxygen needs of the heart with exercise
- **Auto regulation** -coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs

### Normal functions of endothelium:

- local control of vascular tone,
- maintenance of an antithrombotic surface, and
- control of inflammatory cell adhesion and diapedesis

### How does atherosclerosis affect the heart?

- Reduces the lumen of coronary arteries
- Limits appropriate increases in perfusion when the demand for flow is augmented
- Reduced myocardial perfusion at rest (when luminal reduction is severe)

### Other causes of ischemia

- Spasm (Prinzmetal's angina),
- Arterial thrombi,
- coronary emboli -- rare
- Ostial narrowing due to aortitis -- rare.
- Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery -- very rare in adults

### How do risk factors (of IHD) contribute to the pathogenesis?

They disturb the normal functions of the endothelium!

- Inappropriate constriction,
- luminal thrombus formation, and

- Abnormal interactions between **blood cells**, especially monocytes and platelets, and the **activated vascular endothelium**.

## RISK FACTORS OF IHD

MODIFIABLE	NON-MODIFIABLE
- Diabetes	-age (male>50, female>60)
- Smoking	-male sex
- Dyslipidemia	-family history of premature CAD(male <55, female <65)
- Hypertension	
- Sedentary life style	
- Obesity	
- High-fat & energy-rich diet	

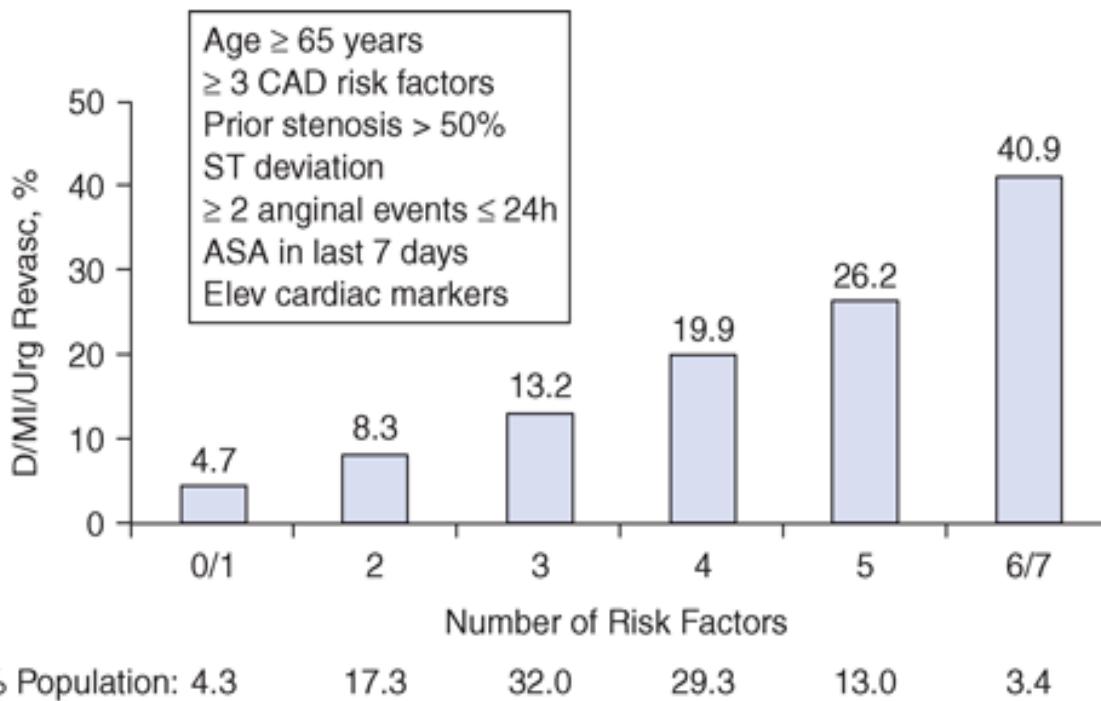
**Emerging risk factors** (high levels of all of the following)

- C-reactive protein (CRP)
- Lipoprotein(a)
- Homocysteinemia
- Prothrombotic factors
- Proinflammatory factors
- Impaired fasting glucose
- Subclinical atherosclerosis

## High likelihood for ACS (Acute Coronary Syndrome)

- prior hx of typical ACS,
- prior hx of typical stable angina,
- hx of established CAD by angiography,
- prior MI,
- CHF,
- new ECG changes, or
- elevated Cardiac Biomarkers

## TIMI risk score for UA/NSTEMI



The TIMI risk score was found to be **predictive of the severity of the vascular disease**, making it a powerful tool to predict the potential blood vessels of coronary circulation that could be involved.

The Thrombolysis in Myocardial Infarction (TIMI) Score is used to **determine the likelihood of ischemic events or mortality in patients with unstable angina or NSTEMI**.

Event rates increased significantly as the TIMI risk score rose. Patients are considered to be at low risk with a score of 0 to 2, intermediate risk with a score of 3 to 4, and high risk with a score of **5 to 7**. [Uptodate 2021]

## CLINICAL MANIFESTATIONS OF IHD

### SUB STERNAL CHEST PAIN:

#### STABLE ANGINA

- occurs with exertion or emotional stress
- relieved by rest or nitro-glycerine
- Radiates to either shoulder and to both arms (especially the ulnar surfaces of the forearm and hand), jaw, or back.
- usually crescendo-decrescendo in nature,
- Lasts 2 to 5 min.

- When the patient is asked to localize the sensation, he or she typically places a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (**Levine's sign**).

### UNSTABLE ANGINA & NSTEMI

**Unstable Angina:** typically, chest discomfort is severe and has at least one of three features:

- occurrence at rest (or with minimal exertion),
- lasting >10 min;
- of relatively recent onset (i.e., within the prior 2 weeks); and/or
- a crescendo pattern, i.e., distinctly more severe, prolonged, or frequent than previous episodes.

**NSTEMI:** Unstable Angina + evidence of myocardial necrosis (elevated cardiac biomarkers)

- In both UA & NSTEMI, the chest discomfort radiates to the left arm, left shoulder, and/or superiorly to the neck and jaw.

### STEMI

- In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as:
  - vigorous physical exercise,
  - emotional stress, or
  - a medical or surgical illness.
- Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.
- The **pain** is deep and visceral,
  - heavy, squeezing, and crushing, & occasionally, stabbing or burning
  - Occurs at rest
  - is usually more severe, and lasts longer (<30min)
  - it radiates to the arms (less commonly to the abdomen, back, lower jaw, and neck)
  - It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom.

**ANGINAL “EQUIVALENTS”, i.e., symptoms other than angina:** - are more common in the elderly and in diabetic patients. These are -

- dyspnea
  - nausea
  - epigastric discomfort
  - fatigue
  - faintness
- Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a

patient with angina should be questioned and examined for:

- **peripheral arterial disease:** presents with,
- Intermittent claudication
  - **stroke, or transient ischemic attacks:** symptoms include:
- Loss of sensory/motor function,
- Change in vision, gait, ability to speak or understand,
- Severe headache

## CLINICAL CLASSIFICATION OF CHEST PAIN

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ACC/AHA/ACP-ASIM Practice Guidelines

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### Typical angina (definite)

(1) Substernal chest discomfort with a characteristic quality and duration that is (2) provoked by exertion or emotional stress and (3) relieved by rest or nitroglycerin

### Atypical angina (probable)

Meets 2 of the above characteristics

### Noncardiac chest pain

Meets  $\leq 1$  of the typical angina characteristics

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## CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (SEVERITY OF ANGINA)

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### Class I

- Ordinary physical activity does not cause angina, such as walking, climbing stairs.

### Class II

- Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals

### Class III

- Marked limitations of ordinary physical activity. Angina on walking one to two blocks on the level and climbing one flight of stairs

#### Class IV

- Inability to carry on any physical activity without discomfort—anginal symptoms at rest.

#### COMPLICATIONS OF MYOCARDIAL INFARCTION

Early (in 2-3 days)	Late
Arrhythmias	MR
Cardiac failure	Rupture of ventricular septum or wall
Heart block	Dressler's syndrome
Pericarditis	Ventricular aneurysm
Myocardial rupture	Recurrent arrhythmias
Thromboembolism	Thromboembolism

#### PHYSICAL EXAMINATION

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##### Stable Angina:

- P/E is often normal when the patients are asymptomatic.
- in patients with diabetes and/or peripheral arterial disease (PAD), search for evidence of atherosclerotic disease at other sites, such as:
  - Abdominal aortic aneurysm,
  - Carotid arterial bruits, and
  - Diminished arterial pulses in the lower extremities.
- Evidence for PAD:**
  - Evaluate the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (**ankle-brachial index**).
- CVS examination**
  - Palpation** may reveal:
    - cardiac enlargement
    - abnormal contraction of the cardiac impulse
  - Auscultation:**
    - arterial bruits,
    - S3 &/or S4
    - If acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation.
- Exam. of the fundi:** look for evidence of hypertension like:

- an increased light reflex &
- Arteriovenous nicking as.
- There also may be **signs of:**
  1. Anaemia,
  2. Thyroid disease, and
  3. Nicotine stains on the fingertips from cigarette smoking.
- It is **unlikely** that the pain is caused by myocardial ischemia if there is:
  - Tenderness of the chest wall,
  - Localization of the discomfort with a single fingertip on the chest, or
  - Reproduction of the pain with palpation of the chest.
- A **protuberant abdomen** may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

### Unstable Angina & NSTEMI

- P/E resembles that in patients with stable angina.
- If the patient has a large area of myocardial ischemia or a large NSTEMI, the **physical findings** can include:
  1. Diaphoresis
  2. Pale, cool Skin
  3. Sinus tachycardia
  4. S<sub>3</sub> &/or S<sub>4</sub>
  5. Basilar Rales; and,
  6. sometimes, Hypotension

### STEMI

- Most patients are anxious and restless,
  - To relieve the pain by moving about in bed, altering their position, and stretching.
- **Pallor** associated with perspiration
- **coolness** of the extremities
- Temperature elevations up to 38°C may be observed in the 1st week after STEMI.
- **Tachycardia** and/or Hypertension (in 25% of patients)
- **Bradycardia** and/or Hypotension (in 50% of patients)
- The precordium is usually quiet, and the apical impulse may be difficult to palpate.
- other **physical signs of ventricular dysfunction** include:
  - S<sub>3</sub> & S<sub>4</sub>
  - Distant S<sub>1</sub>, and
  - Paradoxical splitting of S<sub>2</sub>.

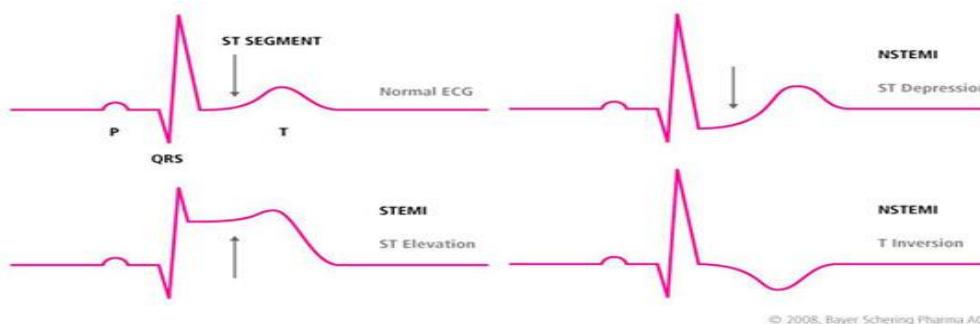
- Pericardial friction rub

## INVESTIGATIONS

The best first line investigation is **ECG**. Then Cardiac biomarkers, particularly of High-sensitivity Troponin (hs-Trop).

### ECG

- ST-segment, T-wave & Q-wave changes,
  - ddx of ST-segment elevations are: -
    - Ischemia/myocardial infarction
    - Acute pericarditis
    - Normal variants (including benign “early repolarization” patterns)
    - Left ventricular hypertrophy/left bundle branch block
    - Other (rarer):
      - **Acute pulmonary embolism**
      - Class 1C antiarrhythmic drugs
      - Hypercalcemia
      - **Hyperkalemia**
      - Hypothermia
      - Nonischemic myocardial injury (like Myocarditis and trauma to the ventricles.
      - left ventricular hypertrophy
      - disturbances of cardiac rhythm or intraventricular conduction



## SERUM CARDIAC BIOMARKERS

- High-sensitivity Troponin (hs-Trops), Troponin I & T: are more specific and sensitive marker of Myocardial Necrosis

- May remain elevated for 7–10 days after STEMI
- Minor troponin elevations have been reported and can be caused by:
  - CHF, Myocarditis, Pulmonary Embolism, or they may be false-positive readings.
- CK-MB: Rises within 4–8 hr and generally returns to normal by 48–72 hr. CK may be elevated with: Skeletal muscle disease or trauma, including intramuscular injection
  - Myoglobin
  - LDH

### ECHOCARDIOGRAPHY

- left ventricular (LV) function
- global and regional wall motion abnormalities of the LV
- RV infarction
- ventricular aneurysm
- pericardial effusion
- LV thrombus
- ventricular septal defect
- valve abnormalities (ex. MR)

### URINALYSIS

- For evidence of DM and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis.

### EXAMINATION OF BLOOD

- lipid profile (cholesterol—total, LDL, HDL and triglycerides)
- glucose (haemoglobin A<sub>1c</sub>),
- creatinine
- haematocrit
- TFT (if indicated based on the P/E)

### HIGH-SENSITIVITY CRP

- Elevated level (specifically, between 0 and 3 mg/dl):
  - Is an independent **risk factor** for IHD
- Useful in therapeutic decision making about the initiation of hypolipidemic treatment
- Used in reclassifying the risk of IHD in patients in the "intermediate" risk category on the basis of traditional risk factors.

### NONSPECIFIC INDICES OF TISSUE NECROSIS AND INFLAMMATION

#### WBC count

- Polymorphonuclear leucocytosis:

- nonspecific reaction to myocardial injury
- appears within a few hours after the onset of pain
- persists for 3–7 days

#### **ESR**

- rises more slowly than the WBC count
- peaks during the 1<sup>st</sup> week
- sometimes remains elevated for 1-2 weeks

#### **CHEST X-RAY**

- It may show the consequences of IHD, i.e.,
- Cardiac enlargement,
- Ventricular aneurysm, or
- Signs of heart failure.

#### **CORONARY ARTERIOGRAPHY**

- Outlines the lumina of the coronary arteries
- To detect or exclude serious coronary obstruction

#### **CARDIAC CATHETERIZATION**

- To assess signs of left ventricular dysfunction, which are associated with a poor prognosis. Most important signs are:
- Elevations of left ventricular end-diastolic pressure and ventricular volume
- Reduced ejection fraction

#### **CT**

- For detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis.

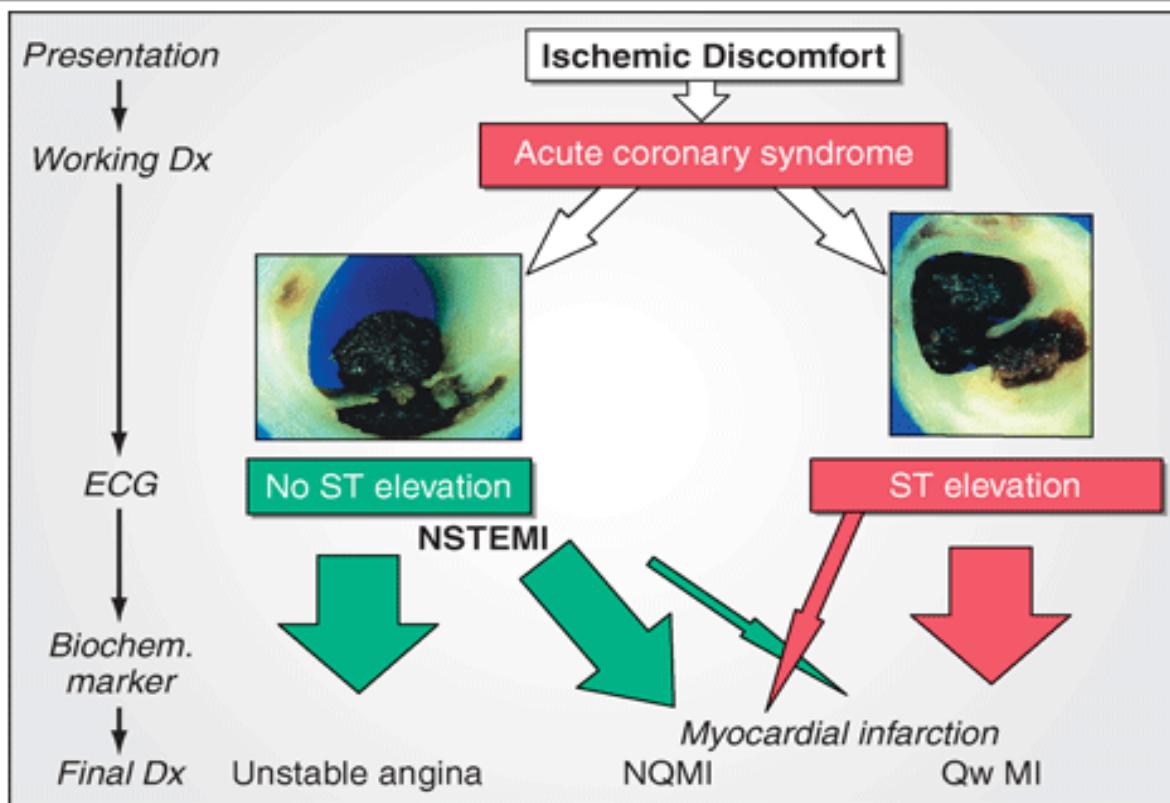
#### **HIGH-RESOLUTION CARDIAC MRI**

- for ventricular evaluation

#### **STRESS TEST**

- Used for diagnosis of IHD and the estimation of risk and prognosis.
- involves recording the 12-lead ECG before, during, and after exercise, usually on a treadmill.
- is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort.

#### **Work-up algorithm of ACS**



## MANAGEMENT PRINCIPLES

### Standard of care for patients with CCS (Stable Angina)

- Risk factor modification
  - Smoking cessation
  - Blood pressure control: Refer Hypertension protocol
  - Dyslipidemia management: Refer Dyslipidemia protocol
  - Obesity: weight loss modifies other risk factors (diabetes, HTN, and hyperlipidemia) and provides other health benefits.
  - Exercise: it minimizes emotional stress, promotes weight loss, and helps reduce other risk factors.
  - Diet: Reduce intake of **saturated** fat and cholesterol
- Antiplatelet therapy
  - ASA 75-100 mg PO daily
  - Alternative: Clopidogrel 75 mg Po daily
- Beta blocker: chest pain, heart rate and blood pressure control
  - Metoprolol succinate 50-200 mg PO daily

- Alternative: Bisoprolol 2.5-10 mg PO daily
- Statin: Target LDL < 70 mg/dl, dose of statin titrated as per the response
  - Atorvastatin 20-80 mg PO daily
  - Alternative: Rosuvastatin 5-20 mg PO daily
- Angina management
  - Betablockers: see above
  - Calcium channel blockers
    - Amlodipine 2.5-10 mg PO daily for those with hypertension
  - Nitrates
    - Nitroglycerine 0.4 mg sublingual tablets for acute relief
    - Isosorbide di nitrate 2.5-20 mg PO single dose or divided doses as needed
  - Trimetazidine 35 mg Po daily
- Review risk factor, symptoms and indication for revascularization
- Refractory cases: Refer patients for Cardiologist evaluation

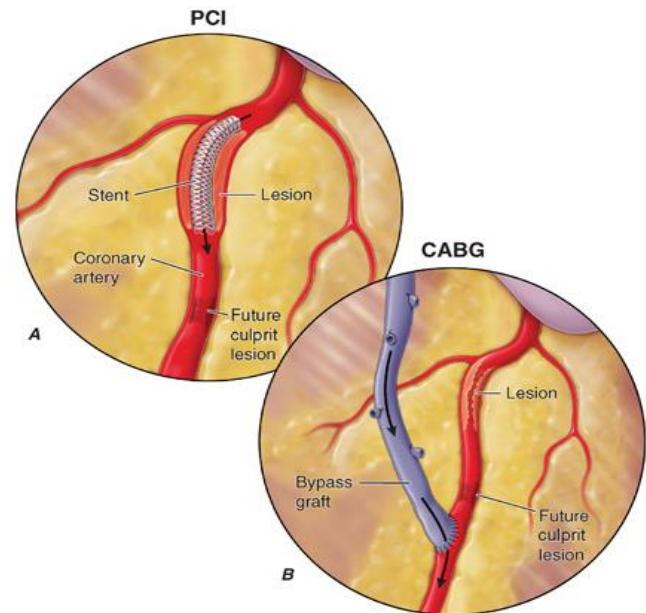
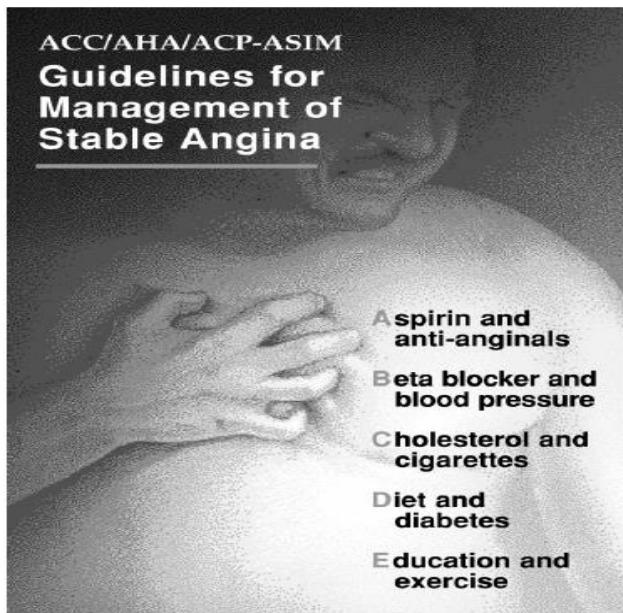
#### TREATMENT OF UNSTABLE ANGINA

- Hospital admission with continuous cardiac monitoring.
- Establish IV access.
- Give supplemental oxygen if patients are hypoxic (SpO<sub>2</sub> < 90 %).
- Provide pain control:
  - Nitroglycerin: short acting (sublingual or spray): don't give nitrates for patients who took phosphodiesterase inhibitors (sildenafil)
  - Morphine 4 mg IV if pain refractory to nitrate therapy alone.
- Aggressive medical management is indicated: treat as in MI
  - Dual antiplatelet therapy:
    - ASA 300 mg loading followed by 81-100 mg Po daily
  - AND**
  - Clopidogrel 300 mg loading followed by 75 mg Po daily
- β-Blockers:
  - Metoprolol 12.5 mg Po BID and titrate as needed
- Anticoagulation using Heparin for the first five days until ambulation starts
  - Enoxaparin 1 mg/kg SC BID
  - Alternative: Unfractionated Heparin 5000 IU IV loading
  - Followed by 17,500 IU SC BID
- High intensity statin therapy
  - Atorvastatin 80 mg PO daily
- After the acute treatment

- Refer to the next referral facility for further evaluation and treatment optimization.

### TREATMENT OF ACUTE MYOCARDIAL INFARCTION (STEMI AND NSTEMI)

- Early referral to the next level facility OR urgent specialist consultation
- Give ASA 300 mg PO: Advice to chew the tablet
- Revascularization (PCI or CABG), when indicated



### Class I (LOE A) Recommendations for Use of An Early Invasive Strategy in UA/NSTEMI

- Recurrent angina at rest/low-level activity despite Rx
- Elevated TnT or Tnl
- New ST-segment depression
- Rec. angina/ischemia with CHF symptoms, rales, MR
- Positive stress test
- EF < 0.40
- Decreased BP
- Sustained VT
- PCI < 6 months, prior CABG
- High-risk score

## MANAGEMENT SUMMARY

	Noncardiac chest pain	Stable angina	Unstable angina	NSTEMI	STEMI
Clinical finding	Atypical pain	Exertional pain	Rest pain, Post-MI, DM, Prior ASA	Ongoing pain	
ECG		Negative	ST-T wave changes		ST elevation
Cardiac markers		Negative		Positive	
Risk assessment	Low probability	Low risk	High risk		STEMI
Diagnostic rule out MI/ACS pathway	Positive	ASA, clopidogrel, anticoagulant, anti-ischemic therapy Early conservative Rx	ASA+ anticoagulant + ADP inhibitor + IIb/IIIa inhibitor if unstable anti-ischemic therapy Early invasive Rx		Primary PCI Thrombolysis
	Negative				
	Discharge				

## VALVULAR HEART DISEASE

### GLOBAL BURDEN OF VALVULAR HEART DISEASE

- Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health.
- Nevertheless, it can cause significant morbidity and lead to premature death.
- Rheumatic fever is the dominant cause of valvular heart disease in low- and middle-income countries.
- Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some endemic countries.
- Although globally the age standardized mortality rate from rheumatic heart disease declined by nearly 50% between 1990 and 2015, the prevalence of heart failure attributable to rheumatic heart disease increased by nearly 90% over the same time interval.
- The prevalence of valvular heart disease increases significantly with age.
- The prevalence of undiagnosed moderate or severe valvular heart disease is ~6% in individuals aged >65 years.
- Significant left-sided valve disease may affect as many as 12–13% of adults aged >75 years.
- Severe aortic stenosis (AS) is estimated to affect 3.5% of the population aged >75 years.
- AS and mitral regurgitation contributed approximately one-half and one-quarter, respectively, of the valvular heart disease diagnoses in this study.
- The incidence of infective endocarditis has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, the growing epidemic of diabetes mellitus, and the opioid crisis.
- An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction.
- The global burden of valvular heart disease will continue to progress.
- As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented, especially for those patients with rheumatic heart disease in low- and middle-income countries.
- In the Society for Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TAVT) registry, blacks comprise <5% of patients in the United States who have received a transcatheter valve for AS.
- Management decisions and outcome differences based on age, sex, race, and geography require intensification of educational efforts and prioritization of resources

## MITRAL STENOSIS (MS)

- Almost all cases of mitral stenosis are due to rheumatic heart disease.
- Patients are usually asymptomatic until the mitral valve area is reduced to approximately  $1.5 \text{ cm}^2$  (normal valve area is 4 to  $6 \text{ cm}^2$ ).
- The disease is much more common in women (about two-third cases).

### ETIOLOGY

- Rheumatic fever - leading cause (>99%)
- Other less common etiologies:
  - Congenital (parachute valve, cor triatriatum),
  - Severe mitral annular calcification with leaflet involvement,
  - Systemic lupus erythematosus,
  - Rheumatoid arthritis,
  - Left atrial myxoma, and
  - Infective endocarditis with large vegetations.
- Pure or predominant MS occurs in ~40% of all patients with rheumatic heart disease and a history of rheumatic fever

### HISTORY

- Exertional dyspnea, orthopnea and paroxysmal nocturnal dyspnea
- Hemoptysis - results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension.
- Chest pain
- Palpitation
- Hoarseness
- Symptoms of right heart failure like ankle swelling and abdominal swelling (due to ascites)

### PHYSICAL FINDING

#### CVS

- **Inspection**
  - Parasternal pulsation is seen due to RV or forward displacement of the heart by dilated left atrium.
- **Palpation**
  - PMI is not displaced and tapping
  - S1 and P2 (in case of Pulmonary Hypertension) may be palpable
  - Parasternal heave, diastolic thrill

- **Auscultation**

- S1 is accentuated in the early stages of the disease and become soft when valve become immobile due to calcification.
- P2 is accentuated, and the two components of S2 are closely split.
- The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex.
- The OS is followed by *a low-pitched, rumbling, mid diastolic murmur, best heard at the apex with the patient in the left lateral recumbent position but no radiation; it is accentuated by mild exercise carried out just before auscultation = Murmur of MS*
- **Associated Lesions**
  - **Pansystolic murmur:** along left lower sternal border due to Tricuspid regurgitation as result of right ventricular dilation secondary to pulmonary hypertension
  - **Graham Steell murmur:** a high-pitched, diastolic, decrescendo blowing murmur heard at pulmonary area due to functional pulmonary regurgitation as result of pulmonary hypertension.

#### Other systems

- Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

#### INVESTIGATION

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- **ECG**
  - Atrial fibrillation
  - RA and LA enlargement
  - RV hypertrophy
- **Echocardiogram (2D and color doppler)** – Gold standard
  - Severity of stenosis
  - Assess valvular lesion, chamber size (e.g. left atrial chamber is enlarged), LV and RV function, and pulmonary arterial pressure
  - Detect thrombosis in left atrium
- **Chest X-Ray**
  - LA enlargement
  - Prominent Pulmonary vessels
  - pulmonary edema - Kerley B lines

- **CARDIAC CATHETERIZATION**

- can be useful when there is a discrepancy between the clinical and noninvasive findings
- is helpful in assessing associated lesions, such as AS and AR.

## MITRAL REGURGITATION

- This condition is due to inadequate closure of the mitral valve.
- It could be acute or chronic.
- Acute form is associated with much higher mortality

### ETIOLOGIES

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- **Acute**

- Infective endocarditis (IE)
- Papillary muscle rupture (post- myocardial infarction)
- Chordal rupture/leaflet flail (mitral valve prolapse, IE)
- Blunt trauma

- **Chronic**

- Primary (affecting leaflets, chordae)
  - Rheumatic fever – leading cause (in about 50%)
  - Myxomatous (MVP, Barlow's, forme fruste)
  - IE (healed)
  - Congenital (cleft, Atrioventricular canal)
  - Radiation
- Secondary (leaflets, chordae are “innocent bystanders”)
  - Ischemic cardiomyopathy
  - Dilated cardiomyopathy
  - hypertrophic obstructive cardiomyopathy (with systolic anterior motion)
  - Chronic atrial fibrillation with LA enlargement and annular dilatation
- Mitral annular calcification - may include elements of both primary and secondary

### HISTORY

- Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic.
- Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR.
- paroxysmal nocturnal dyspnea
- Hemoptysis and systemic embolization are less common than MS

- Palpitations are common and may signify the onset of AF.
- Symptoms of right heart failure like ankle swelling, and abdominal swelling (due to ascites)

## PHYSICAL FINDING

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### CVS

- **Arterial** – carotid pulse is brisk (sharp) and low in volume, may be irregular due to AF
- **Venous** - JVP is normal unless right heart failure occurs
- **Precordium**
  - **Inspection**
    - The apex beat is often visible outside mid clavicular line(displaced) as a result of left ventricular dilatation
    - Parasternal impulse due to left atrial enlargement
  - **Palpation**
    - PMI is displaced laterally and downwards
    - A systolic thrill is often palpable at apex
    - Palpable P2 in case of pulmonary hypertension.
  - **Auscultation**
    - S1 is soft, due to incomplete apposition of the valve cusps
    - A loud S3 may be present due to sudden rush of blood back into the dilated LV in early diastole
    - **Murmur of MR** = High pitched, Blowing, Grade 3(4), holosystolic murmur (plateau shaped) best heard at apex that radiates to axilla, decrease with inspiration & valsalva
  - **Other systems**
    - Auscultation of lung base may reveal crepitation, if patient is in failure.
    - IE is common in MR than MS, so we have to check signs of endocarditis by palpating liver and spleen and measuring temperature

## INVESTIGATION

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### ECG

- LA enlargement,
- Right atrial (RA) enlargement also may be present when pulmonary hypertension is significant and affects RV function and size.
- Chronic severe MR is frequently associated with AF.
- In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle.

- In others, the signs of eccentric LV hypertrophy are present.

#### **Echocardiogram**

- Shows dilated left atrium (LA) and left ventricle (LV)
- It confirms the diagnosis of MR
- Helps in identification of etiology and Severity of MR

#### **Chest X-Ray**

- Cardiomegaly due to LA and LV enlargement
- Pulmonary hypertension – prominent vascular marking
- Pulmonary edema
- Pleural effusion in case of heart failure

## **MITRAL VALVE PROLAPSE (MVP)**

**Definition:** MVP is mitral valve bulging back into the left atrium during systole

#### **ETIOLOGIES**

- In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined (autosomal dominant form of inheritance with incomplete penetrance).
- MVP is a frequent finding in patients with heritable disorders of connective tissue, including
- Marfan syndrome,
- osteogenesis imperfecta, and
- Ehlers-Danlos syndrome
- MVP also may occur rarely as a sequel to
- acute rheumatic fever,
- ischemic heart disease,
- various cardiomyopathies, and
- ostium secundum atrial septal defect (in 20% of patients)

#### **HISTORY**

- MVP is more common in women and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign.
- MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe and requires surgical treatment.
- Most patients are asymptomatic and remain so for their entire lives.
- In symptomatic patient it presents as chest pain, dyspnea, fatigue, palpitation, syncope and sudden death (reason is unknown)
- Palpitations, lightheadedness, and syncope = due to arrhythmias (atrial or ventricular)

- Many patients have chest pain that is difficult to evaluate; it is often substernal, prolonged, and not related to exertion, but may rarely resemble angina pectoris.
- Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported sudden death

### PHYSICAL FINDING

- BP may be normal or low
- Thoracic deformities are more prevalent in MVP such as kyphosis, pectus excavatum and scoliosis.
- A frequent finding is the mid- or late- (nonejection) systolic click
- Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is “whooping” or “honking” and is heard best at the apex.
- The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver, and with any intervention that decreases LV volume (preload)
- The click and murmur will delay with squatting and isometric exercises which increase LV volume and diminish MVP
- Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

### INVESTIGATION

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- **ECG**
  - most commonly normal but may show arrhythmias such as
    - ventricular premature contractions,
    - paroxysmal supraventricular and ventricular tachyarrhythmia,
    - atrial fibrillation (AF) and
    - sinus node dysfunction or varying degrees of heart block
- **Echocardiography – it is diagnostic**
  - Effective in identifying the abnormal position and prolapse of the mitral valve leaflets
  - It shows one or both mitral valve leaflets bulging by at least 2mm into the left atrium (LA) superior to the plane of the mitral annulus during systole; thickening of involved leaflet to >5mm supports the diagnosis.
  - Doppler echo frequently reveals mild MR that is not always associated with an audible murmur and provide semiquantitative estimates of severity.

## AORTIC STENOSIS (AS)

- occurs in about one-fourth of all patients with chronic valvular heart disease
- It causes obstruction to left ventricular outflow, which results in LVH.
- When the aortic valve area falls below 1 cm<sup>2</sup>, cardiac output fails to increase with exertion, causing angina (but may be normal at rest).

### ETIOLOGIES

- Rheumatic fever – most common cause
- Congenital (bicuspid-53%, unicuspido-4%)
- Degenerative calcification – in elderly (>65yrs), smokers, diabetics, hypertensive, chronic kidney disease patient, patient with metabolic syndrome, and hyperlipidemic.
- Radiation
- SLE and severe familial hypercholesterolemia also occasionally cause AS

### HISTORY

- Long asymptomatic phase
- Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades
- Symptomatic AS manifests as
  - **exertional dyspnea**
  - **angina pectoris**
  - **Exertional syncope**

] the three cardinal symptoms
- Heart failure
- Sudden death
- These symptoms appear when valve orifice has narrowed to ~1 cm<sup>2</sup>
- ~80% of adult patients with symptomatic valvular AS are male.

### PHYSICAL FINDING

#### CVS

- **Pulse:** carotid pulse is low volume and slowly rising called anacrotic pulse
- **Pulse pressure:** narrow in late stage
- **JVP:** prominent ‘a’ wave due to diminished compliance of the RV caused by the bulging, hypertrophied interventricular septum.

- **Precordium**
  - **Inspection**
    - Apical impulse is not displaced, visible on its normal position
  - **Palpation**
    - PMI is not shifted because hypertrophy (in contrast to dilatation) doesn't produce cardiomegaly.
    - A double apical impulse (with a palpable S4) may be recognized, particularly with the patient in the left lateral recumbent position
    - Apical heave, systolic thrill may be in the aortic area or suprasternal notch and is frequently transmitted along the carotid arteries.
  - **Auscultation**
    - S1 is normal or soft
    - S2 is soft because only P2 is audible while A2 is inaudible due to immobility of aortic valve as a result of calcification.
    - Paradoxical splitting of S2
      - Normally during inspiration, splitting of S2 becomes wide but in this case, it becomes narrow during inspiration and wide during expiration due to delayed closure of aortic valve.
    - A prominent S4 - audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure
    - **The murmur of AS:** an ejection (mid) systolic murmur that is low-pitched, rough and rasping in character, best heard at aortic area, radiates to carotid arteries and occasionally to the apex (where it may be confused with the systolic murmur of MR; however, remember that systolic murmur at apex is murmur of MR that is pansystolic while murmur of AS is mid-systolic)

## INVESTIGATION

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- **ECG**
  - LV hypertrophy
  - LV strain due to pressure overload (ST-segment depression and T-wave inversion)- in advanced cases
  - Left atrial enlargement
- **Echocardiogram**
  - Key findings are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy.
  - Eccentric closure of the aortic valve cusps is characteristic of congenitally

bicuspid valves.

- The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity.
  - **Severe AS:** valve area <1 cm<sup>2</sup>,
  - **Moderate AS:** a valve area of 1–1.5 cm<sup>2</sup>
  - **Mild AS:** a valve area of 1.5–2 cm<sup>2</sup>.
- Useful for identifying coexisting valvular abnormalities, differentiating valvular AS from other forms of LV outflow obstruction, and measuring the aortic root and proximal ascending aortic dimensions.
- **Chest X-Ray**
  - Heart is usually normal in size or slightly enlarged
  - Post-stenotic dilatation of ascending aorta on PA view is commonly seen.
- **Catheterization**
  - can be useful when there is a discrepancy between the clinical and noninvasive findings.
  - Catheterization is also useful in three distinct categories of patients:
    - patients with multivalvular disease, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment;
    - young, asymptomatic patients with noncalcific congenital AS, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and
    - patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve but rather at the sub- or supravalvular level.

## AORTIC REGURGITATION

- Also called aortic insufficiency; this condition is due to inadequate closure of the aortic valve leaflets.
- For acute aortic regurgitation, mortality is particularly high without surgical repair

### ETIOLOGIES

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- **Valvular**
  - Congenital (bicuspid)
  - Endocarditis
  - Rheumatic fever
  - Myxomatous (prolapse)
  - Traumatic
  - Syphilis
  - Ankylosing spondylitis
  - SLE
- **Root disease**
  - Aortic dissection
  - Cystic medial degeneration
  - Marfan syndrome
  - Osteogenesis
  - Bicuspid aortic valve
  - Nonsyndromic familial aneurysm
  - Aortitis
  - Hypertension

### HISTORY

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- Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary valvular AR who have associated rheumatic mitral valve disease.
- Patients may remain relatively asymptomatic for as long as 10–15 years.
- Uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint and head pounding
- Exertional dyspnea followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis.
- Anginal chest pain, may develop at rest as well as during exertion, can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin
- Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis.

## PHYSICAL FINDING

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- **General examination**
  - Features of etiology (like, marfan's syndrome, ankylosing spondylitis)
- **Vital sign:** BP – Hill sign
- **HEENT:** De Musset's sign, Miller sign and becker sign
- **CVS**
  - Arterial pulse: Corrigan's pulse, Quincke's pulse
  - **Precordium**
  - **Inspection**
    - Active
    - Apical impulse displaced lateral to midclavicular line
  - **Palpation**
    - PMI is diffuse and shifted laterally and inferiorly
    - Apical heave
    - Diastolic thrill at left sternal border ( $3^{\text{rd}}$  ICS, A2 area) – when patient sits, leans forward and expires.
    - Prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries.
  - **Auscultation**
    - Soft S1 due to prolonged PR interval
    - S2 may be single or absent (A2 may be soft or absent, P2 may be obscured by diastolic murmur)
    - occasionally an S4 also may be heard
    - **Murmur of AR:** *high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border with the patient sitting up, leaning forward, and with the breath held in forced expiration.*
    - A mid-systolic ejection murmur is frequently audible in isolated AR which generally heard best at the base of the heart and is transmitted along the carotid arteries.
    - **Austin Flint murmur:** a soft, low-pitched, rumbling mid-to-late diastolic murmur best heard at apex. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream (functional MS) and is not associated with hemodynamically significant mitral obstruction.

- **Abdomen**
  - Rosenbach sign: liver
  - Gerhard sign: spleen
  - Traube's sign, and Duroziez's sign: femoral artery

## INVESTIGATION

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- **ECG**
  - LV hypertrophy
  - LV strain (ST-segment depression and T-wave inversion)- in advanced cases
  - Left-axis deviation and/or QRS prolongation denote diffuse myocardial disease, generally associated with patchy fibrosis, and usually signify a poor prognosis
- **Echocardiography**
  - Detection AR
  - Assessment cause, severity and hemodynamic effects (LV size and LV hypertrophy)
  - Accurate assessment of aortic size and contour.
- **Chest X-Ray**
  - LV enlargement and ascending aorta dilatation.

## TRICUSPID STENOSIS

- It is frequently associated with mitral or aortic valve disease

### ETIOLOGIES

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- Rheumatic – in majority of case
- Congenital

### HISTORY

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- is more common in women than men
- Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion (dyspnea on exertion, orthopnea, PND) and fatigue.
- Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have.
- Abdominal pain (due to hepatomegaly) and swelling (due to ascites) and peripheral edema

## PHYSICAL FINDING

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- JVP: giant “a” wave
- **Murmur of TS:** mid diastolic murmur at tricuspid area (left lower sternal border), loud on inspiration.
- Hepatomegaly, presystolic pulsations of the enlarged liver, edema

## INVESTIGATION

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### ECG

- RA enlargement
- The absence of ECG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease.

### ECHOCARDIOGRAPHY

- The tricuspid valve is usually thickened and domes in diastole
- The transvalvular gradient can be estimated routinely by continuous wave Doppler echocardiography
- Assess severity
- Severe TS is characterized by a valve area  $\leq 1 \text{ cm}^2$  or pressure half-time of  $\geq 190 \text{ ms}$
- provides additional information regarding mitral valve structure and function, LV and RV size and function, and PA pressure

### CHEST X-RAY

- in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS
- engorgement of the azygos vein can often be appreciated

## TRICUSPID REGURGITATION

### ETIOLOGIES

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#### Primary (organic)

- Rheumatic
- Endocarditis
- Myxomatous (tricuspid valve prolapse (TVP))
- Carcinoid
- Radiation
- Congenital (Ebstein's)
- Trauma
- Papillary muscle injury (post- myocardial infarction (MI))

**Secondary (functional)** – in > 80%

- RV and tricuspid annular dilatation due to multiple causes of RV enlargement (e.g., longstanding pulmonary HTN, remodeling post-RV MI, left-sided valve disease, cardiomyopathy, AF)
- Chronic RV apical pacing

**HISTORY**

- Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances.
- Because TR most often coexists with left-sided valve lesions, LV dysfunction, and/or PA hypertension, symptoms related to these lesions may dominate the clinical picture.
- Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR.
- As the disease progresses and RV function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

**PHYSICAL FINDINGS**

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- **CVS**
  - The neck veins are distended with prominent c-v waves and rapid y descents, TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds.
  - Right ventricular heave (parasternal)
  - **Murmur of TR:** blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo's sign) (unlike MR which intensified during expiration).
- **Other systems**
  - marked hepatomegaly, ascites, pleural effusions, edema, systolic pulsations of the liver, and a positive hepatojugular reflex.

**INVESTIGATION**

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- **ECG**
  - RV myocardial infarction, RV Hypertrophy, or a bizarre right bundle branch block-type pattern with preexcitation in patients with Ebstein's anomaly
  - RA enlargement
  - AF is frequently noted

- **Echocardiography**
  - RV dilatation
  - Abnormal tricuspid valve may be present.
  - Estimation of pulmonary artery pressure from Doppler echocardiography.
- **Chest X-Ray**
  - RA and RV enlargement, depending on the chronicity and severity of TR.

## RHEUMATIC HEART DISEASE

- Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age-groups, accounting for up to 50% of all cardiovascular disease and 50% of all cardiac admissions in many developing countries.
- Rheumatic involvement of the cardiac valves is the most important sequela of acute rheumatic fever (ARF) and also the 2nd most common major manifestation after arthritis.
  - The mitral valve is affected most often, followed in frequency by the aortic valve.
  - Isolated aortic valve disease is rare and generally seen with concomitant mitral valve involvement.
  - Right-sided heart manifestations are quite rare and are virtually only associated with left-sided valve disease.
- The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of 1 or more of the heart valves.
- As the inflammation subsides, the verrucae tend to disappear and leave scar tissue
- With repeated attacks of rheumatic fever, new verrucae form near the previous ones, and the mural endocardium and chordae tendineae become involved.
- A single episode of acute rheumatic carditis often results in complete healing of the valvular lesions, while repeated episodes, especially involving previously affected valves, result in chronic rheumatic heart disease (RHD), which is the rationale for secondary prophylaxis.
- Chronic rheumatic heart disease results from single or repeated attacks of rheumatic fever that produce:
  - Rigidity and deformity of valve cusps,
  - Fusion of the commissures, or
  - shortening and fusion of chordae tendinae.
- The diagnosis of ARF requires the fulfillment of the Jones criteria (see under acute rheumatic fever portion), with carditis being a major criterion.
  - Previously, the diagnosis of RHD was based on cardiac auscultatory findings of

- mitral or aortic valve involvement, which was insensitive for early valve injury.
- This was based on endocarditis or valvulitis being seen more frequently in ARF compared with pericarditis or myocarditis, both of which lack more readily apparent physical examination findings.
  - Screening large, high-risk populations with echocardiography demonstrated a substantially greater number of patients with RHD than those detected by auscultation alone.
  - Because access to echocardiography is often available, the current version of the Jones Criteria focused on the concept of subclinical carditis (SCC) detected by echocardiography.
  - SCC is defined as echocardiographic evidence of mitral or aortic valvulitis in the absence of auscultatory findings and not consistent with physiologic mitral or aortic insufficiency.
  - Echocardiography with Doppler should be performed for all cases of confirmed or suspected ARF.
  - Additional recommendations are that echocardiography should be performed in moderate- to high-risk patient populations if ARF is considered likely, and that echocardiography can be used to exclude cardiac findings consistent with ARF in patients with cardiac murmurs thought to be suggestive of rheumatic carditis.
  - Additionally, serial echocardiography should be considered in patients with diagnosed or suspected ARF even if there is no evidence of valvulitis by echocardiography at diagnosis.
  - The echocardiographic finding of SCC now fulfills the major criterion for carditis.

**Table: Echocardiographic Findings in Rheumatic Valvulitis**

PATHOLOGIC MITRAL REGURGITATION*	PATHOLOGIC AORTIC REGURGITATION*
1. Seen in at least 2 views	1. Seen in at least 2 views
2. Jet length $\geq 2$ cm in at least 1 view	2. Jet length $\geq 1$ cm in at least 1 view
3. Peak velocity $> 3$ meters/sec	3. Peak velocity $> 3$ meters/sec
4. Pan-systolic jet in at least 1 envelope	4. Pan-diastolic jet in at least 1 envelope

\*All 4 criteria need to be met.

## HYPERTENSIVE HEART DISEASE

- Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias, including atrial fibrillation.
- Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death.
- Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease.
- CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two.
- Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients.
- Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function.
- Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia

## HISTORY

### SYMPTOMS

- Most patients are asymptomatic
- headache (which occurs in the morning and is localized to occipital region), dizziness, palpitation, easy fatigability and impotence
- Somnolence, confusion, visual disturbances, nausea and vomiting: *hypertensive encephalopathy*
- Symptoms of Heart failure: like dyspnea, orthopnea, PND and body swelling
- Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure
- Evidence of target organ damage: history of **congestive heart failure**, transient ischemic attack, stroke, transient blindness; angina, myocardial infarction; sexual function
- Duration of hypertension for known hypertensive patient

### RISK FACTORS

- Previous therapies: responses and side effects
- Family history of hypertension and cardiovascular disease
- Dietary and psychosocial history

- Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity

## PHYSICAL FINDINGS

- General Appearance
  - Look for evidence of associated disease such as: round face and truncal obesity of Cushing's syndrome
  - Muscular development in upper extremities more than lower extremities suggesting coarctation of aorta
  - Acromegaly, polycythemia and uremia
- Measure BMI
- Pulse: Feel radial pulse and examine for radiofemoral delay and radioradial asymmetry, Quality of femoral and pedal pulses
- Blood pressure: take BP from both arms, and with patient Supine and standing (A rise in diastolic BP on standing occurs typically in essential HTN; a fall in BP on standing may suggest a secondary cause)
- Arteries: auscultation of carotid and femoral arteries for bruit
- Eye: inspect conjunctiva for congestion (polycythemia), Funduscopic examination of retina.
- Neck: hypo or hyperthyroidism
- Examination of precordium
  - Prominent apical heave: LV hypertrophy
  - Loud S<sub>2</sub> due to closure of the aortic valve
  - Displaced apical impulse: LV hypertrophy -> Ischemic dilated cardiomyopathy
  - S<sub>4</sub> gallop secondary to atrial contraction against a non-compliant LV
- Auscultation of chest
  - Basal crepitation (for heart failure)
- Abdomen
  - Palpate for renal or adrenal mass and aortic aneurysm
  - Auscultate for renal bruit
- Other signs
  - Signs of previous stroke
  - Pedal edema

## INVESTIGATION

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- **Initial evaluation**
  - **Urine analysis:** proteinuria, hematuria and casts; signifying primary renal disease
  - **Hematocrit:** to detect polycythemia
  - **Serum urea and creatinine:** renal failure may be the cause or consequence of hypertension.
  - **Serum potassium:** low serum level is typical of hyperaldosteronism.
  - **Fasting blood sugar:** DM is risk factor
  - **Lipid profile:** dyslipidemia is risk factor
  - **Serum uric acid:** because hyperuricemia is a relative contraindication of diuretic therapy.
  - **ECG:** LV hypertrophy and strain pattern
- **Additional investigation**
  - **Chest X-Ray**
    - Cardiomegaly
  - **Echocardiography**
    - LV hypertrophy

## CARDIOMYOPATHIES

### DEFINITION AND CLASSIFICATION

**Cardiomyopathies** are defined as “disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype.”

It excludes cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension.

**ISCHEMIC CARDIOMYOPATHY** - diffuse dysfunction occurring in the presence of multivessel coronary artery disease.

**Non-ischemic cardiomyopathy** - cardiomyopathy from other causes.

Many cardiomyopathies are attributable to genetic disease.

### TRADITIONAL CLASSIFICATION OF CARDIOMYOPATHIES

- Based initially on autopsy specimens and later on echocardiographic findings.
  1. Dilated
  2. Restrictive
  3. Hypertrophic

**Dilated and hypertrophic cardiomyopathies** can be distinguished on the basis of left ventricular wall thickness and cavity dimension;

#### Restrictive cardiomyopathy

- can have variably increased wall thickness and chamber dimensions.
- It is now defined more on the basis of abnormal diastolic function.
- can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies.

### GENERAL PRESENTATION

For all cardiomyopathies, the early symptoms often relate to exertional intolerance with breathlessness or fatigue, usually from inadequate cardiac reserve during exercise.

#### Presentation with Symptomatic Cardiomyopathy

	Dilated	Restrictive	Hypertrophic
<b>Ejection fraction (normal 55%)</b>	Usually <30% when symptoms severe	25-50%	>60%
<b>Left ventricular diastolic dimension (normal &lt;55 mm)</b>	60 mm	>60 mm (may be decreased)	Often decreased
<b>Left ventricular wall</b>	Decreased	Normal or increased	Markedly increased

thickness			
Atrial size	Increased	Increased; may be massive	Increased; related to abnormal
Valvular regurgitation	Related to annular dilation; mitral appears earlier, during decompensation; tricuspid regurgitation in late stages	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation

Features	Dilated	Restrictive	Hypertrophic
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early	Exertional intolerance; may have chest pain
Congestive symptoms*	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion may develop late
Arrhythmia	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

\*Left-sided symptoms of pulmonary congestion; dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea.

Right-sided symptoms of systemic versus congestion: discomfort on bending, hepatic and abdominal distention, peripheral edema.

## APPROACH

### Initial Evaluation of Cardiomyopathy

#### Clinical Evaluation

- Thorough history and physical examination to identify cardiac and noncardiac disorders
- Detailed family history of heart failure, cardiomyopathy, skeletal myopathy,

- conduction disorders and tachyarrhythmias, sudden death
- History of alcohol, illicit drugs, chemotherapy or radiation therapy
- Assessment of ability to perform routine and desired activities
- Assessment of volume status, orthostatic blood pressure, body mass index

## **LABORATORY EVALUATION**

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- ECG
- CXR
- Two-dimensional and Doppler echo
- Chemistry:
  - Serum sodium, potassium, calcium, magnesium
  - Fasting glucose (glycohemoglobin in DM)
  - Creatinine, blood urea nitrogen
  - Albumin, total protein, LFT
  - Lipid profile
  - TSH
  - Serum iron, transferrin saturation
  - Urinalysis
  - Creatine kinase
- Hematology:
  - Hgb/Hct
  - WBC count with differential, including eosinophils
  - ESR

## **Initial Evaluation Only in Patients Selected for Possible Specific Diagnosis**

- Titers for infection in presence of clinical suspicion:
  - Acute viral (coxsackie virus, echovirus, influenza virus)
  - Human immunodeficiency virus,
  - Chagas' disease, Lyme disease, toxoplasmosis
- Catheterization with coronary angiography in patients with angina who are candidates for intervention
- Serologies for active rheumatologic disease
- Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
- Screening for sleep-disordered breathing

## DILATED CARDIOMYOPATHY

An enlarged left ventricle with decreased systolic function as measured by left ventricular ejection fraction.

Has multiple etiologies:

- Up to one-third of cases may be familial.
- **Acquired cardiomyopathy** is often attributed to a brief primary injury such as infection or toxin exposure.

**Mitral regurgitation** commonly develops.

## MAJOR CAUSES OF DILATED CARDIOMYOPATHY

### A. INFLAMMATORY MYOCARDITIS

- **Infective**
  - Viral (Coxsackie, adenovirus, HIV, hepatitis C)
  - Parasitic (*T. cruzi*—Chagas' disease, toxoplasmosis)
  - Bacterial (diphtheria)
  - Spirochetal (*Borellia burgdorferi*—Lyme disease)
  - Rickettsial—(Q fever)
  - Fungal (with systemic infection)
- **Noninfective**
  - Granulomatous inflammatory disease
    - Sarcoidosis
    - Giant cell myocarditis
  - Hypersensitivity myocarditis
  - Polymyositis, dermatomyositis
  - Collagen vascular disease
  - Peripartum cardiomyopathy
  - Transplant rejection

### B. TOXIC

- Alcohol
- Catecholamines: amphetamines, cocaine
- Chemotherapeutic agents: (anthracyclines, trastuzumab)
- Interferon
- Other therapeutic agents (hydroxychloroquine, chloroquine)
- Drugs of misuse (emetine, anabolic steroids)
- Heavy metals: lead, mercury
- Occupational exposure: hydrocarbons, arsenicals

### C. METABOLIC

- Nutritional deficiencies: thiamine, selenium, carnitine
- Electrolyte deficiencies: calcium, phosphate, magnesium
- Endocrinopathy:
- Thyroid disease
- Pheochromocytoma
- Diabetes
- Obesity
- Hemochromatosis

### D. Inherited Metabolic Pathway Defects

- **Familial:**
  - Skeletal and cardiac myopathy
  - Dystrophin-related dystrophy (Duchenne's, Becker's)
  - Mitochondrial myopathies (e.g., Kearns-Sayre syndrome)
  - Arrhythmogenic ventricular dysplasia
  - Hemochromatosis
  - Associated with other systemic diseases
  - Susceptibility to immune-mediated myocarditis

### E. Peripartum Cardiomyopathy

- Develops during the last trimester or within the first 6 months after pregnancy
- inflammation has been implicated.
- Risk factors are:
  - increased maternal age,
  - increased parity,
  - twin pregnancy,
  - malnutrition,
  - use of tocolytic therapy for premature labor, and
  - preeclampsia or toxemia of pregnancy.

## TREATMENT

Treatment of restrictive cardiomyopathy is directed toward the specific etiologic agent. Symptomatic management is always considered.

## RESTRICTIVE CARDIOMYOPATHY

- It is the least common of the triad of cardiomyopathies.
- Dominated by abnormal diastolic function.
- **Both atria are enlarged**, sometimes massively.
- **Subtle exercise intolerance** is usually the first symptom.
- It often presents with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites.
- A fourth heart sound is more common.
- JVP may increase during inspiration (positive Kussmaul's sign).

## CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

- **Amyloidosis** is the major cause of restrictive cardiomyopathy

Infiltrative (Between Myocytes)
Amyloidosis <ul style="list-style-type: none"> <li>- Primary (light chain amyloid)</li> <li>- Familial (abnormal transthyretin)</li> <li>- Senile (normal transthyretin or atrial peptides)</li> </ul>
Inherited metabolic defects
Storage (Within Myocytes)
Hemochromatosis (iron)
Inherited metabolic defects <ul style="list-style-type: none"> <li>- Fabry's disease</li> </ul>
Glycogen storage disease (II, III)
Fibrotic
Radiation
Scleroderma
Endomyocardial
Possibly related fibrotic diseases <ul style="list-style-type: none"> <li>- Tropical endomyocardial fibrosis</li> </ul>
Hypereosinophilic syndrome (Löffler's endocarditis)
Carcinoid syndrome
Radiation
Drugs: e.g., serotonin, ergotamine
Overlap with Other Cardiomyopathies
Hypertrophic cardiomyopathy/"pseudohypertrophic"
"Minimally dilated" cardiomyopathy <ul style="list-style-type: none"> <li>- Early stage dilated cardiomyopathy</li> </ul>
Partial recovery from dilated cardiomyopathy
Sarcoidosis
Idiopathic

## TREATMENT

Treatment of restrictive cardiomyopathy is directed towards the specific etiologic agent.

## HYPERTROPHIC CARDIOMYOPATHY

- It is characterized by marked left ventricular hypertrophy in the absence of other causes, such as hypertension or valve disease.
- It usually presents between the ages of 20 and 40 years.
- **Dyspnea on exertion**
  - is the most common presenting symptom.
- **Chest pain**
  - occurs in more than half of symptomatic patients and is attributed to myocardial ischemia.
- **Palpitations**
  - may result from atrial fibrillation or ventricular arrhythmias.
- The first manifestation of disease may be sudden death from ventricular tachycardia or fibrillation.
- Hypertrophic cardiomyopathy is the most common lesion found at autopsy of young athletes dying suddenly.
- The **physical examination** typically reveals:
  - a harsh murmur heard best at the left lower sternal border
- The **electrocardiogram** usually shows left ventricular hypertrophy.
- The **diagnosis** of hypertrophic cardiomyopathy is confirmed by **echocardiography** demonstrating left ventricular hypertrophy

## TREATMENT

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- Therapy of hypertrophic cardiomyopathy is directed to:
  - symptom management and
  - the prevention of sudden death;
  - it is not known whether treatment will decrease disease progression in
- asymptomatic family members.
- Exertional dyspnea and chest pain are treated by medication to reduce heart rate and ventricular contractility
- Beta-adrenergic blocking drugs and verapamil are most commonly used as initial therapy.
- If there is fluid retention, diuretic therapy.
- Amiodarone - for control of arrhythmias.
- Anticoagulation - to prevent embolic events for patients who have had atrial fibrillation.

- Cardiac surgery can be directed to reduce the size of the upper septum that contributes to the obstruction (myomectomy)
- Cardiac transplantation is considered in fewer than 5% of patients with hypertrophic cardiomyopathy

## PERICARDIAL DISEASE

### NORMAL FUNCTIONS OF THE PERICARDIUM

- The normal pericardium is a double-layered sac of the visceral pericardium and parietal pericardium.
- The visceral pericardium is a serous membrane that is separated from the fibrous parietal pericardium by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma.
- The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, e.g., during exercise.
- It also restricts the anatomic position of the heart and likely retards the spread of infections from the lungs and pleural cavities to the heart.
- Nevertheless, total absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease.
- In partial left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

### CLINICAL CLASSIFICATION

- I. Acute pericarditis (<6 weeks)
  - a) Fibrinous
  - b) Effusive (serous or sanguineous)
- II. Subacute pericarditis (6 weeks to 6 months)
  - a) Effusive-constrictive
  - b) Constrictive
- III. Chronic pericarditis (>6 months)
  - a) Constrictive
  - b) Adhesive (nonconstrictive)

## ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium, has four principal diagnostic features:

### 1) CHEST PAIN

- is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity, autoimmunity, or of unknown cause (idiopathic).
- The pain of acute pericarditis is often severe, retrosternal and/or left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing); however, at times, it is steady, radiates to the trapezius

ridge or into either arm, and resembles that of myocardial ischemia. For this reason, confusion with acute myocardial infarction (AMI) is common. Characteristically, pericardial pain may be intensified by lying supine and relieved by sitting up and leaning forward.

- Pain is often absent in slowly developing tuberculous, postirradiation, neoplastic, and uremic pericarditis.

## 2) A PERICARDIAL FRICTION RUB

- Is audible at some point in the illness in about 85% of patients with acute pericarditis.
- The rub may have up to three components per cardiac cycle and is described as rasping, scratching, or grating; it is heard most frequently at end expiration with the patient upright and leaning forward.

## 3) THE ELECTROCARDIOGRAM (ECG)

- In acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation, and typically evolves through four stages.
  - **In stage 1**, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V<sub>2</sub>–V<sub>6</sub>, with reciprocal depressions only in aVR and occasionally V<sub>1</sub>. In addition, there is depression of the PR segment below the TP segment, reflecting atrial involvement, an early change that may occur prior to ST segment elevation. Usually there are no significant changes in QRS complexes unless a large pericardial effusion develops (see below).
  - **Stage 2** - After several days, the ST segments return to normal, and
  - **Stage 3** - Only then, or even later, do the T waves become inverted.
  - **Stage 4** - Weeks or months after the onset of acute pericarditis, the ECG returns to normal.
- In contrast, in AMI, ST elevations are upwardly convex, and reciprocal depression is usually more prominent; these changes may return to normal within a day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions; by contrast, with acute pericarditis, these changes are usually seen within hours before the ST segments have become isoelectric.

## 4) PERICARDIAL EFFUSION

- is usually associated with pain and/or the ECG changes mentioned above and, if the effusion is large, with electrical alternans .
- Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below).
- Differentiation from cardiac enlargement on physical examination may be difficult,

but heart sounds may be fainter with large pericardial effusion.

- The friction rub and the apex impulse may disappear.
- The base of the left lung may be compressed by pericardial fluid, producing **Ewart's sign**, a patch of dullness, increased fremitus, and egophony beneath the angle of the left scapula.
- The chest roentgenogram may show enlargement of the cardiac silhouette, with a “water bottle” configuration, but may be normal in patients with small effusions.

## DIAGNOSIS

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- **Echocardiography**
  - is the most widely used imaging technique.
  - It is sensitive, specific, simple, and noninvasive; may be performed at the bedside; and allows localization and estimation of the quantity of pericardial fluid.
  - The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium and/or as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall.
- The diagnosis of pericardial fluid or thickening may be confirmed by **computed tomography (CT)** or **magnetic resonance imaging (MRI)**.
  - These techniques may be superior to echocardiography in detecting loculated pericardial effusions, and pericardial thickening, and in the identification of pericardial masses.
  - MRI is also helpful in detecting pericardial inflammation

## TREATMENT

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- There is no specific therapy for acute idiopathic pericarditis, but
  - Bed rest should be recommended, and
  - Ant-inflammatory treatment with aspirin (2–4 g/d) or nonsteroidal anti-inflammatory drugs (NSAIDs), such as
    - ibuprofen (600–800 mg tid) or indomethacin (25–50 mg tid), should be administered along with gastric protection (e.g., omeprazole 20 mg/d).
    - In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks.
- In addition, colchicine (0.5 mg qd [ $<70$  kg] or 0.5 mg bid [ $>70$  kg]) should be administered for 3 months.
  - Colchicine enhances the response to NSAIDs and also aids in reducing the risk of recurrent pericarditis.
  - This drug is concentrated in and interferes with the migration of neutrophils, may

cause diarrhea and other gastrointestinal side effects, and is contraindicated in patients with hepatic or renal dysfunction.

- Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with or do not tolerate NSAIDs and colchicine. However, since they increase the risk of subsequent recurrence, full-dose corticosteroids should be given for only 2–4 days and then tapered.
- Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.
- In patients with multiple, frequent, and disabling recurrences that continue for >2 years, are not prevented by continuing colchicine and other NSAIDs, and are not controlled by glucocorticoids, treatment with azathioprine or anakinra (an interleukin 1 $\beta$  receptor antagonist) has been reported to be of benefit. Rarely, pericardial stripping may be necessary; however, this procedure may not always terminate the recurrences.
- The majority of patients with acute pericarditis can be managed as outpatients with careful follow-up. However, when specific causes (tuberculosis, neoplastic disease, bacterial infection) are suspected, or if any of the predictors of poor prognosis (fever >38°C, subacute onset, or large pericardial effusion) are present, hospitalization is advisable.

## CARDIAC TAMPONADE

**DEFINITION:** is accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles which may be fatal if it is not recognized and treated promptly

- The quantity of fluid necessary to produce this critical state may be:
  - As small as 200 mL, when the fluid develops rapidly
  - >2000 mL, in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume
- Tamponade may also develop more slowly, and in these circumstances the clinical manifestations may resemble those of Heart Failure, including Dyspnea, Orthopnea, and Hepatic Engorgement.
- The three most common causes of tamponade are:
  - Neoplastic Disease,
  - Idiopathic Pericarditis, and
  - Renal Failure.
- It may also result from: tuberculosis, or bleeding into the pericardial space after leakage from an aortic dissection, cardiac operation, trauma, and treatment with anticoagulants.

## HISTORY

- Acute cardiac tamponade — is sudden in onset and life-threatening if not promptly treated.
  - chest pain
  - tachypnea
  - dyspnea
- Subacute cardiac tamponade - is usually a less dramatic process than acute cardiac tamponade.
  - Patients may be asymptomatic early in the course, but once intrapericardial pressure reaches a critical value, they complain of
    - dyspnea,
    - chest discomfort or fullness,
    - peripheral edema,
    - fatigability, or
    - other symptoms referable to increased filling pressures and limited cardiac output.

## PHYSICAL FINDINGS

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- A number of findings may be present depending upon the type and severity of cardiac tamponade, although none of the findings alone are highly sensitive or specific for the diagnosis.
  - The three principal features of tamponade (Beck's triad) are present in only a minority of cases of acute cardiac tamponade
    - Hypotension,
    - Soft or absent heart sounds, and
    - Jugular venous distention with a prominent x (early systolic) descent but an absent y (early diastolic) descent
  - Sinus tachycardia - may indicate significant hemodynamic compromise from cardiac tamponade
  - Kussmaul's sign - the absence of an inspiratory decline in jugular venous pressure
    - not usually seen in cardiac tamponade
  - Pulsus paradoxus — an abnormally large decrease in systolic blood pressure (>10 mmHg) on inspiration.
    - common finding in moderate to severe cardiac tamponade and is the direct consequence of ventricular interdependence.
    - not all patients with cardiac tamponade have pulsus paradoxus (eg, those with chronic hypertension leading to elevated ventricular diastolic

pressures or those with a co-existent atrial septal defect).

- Pericardial rub — due to inflammatory pericarditis.

## INVESTIGATION

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- **Electrocardiography**

- typically shows sinus tachycardia and may also show low voltage.
- If pericarditis is present, the ECG findings typical of that disorder are also seen
- Electrical alternans is characterized by beat-to-beat alterations in the QRS complex.
- is relatively specific but not very sensitive for cardiac tamponade

- **Chest radiograph**

- Cardiomegaly is not usually seen in acute cardiac tamponade since at least 200 mL of pericardial fluid must accumulate before the cardiac silhouette enlarges.
- In general, however, the findings on a chest radiograph are neither sensitive nor specific for the diagnosis of cardiac tamponade.

- **Echocardiography**

- Play major roles in the identification of pericardial effusion and in assessing its hemodynamic significance.
- The following are the major echocardiographic signs of cardiac tamponade, which may not be seen in all patients due to other underlying conditions.
  - Chamber collapse – Collapse of any cardiac chamber, but usually the right sided chambers
  - Respiratory variation in volumes and flows
  - IVC plethora – Dilatation and reduction (<50%) in the diameter of the dilated inferior vena cava (IVC) during inspiration.
  - It is highly sensitive but not at all specific for cardiac tamponade.
  - Hepatic venous flow abnormalities - blunting or frank reversal of diastolic flow with expiration and systolic venous flow predominance

- **Computed tomography (CT) and Cardiovascular magnetic resonance (CMR)**

- are not usually necessary for the evaluation of a pericardial effusion if echocardiography is available.
- findings associated with cardiac tamponade include:
  - pericardial effusion,
  - distention of the venae cavae and hepatic veins,
  - deformity and compression of the cardiac chambers,
  - bowing of the interventricular septum, and

→ reflux of contrast into the azygos vein and inferior vena cava.

- **Cardiac catheterization**
  - not typically performed as the initial diagnostic test
  - can reveal two major findings in patients with cardiac tamponade:
    - equilibration of average intracardiac diastolic pressures (usually between 10 and 30 mmHg) and
    - the inspiratory increase in right-sided pressures and reduction in left-sided pressures that are responsible for pulsus paradoxus.

## DIAGNOSIS

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- Cardiac tamponade is associated with a variety of abnormalities that lead to changes on the electrocardiogram, chest x-ray, and echocardiogram.
- The clinical diagnosis is usually suspected based on the history and physical examination findings, which may include
  - Chest pain
  - Syncope or presyncope
  - Dyspnea and tachypnea
  - Hypotension
  - Tachycardia
  - Peripheral edema
  - Elevated jugular venous pressure
  - Pulsus paradoxus
- The presence of a pericardial effusion on echocardiography with evidence of cardiac chamber collapse, flow variation, or dilation of the inferior vena cava is consistent with, and highly suggestive of, cardiac tamponade.
- However, the diagnosis of cardiac tamponade can only be confirmed by the hemodynamic and clinical response to pericardial fluid drainage.

## MANAGEMENT PRINCIPLE

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- Pericardiocentesis using
  - Apical,
  - Parasternal, or
  - Subxiphoid approach - most commonly
- Surgical drainage through a limited (subxiphoid) thoracotomy - in recurrent tamponade

## CHRONIC CONSTRICTIVE PERICARDITIS

- Constrictive pericarditis is due to progressive thickening, fibrosis and calcification of the pericardium. In effect, the heart is encased in a solid shell and cannot fill properly.
- The calcification may extend into the myocardium, so there may also be impaired myocardial contraction.
- The condition often follows an attack of tuberculous pericarditis (esp in developing country) but can also complicate hemopericardium of different cause, viral pericarditis, rheumatoid arthritis and purulent pericarditis. It is often impossible to identify the original insult.
- The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill owing to the limitations imposed by the rigid, thickened pericardium.
- Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole.
- In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5mmHg of one another).
- Despite these hemodynamic changes, systolic function may be normal or only slightly impaired at rest.
- However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.
- In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic “square root” signs during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies.

### CLINICAL FINDINGS

- Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common.
- The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present.
- Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe.
- The neck veins are distended and may remain so even after intensive diuretic treatment,

and venous pressure may fail to decline during inspiration (Kussmaul's sign).

- The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.
- The pulse pressure is normal or reduced.
- A paradoxical pulse can be detected in about one-third of cases.
- Congestive hepatomegaly is pronounced, may impair hepatic function, and may cause jaundice; ascites is common and is usually more prominent than dependent edema.
- Pleural effusions and splenomegaly may also be present.
- The apical pulse is reduced and may retract in systole (Broadbent's sign).
- The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock) occurring at the cardiac apex with the abrupt cessation of ventricular filling is often conspicuous.
- The condition is sometimes overlooked but should be suspected in any patient with unexplained right heart failure and a small heart calcification.
- In as much as the common physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis.

## INVESTIGATION

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- **ECG**
  - Frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves.
  - Atrial fibrillation is present in about one-third of patients.
- **Chest X-ray** shows
  - a normal or slightly enlarged heart or
  - Pericardial calcification
    - is most common in tuberculous pericarditis.
    - It may, however, occur in the absence of constriction, and constriction may occur without calcification.
- **Transthoracic Echocardiogram**
  - Often shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and
  - A sharp halt to rapid left ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall.
  - There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography.

- During inspiration, there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve, and a leftward shift of the ventricular septum; the opposite occurs during expiration.
- Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration.
- However, echocardiography cannot definitively establish or exclude the diagnosis of constrictive pericarditis; **CT and MRI** are more accurate, with the latter useful in evaluating myocardial involvement.

## TREATMENT

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- Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible.
- Coronary arteriography should be carried out preoperatively in patients aged >50 years to exclude unsuspected accompanying coronary artery disease.
- The benefits derived from cardiac decortication are usually progressive over a period of months.
- The risk of this operation depends on
  - the extent of penetration of the myocardium by the fibrotic and calcific process,
  - the severity of myocardial atrophy,
  - the extent of secondary impairment of hepatic and/or renal function, and
  - the patient's general condition.
- Operative mortality is in the range of 5–10% even in experienced centers; the patients with the most severe disease, especially secondary to radiation therapy, are at highest risk.
- Therefore, surgical treatment should, if possible, be carried out as early as possible.

## SUBACUTE EFFUSIVE-CONSTRICITIVE PERICARDITIS

- This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. As such, it shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction.
- It may be caused by tuberculosis, multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms.
- The heart is generally enlarged, and a paradoxical pulse is usually present.
- After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction.

- Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal.
- The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

### **TUBERCULOUS PERICARDIAL DISEASE**

- This chronic infection is a common cause of chronic pericardial effusion, especially in the developing world where active tuberculosis and HIV are endemic.
- Tuberculous pericarditis may present as pericardial effusion, chronic constrictive pericarditis, or subacute effusive-constrictive pericarditis. The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion.
- It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin.
- If the etiology of chronic pericardial effusion remains obscure despite detailed analysis including culture of the pericardial fluid, a pericardial biopsy, preferably by a limited thoracotomy, should be performed.
- If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy is indicated.
- If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculous therapy, pericardectomy should be performed to prevent the development of constriction.
- Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

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# CHAPTER FOUR

## Liver disease

Introduction

Liver Disease

Chronic liver Disease

### INTRODUCTION

- Liver is largest organ of the body (weighing 1-1.5kg and representing 1.5-2.5% of lean body mass). It receives dual blood supply (20% -oxygen rich blood from hepatic artery and 80% -nutrient rich blood from portal vein)
- **Function includes:**
  - Synthetic function [albumin, carrier protein, coagulation factors, hormone and growth factors]
  - Production of bile and its carrier [bile acid, cholesterol, lecithin, phospholipid]
  - Regulation nutrient [glucose, glycogen, lipid, cholesterol and amino acid]
  - Metabolism and conjugation of lipophilic compound [bilirubin, anion, cathion, drug] for excretion.

### LIVER DISEASE

- Liver disease presents clinically in 3 distinct patterns:
  - Hepatocellular
    - Causes:
      - viral hepatitis,
      - alcoholic liver disease,
      - drugs [isoniazid, acetaminophen]
    - In this case feature of liver injury, inflammation and necrosis predominate.
  - Cholestatic [obstructive]
    - Causes:
      - Gallstone or malignant obstruction
      - Primary biliary cirrhosis
      - Drug induced [methyltestosterone]
    - In this case feature of inhibition of bile flow predominate
  - Mixed
    - Causes:
      - cholestatic form of viral hepatitis

- drug induced [sulfonamide, phenytoin]
- o In this case the feature of both will present.

For this history, physical examination and investigation are important.

## HISTORY

- History of pts with liver disease should focus on symptom of liver disease and on potential risk factors.

## SYMPTOMS

- symptoms of liver dx can be divided in to two:

### 1. Constitutional symptoms:

- fatigue, weakness, nausea, poor appetite, and malaise

### 2. Liver specific symptoms:

- jaundice, dark urine, light stool, itching, abdominal pain, and bloating
- **Nausea** may accompany fatigue or be provoked by odor of food or eating fatty food.
- **Vomiting** can occur but rarely persistent or prominent
- **Diarrhea**- due to lack of bile acids reaching the intestine which lead to steatorrhea [with severe jaundice].
- **Right upper quadrant discomfort or ache** [liver pain-due to stretching of glisson's capsule.]
- **Itching**; appears early in obstructive jaundice and somewhat later in hepatocellular dx
- **Jaundice**; is the hallmark symptom of liver dx and most reliable marker of severity. jaundice is rarely detectable with bilirubin level of <43 mol/l[2.5mg/dl]
- **Darkening** [due to excess conjugated bilirubin in the urine] of urine and lightening of the color of the stools [due to lack bile reaching the intestine] can also occurs.

### NOTE:

Asking the nature of the symptom, pattern of onset, progression is very important.

- For example, fatigue is the most common and most characteristic symptom of liver disease- specifically, fatigue of liver disease arises after activity and rarely present or severe in the morning after adequate resting often intermittent and variable in severity from hr. to hr. and day to day.

### REMEMBER

Evaluation of pts with liver disease should be directed towards:

- Establishing the etiologic diagnosis
- Estimating the dx severity [grading]-active or inactive and mild, moderate, severe
- Establishing the dx stage [staging] –estimating the place in the course of the natural history of the dx [i.e., acute or chronic early or late; precirrhotic, cirrhotic, or end stage].

### RISK FACTORS

- Excess alcohol use [alcoholic liver dx]
- Medication like herbal compounds, birth control pill [drug induced liver dx]
- Sexual activity [HBV, HCV]
- Exposure to jaundiced or high-risk person [ viral hepatitis]
- Injection drug use [HCV]
- Recent surgery [obstructive jaundice]
- Remote or recent blood transfusion [HCV, HBV]
- Occupation
- Family hx of liver dx [alpha1 antitrypsin deficiency, Wilson's dx, hemochromatosis]
- Tattooing and body piercing [HCV, HBV]
- On asking alcoholic history, CAGE questionnaire is helpful to differentiate whether the patient is alcoholic abuse/dependence.
  - if 1 yes - suspect alcohol use problem
  - If>1yes - strong evidence for abuse/dependence

Acronym	Description
C	Have you ever felt you ought to <b>Cut down</b> on your drinking
A	Have people <b>Annoyed</b> you by criticizing your drinking
G	Have you ever felt <b>Guilty</b> or bad about your drinking
E	Have you ever had a drink first thing in morning to steady your nerves or get rid of a hangover ( <b>Eye-opener</b> )

- **Abuse** is defined by a repetitive pattern of drinking alcohol that has adverse effects on social, family, occupational, or health status.
- **Dependence** is defined by alcohol-seeking behavior, despite its adverse effects
- Dependence is the more serious and advanced form of alcoholism

## TIPS

- ☞ Alcohol consumption associated with an increased rate of alcoholic liver disease is probably more than two drinks (22–30 g) per day in women and three drinks (33–45 g) in men.
- ☞ Most patients with alcoholic cirrhosis have a much higher daily intake and have drunk excessively for 10 years before onset of liver disease

## PHYSICAL EXAMINATION

- Typical physical findings in liver disease are;
  - icterus, hepatomegaly, hepatic tenderness, splenomegaly, spider angioma, palmar erythema, and Excoriations.
- Signs of advanced disease include:
  - muscle wasting, ascites, edema, dilated abdominal veins, hepatic fetor, asterixis, mental confusion, stupor, and Coma.
- For detail refer peripheral stigmata of CLD

## INVESTIGATION

- **LIVER FUNCTION TESTS (LFTS)**
  - include the measurement of serum bilirubin, aminotransferases, alkaline phosphatase, gamma-glutamyl transferase and albumin. Most analytes measured by LFTs are not truly ‘function’ tests, but rather provide biochemical markers of liver cell damage. Liver function is best assessed by the serum albumin, prothrombin time and bilirubin. Although abnormalities on LFTs are often non-specific, the patterns are frequently helpful in directing further investigations
- **BILIRUBIN AND ALBUMIN**
  - The degree of elevation of bilirubin reflects the degree of liver damage. A raised bilirubin often occurs earlier in the natural history of biliary disease (e.g., primary biliary cirrhosis) than in disease of the liver parenchyma (e.g., cirrhosis) where the hepatocytes are primarily involved. Serum albumin levels are often reduced in patients with liver disease. This is due to a change in the volume of distribution of albumin, as well as a reduction in synthesis. Since the plasma half-life of albumin is

about 2 weeks, serum albumin levels may be normal in acute liver failure but are almost always reduced in chronic liver failure.

- **ALANINE AMINOTRANSFERASE AND ASPARTATE AMINOTRANSFERASE**

- Both ALT and AST are located in the cytoplasm of the hepatocyte; AST is also located in the hepatocyte mitochondria. Although both transaminase enzymes are widely distributed, expression of ALT outside the liver is relatively low and therefore this enzyme is considered more specific for hepatocellular damage. Large increases of aminotransferase activity favor hepatocellular damage, and this pattern of LFT abnormality is known as ‘hepatitis’.

- **OTHER BIOCHEMICAL TESTS**

- Other widely available biochemical tests may become altered in patients with liver disease
- Hyponatremia occurs in severe liver disease due to increased production of antidiuretic hormone (ADH)
- Serum urea may be reduced in hepatic failure, whereas levels of urea may be increased following gastrointestinal hemorrhage. When high levels of urea are accompanied by raised bilirubin, high serum creatinine and low urinary sodium, this suggests hepatorenal failure, which carries a grave prognosis.

- **ROUTINE HEMATOLOGY**

- Routine hematological investigations are often abnormal in patients with liver disease and can give a clue to the underlying diagnosis:
- A normochromic normocytic anemia may reflect recent gastrointestinal hemorrhage, whereas chronic blood loss is characterized by a hypochromic microcytic anemia secondary to iron deficiency. A high erythrocyte mean cell volume (macrocytosis) is associated with alcohol misuse, but target cells in any jaundiced patient also result in a macrocytosis.
- Leucopenia may complicate portal hypertension and hypersplenism.
- Thrombocytopenia is common in cirrhosis and is due to reduced platelet production, and increased breakdown because of hypersplenism.
- Thrombopoietin, required for platelet production, is produced in the liver and levels fall with worsening liver function.
- Thus, platelet levels are usually more depressed than white cells and hemoglobin in the presence of hypersplenism in patients with cirrhosis.
- A low platelet count is often an indicator of chronic liver disease, particularly in the context of hepatomegaly.

- Thrombocytosis is unusual in patients with liver disease but may occur in those with active gastrointestinal hemorrhage and, rarely, in association with hepatocellular carcinoma.
- **COAGULATION TESTS**
  - Tests of the coagulation system are often abnormal in patients with liver disease.
  - The normal half-lives of the vitamin K-dependent coagulation factors in the blood are short (5–72 hours) and so changes in the prothrombin time occur relatively quickly following liver damage; these changes provide valuable prognostic information in patients with both acute and chronic liver failure.
  - An increased prothrombin time is evidence of severe liver damage in chronic liver disease.
  - Vitamin K does not reverse this deficiency if it is due to liver disease, but will reverse the prothrombin time if due to vitamin K deficiency, as may occur with biliary obstruction due to non-absorption of fat-soluble vitamins.
- **IMMUNOLOGICAL TESTS**
  - A variety of tests are available to evaluate the etiology of hepatic disease.
  - The presence of liver related autoantibodies can be suggestive of the presence of autoimmune liver disease (although false-positive results can occur in non-autoimmune inflammatory disease such as NAFLD).
  - Elevation in overall serum immunoglobulin levels can also indicate autoimmunity (immunoglobulin G (IgG) and IgM).
  - Elevated serum IgA can be seen, often in more advanced alcoholic liver disease and NAFLD, although the association is not specific.

**Table: Chronic liver disease screen**

- |   |
|---|
| <ul style="list-style-type: none"><li>• Hepatitis B surface antigen</li><li>• Hepatitis C antibody</li><li>• Liver autoantibodies (anticentromere antibody, smooth muscle antibody, antimitochondrial antibody)</li><li>• Immunoglobulins</li><li>• Ferritin</li><li>• α<sub>1</sub>-antitrypsin</li><li>• Caeruloplasmin</li></ul> |
|---|

- **ULTRASOUND**
  - Ultrasound is a non-invasive technique most commonly used to identify gallstones and biliary obstruction. It is also very useful in the initial assessment of patients with liver disease to determine whether further, more invasive investigations are

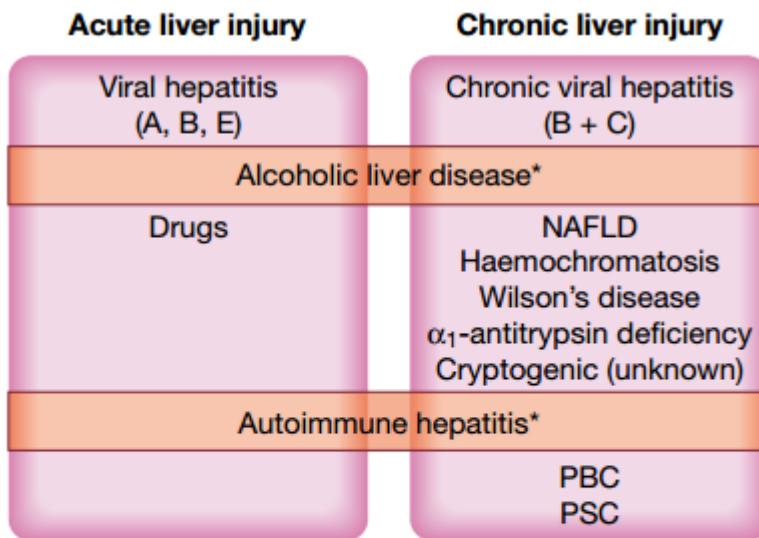
required. Ultrasound is good for the identification of splenomegaly and abnormalities in liver texture. Colour Doppler ultrasound allows blood flow in the hepatic artery, portal vein and hepatic veins to be investigated.

- **CT AND MRI**

- CT can be used for the same purpose as ultrasound but detects smaller focal lesions in the liver, especially when combined with contrast injection. Magnetic resonance imaging (MRI) can also be used to localize and confirm the etiology of focal liver lesions, particularly primary and secondary tumors.

## CHRONIC LIVER DISEASE

- Liver injury may be either acute or chronic
- Acute liver injury may present with non-specific symptoms of fatigue and abnormal LFTs, or with jaundice and acute liver failure.
- Chronic liver injury is defined as hepatic injury, inflammation and/or fibrosis occurring in the liver for more than 6 months.



**Fig. 23.12 Causes of acute and chronic liver injury.** \*Although there is often evidence of chronic liver disease at presentation, may present acutely with jaundice. In alcoholic liver disease this is due to superimposed alcoholic hepatitis (NAFLD = non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis).

- Chronic liver disease consists
  1. Cirrhosis
  2. Hepatocellular ca
  3. Chronic hepatitis

## CIRRHOSIS

- Hepatic cirrhosis is a common disease characterized by diffuse hepatic fibrosis and nodule formation. It can occur at any age, has significant morbidity and is an important cause of premature death.
- World-wide, the most common causes of cirrhosis are chronic viral hepatitis and prolonged excessive alcohol consumption.
- Cirrhosis is the most common cause of portal hypertension and its associated complications.

### What are causes of cirrhosis?

- Any condition leading to persistent or recurrent hepatocyte death, such as chronic hepatitis C infection, may lead to cirrhosis.

**Table: Causes of cirrhosis**

<ul style="list-style-type: none"><li>• Chronic viral hepatitis (B or C)</li><li>• Non-alcoholic fatty liver disease</li><li>• Immune:<ul style="list-style-type: none"><li>▪ Primary sclerosing</li><li>▪ cholangitis</li><li>▪ Autoimmune liver disease</li></ul></li><li>• Biliary:<ul style="list-style-type: none"><li>▪ Primary biliary cholangitis</li><li>▪ Secondary biliary cirrhosis</li><li>▪ Cystic fibrosis</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Genetic:<ul style="list-style-type: none"><li>▪ Haemochromatosis</li><li>▪ Wilson's disease</li><li>▪ α1-antitrypsin deficiency</li></ul></li><li>• Cryptogenic (unknown – 15%)</li><li>• Chronic venous outflow obstruction</li><li>• Any chronic liver disease</li></ul>
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## PATHOPHYSIOLOGY

- The cardinal feature of cirrhosis is an increase in fibrous tissue, progressive and widespread death of liver cells, and inflammation leading to loss of the normal liver architecture.
- Following liver injury, stellate cells in the space of Disse are activated by cytokines produced by Kupffer cells and hepatocytes.
- This transforms the stellate cell into a myofibroblast-like cell, capable of producing collagen, pro-inflammatory cytokines and other mediators which promote hepatocyte damage and cause tissue fibrosis
- Destruction of the liver architecture causes distortion and loss of the normal hepatic vasculature with the development of portosystemic vascular shunts and the formation of nodules.

- Cirrhosis evolves slowly over years to decades, and normally continues to progress even after removal of the etiological agent (e.g., abstinence from alcohol, venesection in haemochromatosis).
- Cirrhosis is a histological diagnosis characterized by diffuse hepatic fibrosis and nodule formation.
- These changes usually affect the whole liver, but in biliary cirrhosis (e.g., primary biliary cirrhosis) they can be patchy.

### CLINICAL FEATURE OF CIRRHOsis

#### SYMPTOMS

- Anorexia, Nausea, Vomiting, Diarrhea,
- Vague RUQ pain,
- Fatigue, weakness,
- Fever, jaundice,
- amenorrhea, impotence, infertility

#### SIGNS (P/E) [peripheral stigmata of CLD]

- **HEENT**
  - icteric sclera [jaundice]
  - Keyser Fleisher rings [willson dx]
- **LGS**
  - lymphadenopathy [2ry to metastasis from HCC]
  - thyroiditis [autoimmune hepatitis]
  - Parotid enlargement [ alcoholic]
  - Gynecomastia [male]
- **CVS**
  - Hemodynamic instability
- **Chest/Respiratory**
  - signs of hepato –pulmonary syndrome [platypnea, orthodeoxia]
  - spider nevi [remember spider nevi present above the nipple line]
  - sign of hepatic hydrothorax[2o to ascites]
- **Abdomen**
  - Ascites
  - Hepatomegaly [early cirrhosis]
  - Hepatic tenderness
  - Hepatic bruits [HCC]

#### NOTE

In CLD patient t if there is hepatomegaly, the DDX are:

- HCC/metastatic tumor
- Alcoholic hepatitis
- Venoocclusive disease
- Infiltrative disease like amyloidosis
- Early in course cirrhosis

- Venus hum [cruveilheirbaumgarten murmur]
- Splenomegaly
- Caputemedosa
- Hernia [ from ascites]

▪ **GUS**

- Urinary system
  - Sign of hepatorenal syndrome [decreased urine output]
  - Dark or coca cola colored urine [conjugated hyper bilirubinemia]
- Genital system
  - Testicular atrophy [male]

▪ **I/S**

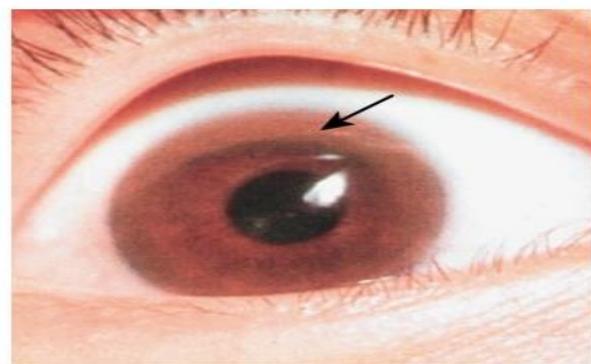
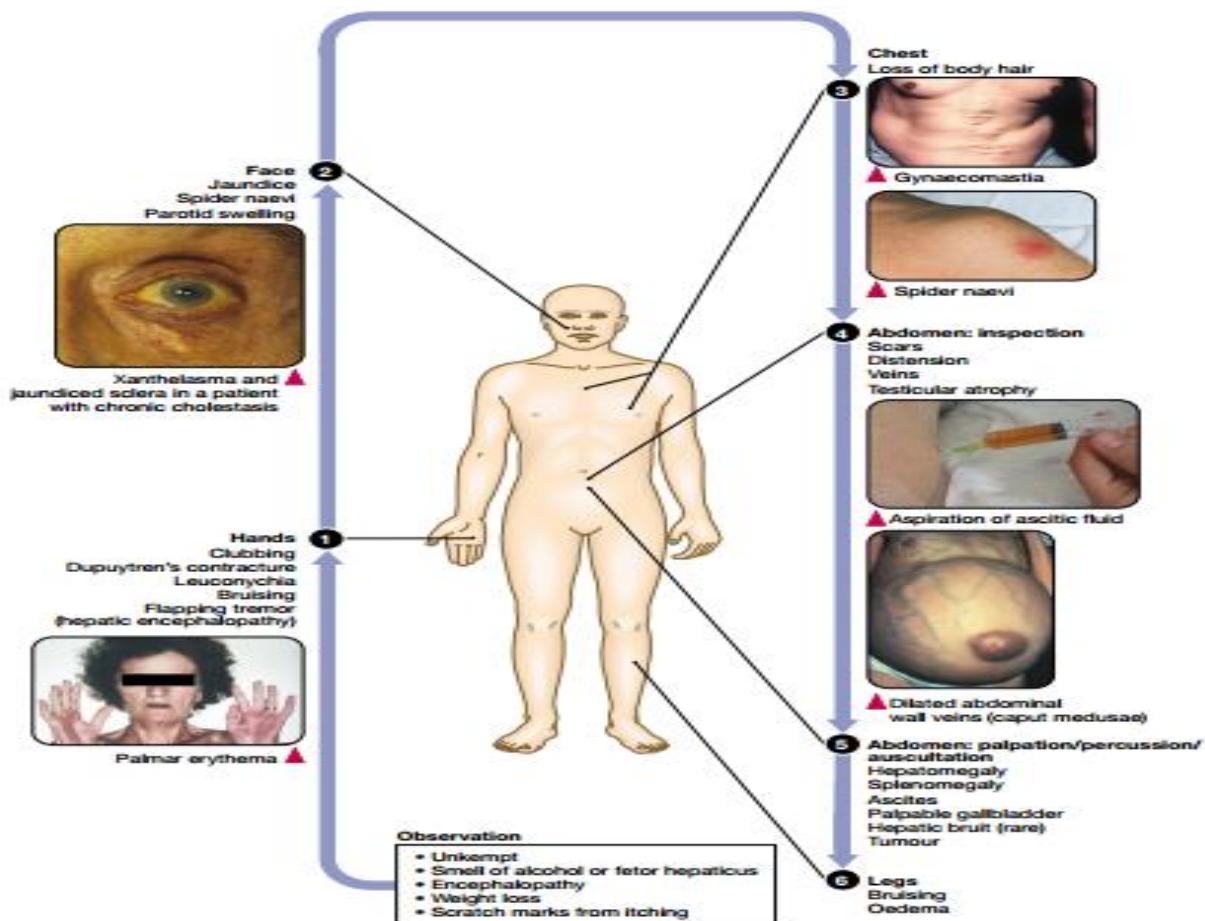
- Skin
  - Palmar erythema
  - Spider angioma
  - Palmar pallor [ 2o to anemia]
  - Xanthelasma and tanthomata[sign of dyslipidemia]
  - Jaundice
  - Excoriation [2o to scratching for pruritus]
- Hair
  - Loss of male hair pattern
- Nail
  - Muehrcke's nail [paired horizontal white band separated by normal color]— due to hypoalbuminemia
  - Terry's nails [characterized by proximal 2/3 of nail is white and distal 1/3 of nail is red]
  - Clubbing [PBC]

▪ **MSS**

- Muscular wasting and cachexia [specially in HCC]
- Peripheral edema
- Thenar and hypothenar atrophy
- Dupuytren's contracture
- Arthropathy [hemochromatosis]

▪ CNS

- Sign of hepatic encephalopathy [refer on complication of cirrhosis]



Kayser–Fleischer rings in Wilson's disease.

## INVESTIGATION

- See under approach to liver disease

## HIGHLIGHT OF CAUSE CIRRHOSIS

- **VIRAL HEPATITIS**

- Viral hepatitis is a common cause of jaundice and must be considered in anyone presenting with hepatitis liver blood tests (high transaminases). The causes are listed in Box All these viruses cause illnesses with similar clinical and pathological features and which are frequently anicteric or even asymptomatic. They differ in their tendency to cause acute and chronic infections

**Table: Causes of viral hepatitis**

Common	
Hepatitis A	Hepatitis C
Hepatitis B ± hepatitis D	Hepatitis E
Less common	
Cytomegalovirus	Epstein–Barr virus
Rare	
Herpes simplex	Yellow fever

The features of the major hepatitis viruses are shown below

**Table: Features of the main hepatitis viruses**

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
<b>Virus</b>					
Group	Enterovirus	Hepadnavirus	Flavivirus	Incomplete virus	Calicivirus
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Size (diameter)	27 nm	42 nm	30–38 nm	35 nm	27 nm
Incubation (weeks)	2–4	4–20	2–26	6–9	3–8

Spread*					
Faeces	Yes	No	No	No	Yes
Blood	Uncommon	Yes	Yes	Yes	No
Saliva	Yes	Yes	Yes	Unknown	Unknown
Sexual	Uncommon	Yes	Uncommon	Yes	Unknown
Vertical	No	Yes	Uncommon	Yes	No
Chronic infection	No	Yes	Yes	Yes	No (except immunocompromised)
Prevention					
Active	Vaccine	Vaccine	No	Prevented by hepatitis B vaccination	No
Passive	Immune serum globulin	Hyperimmune serum globulin	No	-	No

\*All body fluids are potentially infectious, although some (e.g. urine) are less infectious than others.

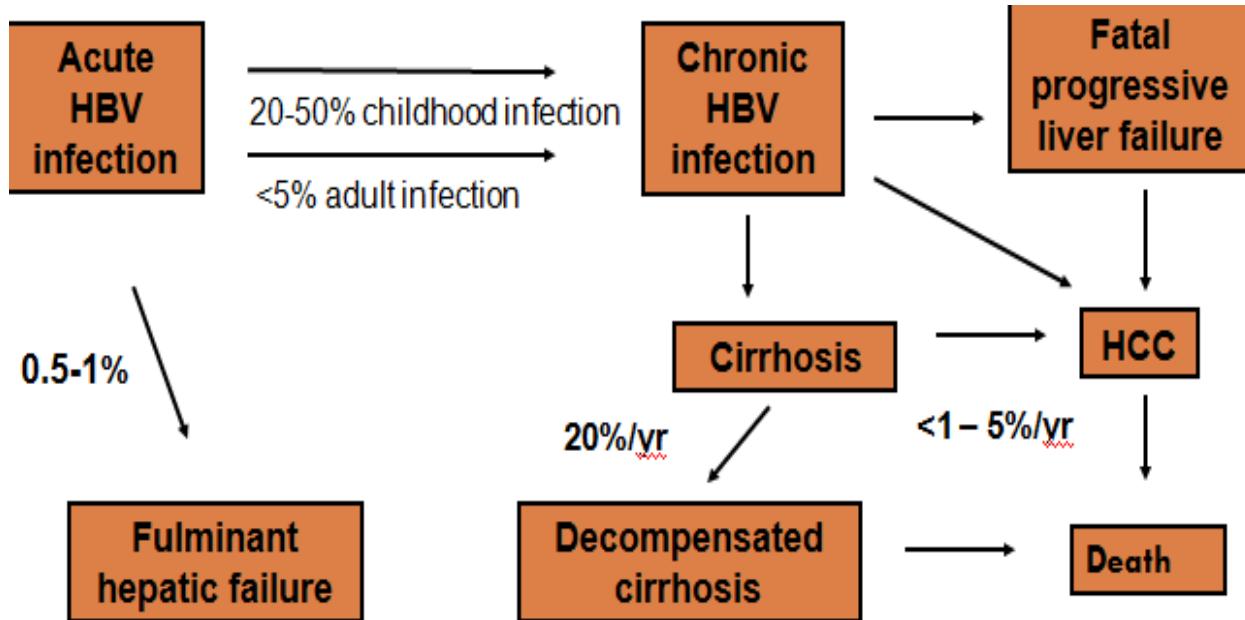
## HEPATITIS B

### INVESTIGATIONS

- **Serology**

- HBV contains several antigens to which infected persons can make immune responses; these antigens and their antibodies are important in identifying HBV infection
- The hepatitis B surface antigen (HBsAg) is an indicator of active infection, and a negative test for HBsAg makes HBV infection very unlikely.
- In acute liver failure from hepatitis B the liver damage is mediated by viral clearance and so HBsAg is negative, with evidence of recent infection shown by the presence of hepatitis B core IgM.
- HBsAg appears in the blood late in the incubation period but before the prodromal phase of acute type B hepatitis; it may be present for a few days only, disappearing even before jaundice has developed, but usually lasts for 3–4 weeks and can persist for up to 5 months.
- The persistence of HBsAg for longer than 6 months indicates chronic infection.
- Antibody to HBsAg (anti-HBs) usually appears after about 3–6 months and persists for many years or perhaps permanently.
- Anti-HBs implies either a previous infection, in which case anti-HBc (see below) is usually also present, or previous vaccination, in which case anti-HBc is not present.

- The hepatitis B core antigen (HBcAg) is not found in the blood, but antibody to it (anti-HBc) appears early in the illness and rapidly reaches a high titre, which subsides gradually but then persists.
- Anti-HBc is initially of IgM type with IgG antibody appearing later.
- Anti-HBc (IgM) can sometimes reveal an acute HBV infection when the HBsAg has disappeared and before anti-HBs has developed



- The hepatitis B e antigen (HBeAg) is an indicator of viral replication.
- In acute hepatitis B it may appear only transiently at the outset of the illness; its appearance is followed by the production of antibody (anti-HBe). The HBeAg reflects active replication of the virus in the liver.
- The likelihood of chronicity after acute hepatitis B varies as a function of age; Infection at birth is associated with clinically silent acute infection but a 90% chance of chronic infection, Infection in young adulthood and immunocompetent persons is typically associated with clinically apparent acute hepatitis. - But have a risk of chronicity of only approximately 1%

**Table: How to interpret the serological tests of acute hepatitis B virus infection**

Interpretation	HBsAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs
Incubation period	+	+	-	-
<b>Acute hepatitis</b>				
Early	+	+	-	-
Established (occasional)	+	+	+	-
-	-	+	+	-
<b>Convalescence</b>				
(3–6 months)	-	±	+	±
(6–9 months)	-	-	+	+
Post-infection	-	-	+	±
Immunization without infection	-	-	-	+

+ = positive; - = negative; ± = present at low titer or absent.  
(anti-HBc IgM/IgG = antibody to hepatitis B core antigen of immunoglobulin M/G type; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen)

## CLINICAL FEATURES

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- The spectrum of clinical features of chronic hepatitis B is broad, ranging from asymptomatic infection to debilitating disease or even end-stage, fatal hepatic fail
- Extra Hepatic Manifestations of HBV**
  - Occurs in about 10-20 % of pts with HBV infection due to accumulation of circulating HBsAg-anti HBs immune complexes in tissues
  - The two most common manifestations are
    - Polyarthritis nodosa and
    - glomerular disease
  - Immune complex deposition mediated glomerular disease may give picture of
    - membranous glomerulopathy or
    - membranoproliferative GN (result in NS)

## MANAGEMENT

- There is widespread agreement that the decision whether to initiate treatment should be made on the criteria:
  1. serum HBV DNA levels
  2. ALT elevation and
  3. histologic changes of liver tissue
- Indication for treatment should also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations.
- Differentiation between HBeAg positive and HBeAg negative chronic hepatitis B is not necessary anymore for treatment indication, although with respect to the choice of the appropriate antiviral drug (NAs vs. interferon  $\alpha$ ) these criteria may be still useful.
- Current recommendations for treatment indications may vary across different regions, and the criteria of different national and international societies are displayed on the table below.

### HBV infection Prevention

- ↳ For post exposure prophylaxis, HBIG which has high titer of anti-HBs can be used as passive immunization.
- ↳ As pre-exposure prophylaxis for risky individuals recombinant HBsAg vaccines can be administered

**Recommendations for initial treatment of chronic hepatitis B in nonpregnant adults**

HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
<b>Patients without cirrhosis*</b>			
+	>20,000 international units/mL	≤2 x ULN <sup>¶</sup>	<p>Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (&gt;40 years) and in those with family history of HCC.</p> <p>Patients should be monitored<sup>Δ</sup> and treatment considered if ALT becomes elevated &gt;2 x ULN, liver biopsy shows moderate/severe inflammation or fibrosis<sup>◊</sup> (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.</p>
+	>20,000 international units/mL	>2 x ULN <sup>¶</sup>	<p>Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss.</p> <p>Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation).</p> <p>ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.<sup>§¥</sup></p> <p>End-point of treatment – Seroconversion from HBeAg to anti-HBe.<sup>‡</sup></p> <p>Duration of therapy:</p> <ul style="list-style-type: none"> <li>▪ PegIFN alfa: 48 weeks.</li> <li>▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.</li> </ul>
-	>2000 international units/mL	<p>&gt;2 x ULN<sup>¶</sup></p> <p>OR</p> <p>1 to 2 x ULN<sup>¶</sup> if liver biopsy shows moderate/severe necroinflammation or significant fibrosis<sup>◊</sup> (eg, METAVIR score ≥F2) or non-invasive testing shows significant fibrosis</p>	<p>ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.<sup>§¥</sup></p> <p>End-point of treatment – HBsAg loss.</p> <p>Duration of therapy:</p> <ul style="list-style-type: none"> <li>▪ PegIFN alfa: One year.</li> <li>▪ ETV, TAF, or TDF: Several years or indefinite.<sup>†</sup></li> </ul>
-	≤2000 international units/mL	≤ULN <sup>¶</sup>	Monitor and treat if HBV DNA and ALT increase as described above.
<b>Patients with cirrhosis*</b>			
+/-	Detectable	Any ALT	<p><b>Compensated:</b></p> <ul style="list-style-type: none"> <li>▪ HBV DNA &gt;2000 international units/mL – Treat with ETV, TAF, or TDF.<sup>§¥</sup> Treatment should be continued indefinitely.<sup>**</sup></li> <li>▪ HBV DNA &lt;2000 international units/mL – Consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated.</li> </ul> <p><b>Decompensated:</b></p> <ul style="list-style-type: none"> <li>▪ Treat immediately, regardless of ALT or HBV DNA levels. ETV preferred.<sup>§¥</sup> TDF may be used with close monitoring of renal function. Refer for liver transplant.</li> </ul>
+/-	Undetectable	Any ALT	<p><b>Compensated:</b> Observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable.</p> <p><b>Decompensated:</b> Refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.</p>

## ACCORDING TO OUR NATIONAL GUIDELINE

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- indications are determined based on the presence or absence of cirrhosis, APRI score, ALT, HBV DNA level, and HBeAg.
- The following are the indications
  - All patients with cirrhosis (decompensated) and any detectable viral load: Irrespective of ALT and HBeAg status.
  - If no liver cirrhosis, one of the following is an indication for antiviral treatment
    - HBV DNA > 20,000 IU/ml and elevated ALT (above the UNL) : Irrespective of HBeAg status
    - Detectable HBV DNA and APRI score  $\geq 2$  or elevated ALT (above UNL): Irrespective of HBeAg status
    - Age above 30, HBeAg-positive and HBV DNA > 2,000: Irrespective of ALT
    - Co-infection with HIV.
    - Patients with chronic HBV to be started on immunosuppressives.
    - Extra hepatic manifestation
- Two drug classes are available for the treatment of chronic HBV infections: the immune modulator interferon  $\alpha$  (standard or pegylated (PEG)-INF  $\alpha$ ) as well as nucleoside or nucleotide analogues (NA), which act as reverse transcriptase inhibitors of the HBV polymerase.
- Currently, the nucleoside analogues lamivudine (LAM), telbivudine (LdT), entecavir (ETV) and the acyclic nucleotide analogues adefovir dipivoxil (ADV) and tenofovir in the two formulations tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are available
- **Monitoring treatment response**
  - HBV DNA: every three months until undetectable then every six months.
  - ALT: every three months.
  - HBeAg and antibody to HBeAg (anti-HBe): every six months in patients who are HBeAg positive.
  - Monitoring side effects of tenofovir: serum creatinine and phosphate every 3-6 months.
- **Duration of antiviral therapy**
  - Most patients require indefinite treatment
  - For patients with cirrhosis treatment should be continued indefinitely.
  - For patients without cirrhosis: HBeAg seroconversion to negative and development of HBeAb, if initially HBeAg is positive is considered as possible endpoint of treatment.

- For patients without cirrhosis and initially HBeAg is negative, it's only loss of HBsAg which is considered an endpoint but it happens very rarely; hence, treatment is generally indefinite

## **HEPATITIS C**

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- This is caused by an RNA flavivirus. Acute symptomatic infection with hepatitis C is rare. Most individuals are unaware of when they became infected and are only identified when they develop chronic liver disease. Eighty percent of individuals exposed to the virus become chronically infected and late spontaneous viral clearance is rare.

### **CHRONIC HEPATITIS C**

- Regardless of the mode of acquisition of HCV infection, about 85 % of acute infection will generally lead to chronic HCV carriage. ~20 % of the 85 % will finally end up in liver cirrhosis in 10-20 years' time. Patients with HCV induced cirrhosis are at risk of developing HCC as is also the case with HBV induced liver cirrhosis.

### **CLINICAL MANIFESTATION**

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- Hepatic manifestation almost the same with Chronic HBV
- Extra Hepatic Manifestation of HCV Infection includes:
  - Hematologic
    - Essential Mixed Cryoglobulinemia
    - B-cell NHL
  - Renal
    - Membranous and
    - membranoproliferative GN (result in NS)
  - Autoimmune
    - ITP
    - Myasthenia Gravis
    - Autoimmune thyroiditis.
  - Dermatologic
    - Porphyria cutanata
    - Lichen planus
  - Endocrine
    - DM
  - CVS
    - myocarditis
    - cardiomyopathy

## INVESTIGATIONS

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- Serology and virology
  - The HCV protein contains several antigens that give rise to antibodies in an infected person, and these are used in diagnosis.
  - it may take 6–12 weeks for antibodies to appear in the blood following acute infection such as a needlestick injury. In these cases, hepatitis C RNA can be identified in the blood as early as 2–4 weeks after infection.
  - Active infection is confirmed by the presence of serum hepatitis C RNA in anyone who is antibody- positive. Anti-HCV antibodies persist in serum even after viral clearance, whether spontaneous or post-treatment.

## MANAGEMENT

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- Who should be treated with direct acting antivirals (DAA)?
  - All patients with HCV infection, who are willing to be treated, should be treated.
  - Treatment should be started without delay in patients with significant fibrosis or cirrhosis, including decompensated cirrhosis; patients with clinically significant extra-hepatic manifestations.
- Which agent to use?
  - A simplified, pangenotypic anti-HCV treatment is preferred.

## PREVENTION

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- No active or passive immunization so far known

## ALCOHOLIC LIVER DISEASE

- Chronic and excessive alcohol ingestion is a major cause of liver disease and is responsible for nearly 50% of the mortality from all cirrhosis.
- The pathology of alcoholic liver disease consists of three major lesions, with the progressive injury rarely existing in a pure form:
  - a) fatty liver
  - b) alcoholic hepatitis, and
  - c) cirrhosis.
- Fatty liver is present in >90% of daily as well as binge drinkers. A much smaller percentage of heavy drinkers will progress to alcoholic hepatitis, thought to be a precursor to cirrhosis.

## RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

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- Quantity
  - In men, 40–80 g/d of ethanol produces fatty liver; 160 g/d for 10–20 years causes hepatitis or cirrhosis. Only 15% of alcoholics develop alcoholic liver disease.
- Gender
  - Women exhibit increased susceptibility to alcoholic liver disease at amounts >20 g/d; two drinks per day is probably safe.
- Hepatitis C
  - HCV infection concurrent with alcoholic liver disease is associated with younger age for severity, more advanced histology, and decreased survival.
- Genetics
  - Patatin-like phospholipase domain-containing protein 3 (PNPLA3) has been associated with alcoholic cirrhosis.
- Fatty liver
  - Alcohol injury does not require malnutrition, but obesity and nonalcoholic fatty liver are risk factors. Patients should receive vigorous attention to nutritional support.

## CLINICAL FEATURE

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**Table: Clinical syndromes of alcoholic liver disease**

<b>Fatty liver</b>	
Asymptomatic abnormal liver biochemistry	Normal/large liver
<b>Alcoholic hepatitis</b>	
Jaundice	Features of portal hypertension (e.g., ascites, encephalopathy)
Malnutrition	
Hepatomegaly	
<b>Cirrhosis</b>	
Stigmata of chronic liver disease	Large, normal or small liver
Ascites/varices/ encephalopathy	Hepatocellular carcinoma

## INVESTIGATIONS

- AST
  - Increased two- to sevenfold, <400 IU/L, greater than ALT
- ALT
  - Increased two- to sevenfold, <400 IU/L
- AST/ALT
  - Usually, >1
- GGTP
  - Not specific to alcohol, easily inducible, elevated in all forms of fatty liver
- Bilirubin
  - May be markedly increased in alcoholic hepatitis despite modest elevation in alkaline phosphatase

## TREATMENT

- Complete abstinence from alcohol is the cornerstone in the treatment of alcoholic liver disease. Improved survival and the potential for reversal of histologic injury regardless of the initial clinical presentation are associated with total avoidance of alcohol ingestion.
- Patients with severe alcoholic hepatitis, defined as a discriminant function  $>32$  or MELD  $>20$ , should be given prednisone, 40 mg/d, or prednisolone, 32 mg/d, for 4 weeks, followed by a steroid taper. Exclusion criteria include active gastrointestinal bleeding, renal failure, or pancreatitis.
- In severe alcoholic hepatitis, oral pentoxifylline (which has a weak anti-TNF action) reduces inpatient mortality, particularly from hepatorenal failure, from 46% to 25%
- Good nutrition is very important, and enteral feeding via a fine-bore nasogastric tube may be needed in severely ill patients.

## NOTE

A discriminant function can be calculated as  $4.6 \times (\text{patients PT in seconds}) - (\text{control PT in seconds}) + \text{serum bilirubin (mg/dL)}$ .

## AUTOIMMUNE HEPATITIS

- Autoimmune hepatitis is a liver disease of unknown etiology characterized by;
  - A strong association with other autoimmune diseases
  - High levels of serum immunoglobulins (hypergammaglobulinemia)
  - Autoantibodies in the serum.

### PATOPHYSIOLOGY

- Several subtypes of this disorder have been proposed which have differing immunological markers:
  - Classical (type I) autoimmune hepatitis
    - Characterized by a high frequency of other autoimmune disorders, such as Graves' disease. These patients have high titers of antinuclear and anti-smooth muscle antibodies, but none of these antibodies is cytotoxic. A suggested hypothesis for the development of type I autoimmune hepatitis is the aberrant expression on the hepatocyte of HLA antigen, influenced by viral, genetic and environmental factors.
  - Type II autoimmune hepatitis
    - characterized by the presence of anti-LKM (liver-kidney microsomal) antibodies and lack of antinuclear and anti-smooth muscle antibodies.
  - Type III autoimmune hepatitis
    - characterized elevated serum immunoglobulin levels; the antibodies described above are absent, whilst antibodies against soluble liver antigen are present.

### NOTE

It occurs most often in women, particularly in the second and third decades of life, but may develop in either sex at any age

### CLINICAL FEATURES

- The onset is usually insidious, with fatigue, anorexia and jaundice.
- In about one-quarter of patients the onset is acute, resembling viral hepatitis, but resolution does not occur.
- This acute presentation can lead to extensive liver necrosis and liver failure.
- Other features include fever, arthralgia, vitiligo and epistaxis.
- Amenorrhea is the rule but general health may be good.
- Jaundice is mild to moderate or occasionally absent, but signs of chronic liver disease, especially spider naevi and hepato splenomegaly, are usually present.
- Some patients have a 'Cushingoid' face with acne, hirsutism and pink cutaneous striae, especially on the thighs and abdomen.
- Approximately two-thirds of patients have associated autoimmune disease such as Hashimoto's thyroiditis, renal tubular acidosis and rheumatoid arthritis.

## INVESTIGATIONS

- Elevated anti-smooth muscle antibody
- Anti-nuclear antibody
- Anti-liver-kidney microsomal antibody
- Biopsy is most accurate. It typically shows interface hepatitis, with or without cirrhosis.

## NOTE

The histopathological features of all forms of autoimmune hepatitis are similar.

## MANAGEMENT

- Treatment with corticosteroids is life-saving in autoimmune hepatitis, particularly during exacerbations of active and symptomatic disease. Initially, prednisolone 40 mg/day is given orally; the dose is then gradually reduced as the patient and LFTs improve.
- Maintenance therapy is required for at least 2 years after LFTs have returned to normal, and withdrawal of treatment should not be considered unless a liver biopsy is also normal.
- Most individuals require long-term immunosuppression. Azathioprine 1.0–1.5 mg/kg/day orally may allow the dose of prednisolone to be reduced
- Azathioprine can also be used as the sole maintenance immunosuppressive agent. Corticosteroids treat acute exacerbations but do not prevent cirrhosis; they are therefore less important in mild asymptomatic auto immune hepatitis.
- The disease is characterized by exacerbations and remissions, but most patients eventually develop cirrhosis and its complications. Hepatocellular carcinoma is uncommon.

## CARDIAC CIRRHOSIS

- Due to long-standing right-side Hart failure which lead to chronic liver injury and cardiac cirrhosis [passive congestion and relative ischemia due to poor circulation]

## CLINICAL MANIFESTATIONS

- Symptom of HF
- Enlarged and firm liver
- Slight elevation of liver enzyme

## COMPLICATIONS OF CIRRHOSIS

### PORTAL HYPERTENSION

- Portal hypertension is defined as elevation of the hepatic venous pressure gradient to >5 mmHg
- Causes
  - Prehepatic causes
    - Portal hypertension
    - Splenic vein thrombosis
    - Massive splenomegaly [Banti's syndrome]
  - Hepatic causes
    - Presinusoidal
      - Schistosomiasis
      - Congenital hepatic fibrosis
    - Sinusoidal
      - Cirrhosis
      - Alcoholic hepatitis
    - Postsinusoidal
      - Hepatic sinusoidal obstruction [Venoocclusive Syndrome]
  - Posthepatic causes
    - Budd-Chiari syndrome [hepatic vein thrombosis]
    - IVC web
    - Cardiac cause [constrictive pericarditis, restrictive cardiomyopathy, severe CHF]

### NOTE

Approximately 50% of symptomatic patients will die of liver failure within 5 years if no treatment is given, but this falls to

## COMPLICATION OF PORTAL HYPERTENSION

**Table: Complications of portal hypertension**

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>– Variceal bleeding: esophageal, gastric, other(rare)</li> <li>– Congestive gastropathy</li> <li>– Hypersplenism</li> </ul> | <ul style="list-style-type: none"> <li>– Ascites</li> <li>– Iron deficiency anemia</li> <li>– Renal failure</li> <li>– Hepatic encephalopathy</li> </ul> |
|--|--|

### ASCITES

- Ascites is present when there is accumulation of free fluid in the peritoneal cavity.
- Small amounts of ascites are asymptomatic, but with larger accumulations of fluid (> 1 L) there is abdominal distension, fullness in the flanks, shifting dullness on percussion and, when the ascites is marked, a fluid thrill.
- In obese patients, much larger volumes of ascites may accumulate before they are detectable clinically.
- Other features include distortion or eversion of the umbilicus, hernia, abdominal striae, divarication of the recti and scrotal oedema.
- Dilated superficial abdominal veins may be seen if the ascites is due to portal hypertension

### CAUSES OF ASCITES

**Table: Causes of ascites**

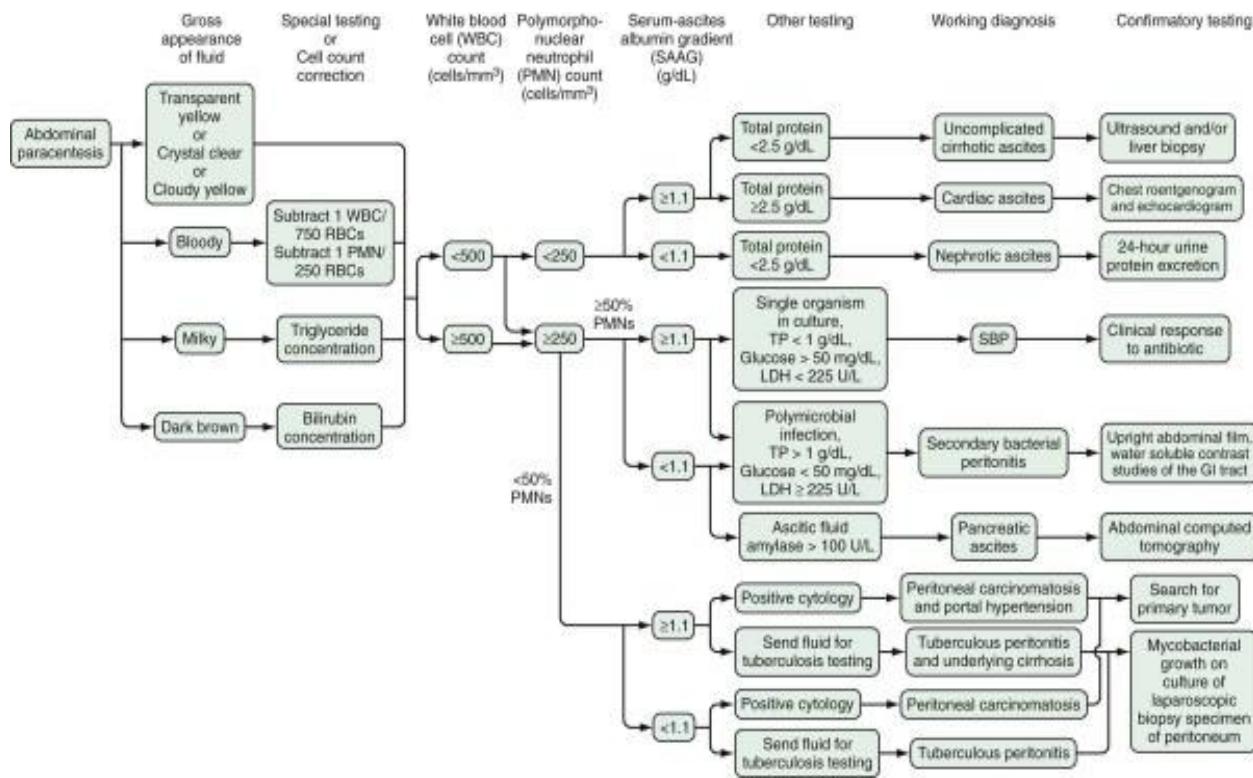
Low SAAG (exudative)	High SAAG (transudative)
<b>Common causes</b> Malignant disease: <ul style="list-style-type: none"> <li>– Hepatic</li> <li>– Peritoneal</li> </ul>	Cardiac failure Hepatic cirrhosis
<b>Other causes</b> Acute pancreatitis Lymphatic obstruction Infection: <ul style="list-style-type: none"> <li>– Tuberculosis</li> </ul> Nephrotic syndrome	Hypoproteinemia: <ul style="list-style-type: none"> <li>– Protein-losing enteropathy</li> <li>– Malnutrition</li> </ul> Hepatic venous occlusion: <ul style="list-style-type: none"> <li>– Budd–Chiari syndrome</li> <li>– Sinusoidal obstruction syndrome</li> <li>– (Veno-occlusive disease)</li> </ul>
<b>Rare causes</b> Hypothyroidism	Meigs' syndrome* Constrictive pericarditis

\*Meigs' syndrome is the association of a right pleural effusion with or without ascites and a benign ovarian tumor. The ascites resolves on removal of the tumor.

(SAAG = serum ascites albumin gradient)

## INVESTIGATIONS

- Ultrasonography is the best means of detecting ascites, particularly in the obese and those with small volumes of fluid. Paracentesis (if necessary under ultrasonic guidance) can also be used to confirm the presence of ascites but is most useful for obtaining ascitic fluid for analysis.
- The appearance of ascitic fluid may point to the underlying cause (see below).
- Pleural effusions are found in about 10% of patients, usually on the right side (hepatic hydrothorax); most are small and only identified on chest X-ray, but occasionally a massive hydrothorax occurs.
- Pleural effusions, particularly those on the left side, should not be assumed to be due to the ascites.
- Measurement of the protein concentration and the serum–ascites albumin gradient (SAAG) are used to distinguish a transudate from an exudate.
- Cirrhotic patients typically develop a transudate with a total protein concentration below 25 g/L and relatively few cells.
- However, in up to 30% of patients, the total protein concentration is more than 30 g/L. In these cases it is useful to calculate the SAAG by subtracting the concentration of the ascites fluid albumin from the serum albumin.
- A gradient of more than 11 g/L is 96% predictive that ascites is due to portal hypertension.
- Venous outflow obstruction due to cardiac failure or hepatic venous outflow obstruction can also cause a transudative ascites, as indicated by an albumin gradient above 11 g/L, but unlike in cirrhosis the total protein content is usually above 25 g/L.
- Exudative ascites (ascites protein concentration above 25 g/L or a SAAG of less than 11 g/L) raises the possibility of infection (especially tuberculosis), malignancy, hepatic venous obstruction, pancreatic ascites or, rarely, hypothyroidism.
- Ascites amylase activity above 1000 U/L identifies pancreatic ascites, and low ascites glucose concentrations suggest malignant disease or tuberculosis.
- Cytological examination may reveal malignant cells (one third of cirrhotic patients with a bloody tap have a hepatoma). Polymorphonuclear leucocyte counts above  $250 \times 10^6/L$  strongly suggest infection (spontaneous bacterial peritonitis,)
- Laparoscopy can be valuable in detecting peritoneal disease.



## ASCITES TREATMENT

### SODIUM AND WATER RESTRICTION

- Restriction of dietary sodium intake is essential to achieve negative sodium balance in ascites, and a few patients can be managed satisfactorily on this treatment alone.
  - Restriction of sodium intake to 100 mmol/day [ $<2$  g] ('no added salt diet') is usually adequate.
  - Drugs containing relatively large amounts of sodium and those promoting sodium retention, such as non-steroidal anti-inflammatory drugs, must be avoided.
- Restriction of water intake to 1.0–1.5 L/day is necessary only if the plasma sodium falls below 125 mmol/L.

**Table: Some drugs containing relatively large amounts of sodium or causing sodium retention**

<b>High sodium content</b>	
– Alginate	– Effervescent preparations (e.g. aspirin, calcium, paracetamol)
<b>Sodium retention</b>	
– Carbenoxolone	– Non-steroidal anti-inflammatory drugs
– Glucocorticoids	– Estrogens
– Metoclopramide	

- **DIURETICS**

- When a moderate amount of ascites is present, diuretic therapy is usually necessary.
- Traditionally, spironolactone at 100–200 mg/d as a single dose is started, and furosemide maybe added at 40–80 mg/d, particularly in patients who have peripheral edema.
- In patients who have never received diuretics before, the failure of the above-mentioned dosages suggests that they are not being compliant with a low-sodium diet.
- If compliance is confirmed and ascitic fluid is not being mobilized, spironolactone can be increased to 400–600 mg/d and furosemide increased to 120–160 mg/d. If ascites is still present with these dosages of diuretics in patients who are compliant with a low-sodium diet, then they are defined as having refractory ascites, and alternative treatment modalities including

- **PARACENTESIS**

- The first-line treatment of refractory ascites is large volume paracentesis with intravenous albumin replacement.
- Paracentesis to dryness or the removal of 3–5 L daily is safe, provided the circulation is supported with an intravenous colloid such as human albumin (6–8 g per liter of ascites removed, usually as 100 mL of 20% human albumin solution (HAS) for every 3 L of ascites drained) or another plasma expander.
- Paracentesis can therefore be used as an initial therapy or when other treatments fail.

- **PERITONEO-VENOUS SHUNT**

- The peritoneo-venous shunt is a long tube with a nonreturn valve running subcutaneously from the peritoneum to the internal jugular vein in the neck (it allows ascitic fluid to pass directly into the systemic circulation).

- It is effective in ascites resistant to conventional treatment but complications, including infection, superior venacaval thrombosis, pulmonary oedema, bleeding from esophageal varices and disseminated intravascular coagulopathy, limit its use and insertion of these shunts is now rare.
- **TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNT (TIPSS)**
  - can relieve resistant ascites but does not prolong life; it may be an option where the only alternative is frequent, large-volume paracentesis. It can be used when liver function is reasonable or in patients awaiting liver transplantation.

### SPONTANEOUS BACTERIAL PERITONITIS

- SBP is a common and severe complication of ascites characterized by spontaneous infection of the ascitic fluid without an intraabdominal source.
- In patients with cirrhosis and ascites severe enough for hospitalization, SBP can occur in up to 30% of individuals and can have a 25% in-hospital mortality rate.
- Bacterial translocation is the presumed mechanism for development of SBP, with gut flora traversing the intestine into mesenteric lymph nodes, leading to bacteremia and seeding of the ascitic fluid.
- The most common organisms are Escherichia coli and other gut bacteria; however, gram-positive bacteria, including Streptococcus viridans, Staphylococcus aureus, and Enterococcus sp., can also be found.
- If more than two organisms are identified, secondary bacterial peritonitis due to a perforated viscus should be considered.
- The diagnosis of SBP is made when the fluid sample has an absolute neutrophil count  $>250/\mu\text{L}$ . Bedside cultures should be obtained when ascitic fluid is tapped.
- Patients with ascites may present with fever, altered mental status, elevated white blood cell count, and abdominal pain or discomfort, or they may present without any of these features.
- Treatment is commonly with a third-generation cephalosporin.
- In patients with variceal hemorrhage, the frequency of SBP is significantly increased, and prophylaxis against SBP is recommended when a patient presents with upper GI bleeding.
- Furthermore, in patients who have had an episode(s) of SBP and recovered, once-weekly administration of antibiotics is used as prophylaxis for recurrent SBP

## VARICEAL BLEEDING

- Acute upper gastrointestinal hemorrhage from esophagogastric varices is a common manifestation of chronic liver disease. However, gastrointestinal bleeding can also occur as the result of peptic ulceration, which is more common in patients with liver disease than in the general population.

### NOTE:

Esophageal varices: Rule of 1/3rd

- 1/3rd of patient with cirrhosis develop varices
- 1/3rd of them will develop bleeding
- 1/3rd of them will die.

## MANAGEMENT

- Treatment for variceal hemorrhage as a complication of portal hypertension is divided into two main categories:
  - primary prophylaxis and
  - prevention of rebleeding once there has been an initial variceal hemorrhage.
- Primary prophylaxis requires routine screening by endoscopy of all patients with cirrhosis. Once varices that are at increased risk for bleeding are identified, primary prophylaxis can be achieved either through nonselective beta blockade or by variceal band ligation.

## PRINCIPLES

- The priority in acute bleeding from esophageal varices is to restore the circulation with blood and plasma, not least because shock reduces liver blood flow and causes further deterioration of liver function. Even in patients with known varices, the source of bleeding should always be confirmed by endoscopy because about 20% of patients are bleeding from some other lesion, especially acute gastric erosions.
- All patients with cirrhosis and gastrointestinal bleeding should receive prophylactic broad-spectrum antibiotics, such as oral ciprofloxacin or intravenous cephalosporin, because sepsis is common and treatment with antibiotics has been shown to improve outcome. The measures used to control acute variceal bleeding include endoscopic therapy (banding or sclerotherapy), balloon tamponade and esophageal transection.

## BANDING LIGATION AND SCLEROTHERAPY

- This is the most widely used initial treatment and is undertaken, if possible, at the time of diagnostic endoscopy.
- It stops variceal bleeding in 80% of patients and can be repeated if bleeding recurs.

- Band ligation involves the varices being sucked into a cap placed on the end of the endoscope, allowing them to be occluded with a tight rubber band.
- The occluded varix subsequently sloughs with variceal obliteration.
- Banding is repeated every 1–2 weeks until the varices are obliterated.
- Regular follow-up endoscopy is required to identify and treat any recurrence of varices.
- Band ligation has fewer side-effects than sclerotherapy, a technique in which varices are injected with a sclerosing agent, which has now been largely abandoned in preference to banding ligation.
- Banding is associated with less risk of esophageal perforation and esophageal strictures.
- Prophylactic acid suppression with proton pump inhibitors reduces the risk of secondary bleeding from banding-induced ulceration.
- Active bleeding at endoscopy may make endoscopic therapy difficult; in such cases, bleeding should be controlled by balloon tamponade prior to endoscopic therapy.
- Protection of the patient's airway with endotracheal intubation may allow an improved endoscopic view, facilitating endoscopic therapy, and significantly reduce the risk of pulmonary aspiration.

#### **PHARMACOLOGICAL REDUCTION OF PORTAL VENOUS PRESSURE**

- Pharmacological reduction of portal pressure is less important than banding in preventing rebleeding, but is useful in reducing active bleeding while endoscopy is being arranged.
- Terlipressin is the current drug of choice and releases the vasoconstrictor, vasopressin, over several hours in amounts sufficient to reduce the portal pressure without producing systemic effects.
- It is given in a dose of 2 mg i.v. 6-hourly until bleeding stops, and then 1 mg 6-hourly for a further 24 hours.

#### **BALLOON TAMPOONADE**

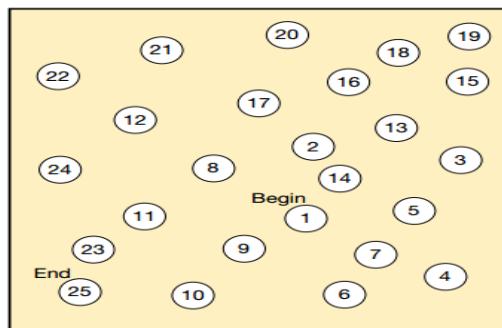
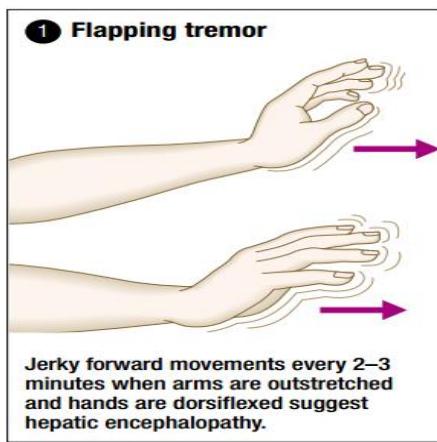
- This technique employs a Sengstaken–Blakemore tube possessing two balloons which exert pressure in the fundus of the stomach and in the lower esophagus respectively.

#### **PROGNOSIS**

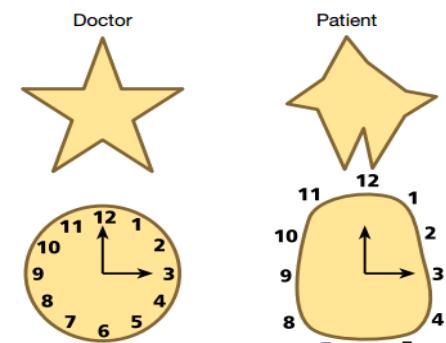
- In the presence of portal hypertension, the risk of a variceal bleed occurring within 2 years varies from 7% for small varices up to 30% for large varices.
- The mortality following a variceal bleed has improved to around 15% overall but still is about 45% in those with poor liver function, i.e. Child–Pugh C patients.

## HEPATIC ENCEPHALOPATHY

- Hepatic encephalopathy is a neuropsychiatric syndrome caused by chronic liver diseases.
- Features include changes of intellect, personality, emotions and consciousness, with or without neurological signs.
- The degree of encephalopathy can be graded from 1 to 4, depending on these features, and this is useful in assessing response to therapy.
- When an episode develops acutely, a precipitating factor may be found.
- The earliest features are very mild and easily overlooked but, as the condition becomes more severe, apathy, inability to concentrate, confusion, disorientation, drowsiness, slurring of speech and eventually coma develop. Convulsions sometimes occur.
- Examination usually shows a flapping tremor (asterixis,), inability to perform simple mental arithmetic tasks (Fig. below) or to draw objects such as a star (constructional apraxia, Fig. below), and, as the condition progresses, hyper-reflexia and bilateral extensor plantar responses.



**Fig. 23.18 Number connection test used in assessing encephalopathy.** These 25 numbered circles can normally be joined together within 30 seconds. Serial observations may provide useful information as long as the position of the numbers is varied to avoid the patient learning their pattern.



**Fig. 23.19 Constructional apraxia in encephalopathy.** Drawing stars and clocks may reveal marked abnormality.

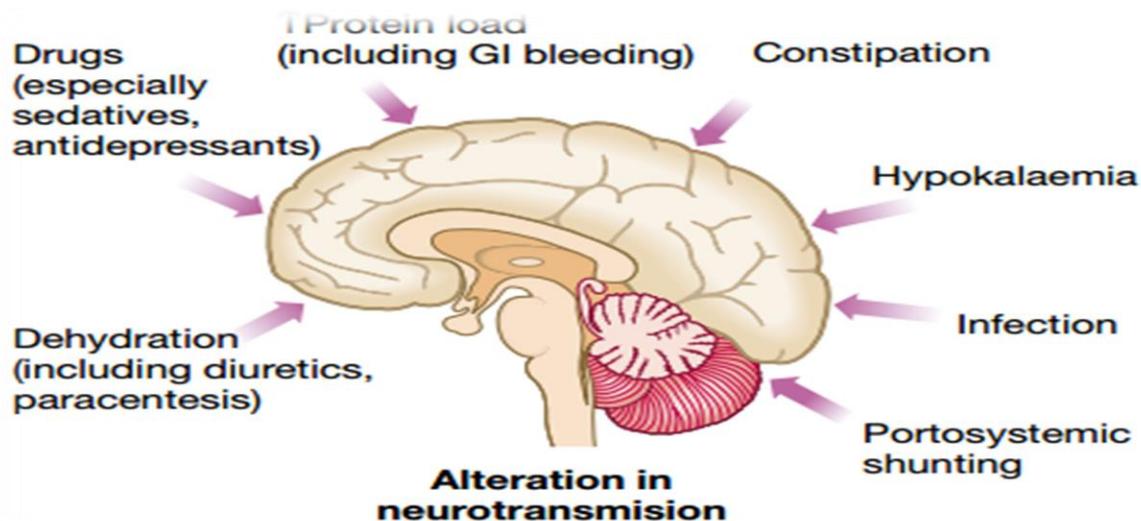
- Hepatic encephalopathy rarely causes focal neurological signs, and if these are present, other causes must be sought.
- Fetur hepaticus, a sweet musty odor to the breath, is usually present but is more a sign of liver failure and portosystemic shunting than of hepatic encephalopathy

**Table: How to assess clinical grade of hepatic encephalopathy**

Clinical grade	Clinical signs
Grade 1	Poor concentration, slurred speech, slow mentation, disordered sleep rhythm
Grade 2	Drowsy but easily rousable, occasional aggressive behavior, lethargic
Grade 3	Marked delirium, drowsy, sleepy but responds to pain and voice, gross disorientation
Grade 4	Unresponsive to voice, may or may not respond to painful stimuli, unconscious

### PATOPHYSIOLOGY

- Hepatic encephalopathy is thought to be due to a disturbance of brain function provoked by circulating neurotoxins that are normally metabolized by the liver.
- Accordingly, most affected patients have evidence of liver failure and portosystemic shunting of blood, but the balance between these varies from individual to individual.
- Some degree of liver failure is a key factor, as portosystemic shunting of blood alone hardly ever causes encephalopathy.
- Little is known of the biochemical ‘neurotoxins’ causing the encephalopathy, but they are thought to be mainly nitrogenous substances produced in the gut, at least in part by bacterial action.
- These substances are normally metabolized by the healthy liver and therefore excluded from the systemic circulation.
- Ammonia has traditionally been considered an important factor and ammonia induced alteration in astrocyte glutamine and glutamate concentrations may be important.
- Recent interest has focused on  $\gamma$ -aminobutyric acid as a mediator, along with other factors such as octopamine, amino acids, mercaptans and fatty acids which can act as neurotransmitters.



- Some factors appear to precipitate hepatic encephalopathy by increasing the availability of these substances; in addition, the brain in cirrhosis may be sensitized to other factors such as drugs that are able to precipitate hepatic encephalopathy (see fig above.)
- Disruption of the function of the blood–brain barrier is a feature of acute hepatic failure and may lead to cerebral edema.

### INVESTIGATIONS

- The diagnosis can usually be made clinically, but when doubt exists, an electroencephalogram (EEG) shows diffuse slowing of the normal alpha waves with eventual development of delta waves.
- The arterial ammonia is usually increased in patients with hepatic encephalopathy.
- However, increased concentrations can occur in the absence of clinical encephalopathy, so this investigation is of little or no diagnostic value.

### MANAGEMENT

- The principles of management are to treat or remove precipitating causes and to suppress the production of neurotoxins by bacteria in the bowel.
- Dietary protein restriction is rarely needed and is no longer recommended as first-line treatment because it is unpalatable and can lead to a worsening nutritional state in already malnourished patients.
- Lactulose (15–30 mL8-hourly) is a disaccharide which is taken orally and reaches the colon intact, to be metabolized by colonic bacteria.
- The goal of lactulose therapy is to promote 2–3 soft stools per day. It produces an osmotic laxative effect, reduces the pH of the colonic content, thereby limiting colonic ammonia absorption, and promotes the incorporation of nitrogen into bacteria.

- Lactitol is a rather more palatable alternative to lactulose, with a less explosive action on bowel function. Poorly absorbed antibiotics are often used as adjunctive therapies for patients who have a difficult time with lactulose.
- The alternating administration of neomycin and metronidazole has been used in the past to reduce the individual side effects of each: neomycin for renal insufficiency and ototoxicity and metronidazole for peripheral neuropathy.
- More recently, rifaximin at 550 mg twice daily has been very effective in treating encephalopathy without the known side effects of neomycin or metronidazole.
- Zinc supplementation is sometimes helpful in patients with encephalopathy and is relatively harmless.
- Chronic or refractory hepatic encephalopathy is one of the main indications for liver transplantation.

### HEPATORENAL SYNDROME

- This occurs in 10% of patients with advanced cirrhosis complicated by ascites.
- There are two clinical types; both are mediated by renal vasoconstriction due to underfilling of the arterial circulation.
  - **Type 1 hepatorenal syndrome** is characterized by progressive oliguria, a rapid rise of the serum creatinine and a very poor prognosis (without treatment, median survival is less than 1 month).
  - There is usually no proteinuria, a urine sodium excretion below 10 mmol/day and a urine/plasma osmolarity ratio of > 1.5. Other non-functional causes of renal failure must be excluded before the diagnosis is made.
    - Treatment consists of albumin infusions in combination with terlipressin and is effective in about two-thirds of patients. Hemodialysis should not be used routinely because it does not improve the outcome. Patients who survive should be considered for liver transplantation.
  - **Type 2 hepatorenal syndrome** usually occurs in patients with refractory ascites, is characterized by a moderate and stable increase in serum creatinine, and has a better prognosis.

### MALNUTRITION IN CIRRHOsis

- Because the liver is principally involved in the regulation of protein and energy metabolism in the body, it is not surprising that patients with advanced liver disease are commonly malnourished.
- Once patients become cirrhotic, they are more catabolic, and muscle protein is metabolized.

- There are multiple factors that contribute to the malnutrition of cirrhosis, including poor dietary intake, alterations in gut nutrient absorption, and alterations in protein metabolism.
- Dietary supplementation for patients with cirrhosis is helpful in preventing patients from becoming catabolic.

### **ABNORMALITIES IN COAGULATION**

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- Coagulopathy is almost universal in patients with cirrhosis.
- There is decreased synthesis of clotting factors and impaired clearance of anticoagulants.
- In addition, patients may have thrombocytopenia from hypersplenism due to portal hypertension.
- Vitamin K-dependent clotting factors are factors II, VII, IX, and X. Vitamin K requires biliary excretion for its subsequent absorption; thus, in patients with chronic cholestatic syndromes, vitamin K absorption is frequently diminished.
- Intravenous or intramuscular vitamin K can quickly correct this abnormality.
- More commonly, the synthesis of vitamin K-dependent clotting factors is diminished because of a decrease in hepatic mass, and, under these circumstances, administration of parenteral vitamin K does not improve the clotting factors or the prothrombin time.
- Platelet function is often abnormal in patients with chronic liver disease, in addition to decreases in platelet levels due to hypersplenism.

### **BONE DISEASE IN CIRRHOsis**

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- Osteoporosis is common in patients with chronic cholestatic liver disease because of malabsorption of vitamin D and decreased calcium ingestion.
- The rate of bone resorption exceeds that of new bone formation in patients with cirrhosis, resulting in bone loss.
- Dual x-ray absorptiometry (DEXA) is a useful method for determining osteoporosis or osteopenia in patients with chronic liver disease.
- When a DEXA scan shows decreased bone mass, treatment should be administered with bisphosphonates that are effective at inhibiting resorption of bone and efficacious in the treatment of osteoporosis.

### **HEMATOLOGIC ABNORMALITIES IN CIRRHOsis**

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- Numerous hematologic manifestations of cirrhosis are present, including anemia from a variety of causes including hypersplenism, hemolysis, iron deficiency, and perhaps folate deficiency from malnutrition.

- Macrocytosis is a common abnormality in red blood cell morphology seen in patients with chronic liver disease, and neutropenia may be seen as a result of hypersplenism.

## PROGNOSIS

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- The overall prognosis is poor.
- Many patients present with advanced disease and/or serious complications that carry a high mortality.
- Overall, only 25% of patients survive 5 years from diagnosis, but where liver function is good, 50% survive for 5 years and 25% for up to 10 years.
- The prognosis is more favourable when the underlying cause can be corrected as
  - alcohol misuse,
  - haemochromatosis or
  - Wilson's disease.
- Laboratory tests give only a rough guide to prognosis in individual patients.
- Deteriorating liver function, as evidenced by jaundice, ascites or encephalopathy, indicates a poor prognosis unless a treatable cause such as infection is found.
- Increasing bilirubin, falling albumin (or an albumin concentration of < 30 g/L(3.0 g/dL)), marked hyponatraemia (< 120 mmol/L) not due to diuretic therapy, and a prolonged PT are all bad prognostic features.
- The Child–Pugh and MELD (Model for End-stage Liver Disease) scores can be used to assess prognosis.
- The MELD is more difficult to calculate at the bedside but, unlike the Child–Pugh score, includes renal function; if this is impaired, it is known to be a poor prognostic feature in end-stage disease. Although these scores give a guide to prognosis, the course of cirrhosis can be unpredictable, as complications such as variceal bleeding may occur.

Child-Pugh classification of prognosis in cirrhosis			
Score	1	2	3
<b>Encephalopathy</b>	None	Mild	Marked
<b>Bilirubin (μmol/L (mg/dL))*</b>			
– Primary biliary cholangitis/sclerosing cholangitis	< 68 (4 )	68–170 (4–10 )	> 170 (10 )
– Other causes of cirrhosis	< 34 (2 )	34–50 (2–3 )	> 50 (3 )
<b>Albumin (g/L (g/dL))</b>	> 35 (3.5 )	28–35 (2.8–3.5 )	< 28 (2.8 )
<b>Prothrombin time (secs prolonged)</b>	< 4	4–6	> 6
<b>Ascites</b>	None	Mild	Marked
Add the individual scores: < 7 = Child's A, 7– 9= Child's B, > 9 = Child's C			
*To convert bilirubin in μmol/L to mg/dL, divide by 17.			

Decompensation indicates cirrhosis with a Child-Pugh score of >7 (class B).

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# CHAPTER FIVE

## Diabetes mellitus

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Introduction

Type 1 diabetes mellitus

Type 2 diabetes mellitus

Complication of diabetes mellitus

Management of diabetes mellitus

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### INTRODUCTION

DM is a group of common metabolic disorders that share the phenotype of hyperglycemia

Factors contributing to hyperglycemia include

- Reduced insulin secretion,
- Decreased glucose utilization, and
- Increased glucose production.

In the United States, DM is the **leading cause of**

- End-stage renal disease (ESRD),
- Nontraumatic lower extremity amputations, and
- Adult blindness.

### ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

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#### I. Type 1 diabetes

- Immune-mediated beta cell destruction, usually leading to absolute insulin deficiency
  - A. . Immune mediated
    - Autoantibodies identified
    - Autoimmune origin
  - B. Idiopathic
    - Associated with strong hereditary component
    - Autoantibodies are absent

## II. Type 2 diabetes

- Ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance

## III. Specific types of diabetes

- A. Genetic defects of beta cell development or function
  - Maturity-onset diabetes of the young (MODY) characterized by:
    - Autosomal dominant inheritance,
    - Early onset of hyperglycemia (usually <25 years; sometimes in neonatal period), and
    - Impaired insulin secretion
- B. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, etc.
- C. Drug- or chemical-induced—glucocorticoids and etc.
- D. Infections—congenital rubella, cytomegalovirus, coxsackievirus
- E. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism
- F. Genetic defects in insulin action
- G. Transient neonatal diabetes

## IV. Gestational diabetes mellitus (GDM)

- Glucose intolerance developing during the second or third trimester of pregnancy
- Diagnosed commonly after 20 weeks
- Screening 24- 28 weeks

## EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS

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Diabetes is one of the largest global health emergencies of the 21<sup>st</sup> century

Type 2 diabetes is the most prevalent form, affecting 91 to 95% of adults

The prevalence of type 2 DM is rising much more rapidly, presumably because of

- Increasing obesity,
- Reduced activity levels as countries become more industrialized, and
- The aging of the population.

Type 2 Diabetes is one of the **four major non-communicable diseases** (Stroke and Heart disease, **DM**, cancer, and Chronic lung disease)

Who does have DM?

- Worldwide, 415 million people aged between **20 and 79 years**
- Of which 75% is living in low- and middle-income countries

The Burden of DM IN AFRICA (2021 report)

- Africa: 24 million adults with DM
- Ethiopia accounts for 1.9 million (5% of total population)

**Cardiovascular death (MI) is the leading cause for early death in diabetic population**

## APPROACH

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### HISTORY

DM-relevant aspects

- Weight
- Family history of DM
- Complications
- Risk factors for cardiovascular disease
- Exercise
- Smoking
- Ethanol use

Symptoms of hyperglycemia

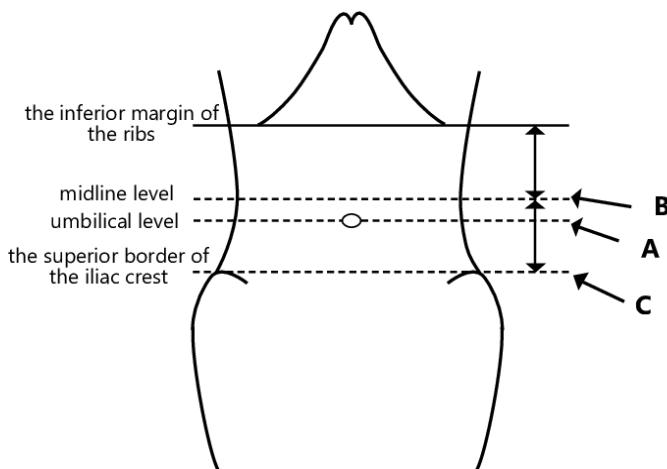
- Polyuria, polydipsia, nocturia, blurred vision and weight loss (**classic symptoms**)
  - polyuria occurs when glucose concentration is  $> 180 \text{ mg/dl}$ , exceeding renal reabsorption threshold
  - polydipsia occurs due to hypovolemia secondary to polyuria
- Fatigue, weakness
- Frequent superficial infections (vaginitis, fungal skin infections)
- Slow healing of skin lesions after minor trauma

In a patient with established DM

- prior diabetes care, including the type of therapy
- prior HbA1c levels
- frequency of hypoglycemia
- presence of DM-specific complications
- nutrition
- DM-related comorbidities (cardiovascular disease, hypertension, dyslipidemia)

## GENERAL PHYSICAL EXAMINATION

- Thyroid palpation (goiter)
- BP, including orthostatic measurements
- Ankle to brachial index
- BMI, waist circumference
  - Waist circumference (measure midway between lower costal margin & iliac crest)
  - Normal (Males <94 cm and Females <80 cm)



Acanthosis nigricans



- Skin: Acanthosis nigricans, infections, insulin injection sites
- Neurologic exam (see neurologic complication)
- Fundoscopic examination (see ophthalmologic complication)
- Comprehensive foot exam

## DIAGNOSIS

Glucose tolerance is classified into three broad categories:

1. Normal glucose homeostasis
  - FPG <100 mg/dL, a plasma glucose <140 mg/dL following OGTT and HbA1c <5.7%
2. Impaired glucose homeostasis,
  - FPG 100-125 mg/dL, a plasma glucose 140 and 199 mg/dL following OGTT and HbA1c of 5.7-6.4%
3. Diabetes Mellitus

**NOTE**

DM is defined as the level of glycemia at which diabetes-specific complications occur rather than deviation from a population-based mean. So, the following values are determined based on this consideration

## CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- **SYMPOMATIC HYPERGLYCEMIA**
  - Classic symptoms of DM (polyuria, polydipsia, weight loss) **plus** random blood glucose concentration **200 mg/dL**, [enough to diagnose DM] or
- **ASYMPTOMATIC HYPERGLYCEMIA** (usually in type 2 DM)
  - Fasting plasma glucose (FPG)  $\geq 126$  mg/dl \*or
  - Hemoglobin A1c  $\geq 6.5\%$  \*or
  - 2-hr plasma glucose  $\geq 200$  mg/dl during a 75 g oral glucose tolerance test (OGTT). \*

\*2x on different day, is needed to diagnose DM

## ADDITIONAL DIAGNOSTIC STUDIES

- These studies are not routinely indicated or required to establish diagnosis
  - **C-peptide:** help to differentiate between types of DM
    - ↑ C-peptide- indicate insulin resistance & hyperinsulinemia → **T2DM**
    - ↓ C-peptide- indicate an absolute insulin deficiency → **T1DM**
  - **Urinalysis**
    - Glycosuria (expected when  $>180$  mg/dl serum glucose)  
→ **Nonspecific for DM**
    - Ketone bodies: in DKA
    - Microalbuminuria: early sign of Diabetic Nephropathy
  - **Antibody testing:** when there is clinical suspicion of T1DM

**NOTE**

- Random is defined as without regard to time since the last meal.
- Fasting is defined as no caloric intake for at least 8 h (**they can take water**)
- **HbA1c & FPG** are most reliable and convenient tests for **screening DM in asymptomatic individuals**

- **Point of care**, hemoglobin A1c should not be used for diagnostic purposes
  - Because of variation in assays
- OGTT usually used to screen gestational diabetes
- In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day

## SCREENING

Widespread use of the FPG or the HbA1c as a screening test for **type 2 DM** is recommended because

- Most patients who meet DM diagnostic criteria are asymptomatic
- Type 2 DM may be present for up to a decade before diagnosis
- Patients may present with diabetes-specific complications at the time of their diagnosis
- Treatment of type 2 DM may favorably alter the natural history of DM
- Diagnosis of prediabetes should spur efforts for diabetes prevention

## TYPE 1 DM

- Develops as a result of destruction of β-cells of pancreas by a synergistic action of **genetic, environmental and immunologic factors**
- Commonly develops before 20 years of age
- Most, but not all, individuals have evidence of islet-directed autoimmunity
- The autoimmune process is thought to be triggered by an infectious, environmental or genetic stimulus
- These triggering events cause beta cell destruction followed by progressive loss of insulin secretion.
- The rate of decline in beta cell function varies widely among individuals
- Features of diabetes do not become evident until a threshold (**around 70-80%**) loss of insulin secretion and beta cell mass occurs
- Increased insulin requirement (**during infections or at puberty**) is the triggering event for transition from glucose intolerance to frank diabetes

Comparison of Type 1 vs Type 2 DM

Clinical features	Type 1	Type 2
Age of diagnosis	Majority < 30 years*, but may occur at any age	Typically, > 30 years*, but incidence increasing in adolescent and also in children (increased obesity)

Weight	Usually, thin	> 90 % at least overweight
Insulin dependent	yes	May not require insulin therapy initially
Risk of DKA	High	Low
Autoantibodies	Present	Mostly absent
Insulin sensitivity	Normal when controlled	Decreased
Family history of diabetes	Infrequent (5 to 10%)	Frequent (75 to 90%)

\*In westerns they use 25 years rather than 30 years

### GENETIC CONSIDERATIONS

- Concordance\* in identical twin's ranges between **40 and 60%**
- The major susceptibility gene for type 1 DM is located in the **HLA region on chromosome 6**
- Polymorphism of HLA complex** account for **40–50% of the genetic risk**
- The risk of developing type 1 DM is
  - 3–4% if the parent** has type 1 DM and
  - 5–15% in a sibling** (depending on which HLA haplotypes are shared)
  - If mother has DM → child's risk **2%**
  - If father has DM → child's risk **4.6%**
  - If both parents have DM → child's risk **10%**
- Hence, 75% of individuals with type 1 DM do not have a first-degree relative with this disorder

\* The probability that a pair of individuals will both have certain characteristic, given that one pair has the characteristic

### PATOPHYSIOLOGY

- In autoimmune reaction against β-cell, other cells (**α, β, δ and PP cells**) are inexplicably spared
- In this autoimmune process: -
  - Islet cell autoantibodies are formed
  - T-cell infiltrates the pancreas
  - Release of cytokines (TNF-α, IL-1, INF-γ) takes place
- Islet cell autoantibodies that help us to diagnose type 1 DM are against **GAD (glutamic acid decarboxylase), insulin, IA-2/ICA-512**

- The three identified environmental factor triggering autoimmune destruction of islet cell in a genetically susceptible individual are
  - Virus (coxsackie and rubella)
    - The most studied and most common cause is viral (rubella)
  - Bovine milk protein
  - Nitrosourea

## TYPE 2 DM

- Insulin resistance and abnormal insulin secretion are central causes
- Most studies support the view that insulin resistance precedes an insulin secretory defect
  - But diabetes develops only when insulin secretion becomes inadequate

## RISK FACTORS FOR TYPE 2 DM

- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Overweight or obese ( $BMI \geq 25 \text{ kg/m}^2$ )
- Physical inactivity
- Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Previously identified with impaired fasting glucose (IFG), IGT, or HbA1c of **5.7-6.4%**
- History of Gestational DM
- Hypertension (blood pressure  $\geq 140/90 \text{ mmHg}$ )
- HDL cholesterol level  $<35 \text{ mg/dL (0.90 mmol/L)}$  and/or a triglyceride level  $>250 \text{ mg/dL (2.82 mmol/L)}$
- Polycystic ovary syndrome or acanthosis nigricans
- History of cardiovascular disease

## GENETIC CONSIDERATIONS

- Has a strong genetic component
- Concordance in identical twins is between **70 and 90%**
- In individuals with both parents having type 2 DM, the risk approaches **40%**

## PATHOPHYSIOLOGY

- Type 2 DM is characterized by
  - impaired insulin secretion,
  - insulin resistance,
  - excessive hepatic glucose production,
  - abnormal fat metabolism, and
  - systemic low-grade inflammation.
- Patients  $\geq 80\%$  are obese, visceral, or central (as evidenced by the hip-waist ratio)
- Adipocytes secrete biologic product like (**leptin, TNF- $\alpha$ , free fatty acids, resistin, adiponectin, retinol binding protein 4**) which modulate insulin sensitivity
  - These, resulting in insulin resistance in liver and skeletal muscles
- **Insulin resistance:**
  - Results from a combination of genetic susceptibility and obesity
  - It is a prominent feature of type 2 DM
  - Insulin-sensitive tissues affected are **muscle, liver, and fat**
  - Impairs glucose utilization by insulin-sensitive tissues (resulting in **postprandial hyperglycemia**) and
  - Increases hepatic glucose output (resulting in **increased FPG level**)
- **Impaired insulin secretion:**
  - Insulin secretion initially increases in response to insulin resistance
  - Then after it subsequently decreases, **why?**
  - Proposed causes for the decrement are:
    - Amyloid deposition around the islets in longstanding DM.
    - Chronic hyperglycemia paradoxically impairs insulin secretion (**glucose toxicity**) and
    - Elevated free fatty acid may reduce insulin secretion (**lipotoxicity**).
- **Increased hepatic glucose and lipid production**
  - Insulin resistance in the liver reflects
    - Failure of hyperinsulinemia to suppress gluconeogenesis
    - Which results in fasting hyperglycemia and decreased glycogen storage
  - Insulin resistance in adipose tissue results
    - Increased lipolysis and free fatty acid flux from adipocytes

- Leading to **increased VLDL-triglyceride, decreased HDL and increased LDL**
- These causing **dyslipidemia**
- Leads to nonalcoholic fatty liver disease and abnormal liver function tests

## PREVENTION

- Lifestyle modifications and pharmacologic agents prevent or delay the onset of DM
  - Because type 2 DM is preceded by a period of **IGT or IFG**
- **Diet and exercise for 30 min/d five times/week** in individuals with IGT prevented or delayed by **58%, development of type 2 DM.**
- **Metformin** is considered in individuals with **both IFG and IGT**, with.
  - Age <60 years,
  - BMI  $\geq 35$  kg/m<sup>2</sup>, and
  - Women with a history of GDM
- Metformin prevented or delayed diabetes by **31%** compared to placebo
- Individuals with **IFG, IGT, or an HbA1c of 5.7–6.4%** should be monitored annually

## COMPLICATIONS OF DIABETES MELLITUS

Acute complications	Chronic complication
<ol style="list-style-type: none"> <li>1. Diabetic ketoacidosis</li> <li>2. Hyperglycemic hyperosmolar state</li> <li>3. Hypoglycemia</li> </ol>	<p><b>Vascular</b></p> <ol style="list-style-type: none"> <li>1. Microvascular           <ul style="list-style-type: none"> <li>– Retinopathy</li> <li>– Neuropathy</li> <li>– Nephropathy</li> </ul> </li> <li>2. Macrovascular           <ul style="list-style-type: none"> <li>– Coronary artery disease</li> <li>– Peripheral arterial disease</li> <li>– Cerebrovascular disease</li> </ul> </li> </ol> <p><b>Avascular complications</b></p> <ul style="list-style-type: none"> <li>– GI</li> <li>– Genitourinary</li> <li>– Dermatologic</li> <li>– Infections, etc.</li> </ul>

## ACUTE COMPLICATIONS

### 1. DIABETIC KETOACIDOSIS

- Associated with absolute or relative **insulin deficiency, volume depletion, and acid-base abnormalities**
- Consists of the biochemical triad of **hyperglycemia, ketonemia, and high anion gap metabolic acidosis**
- Commonly occurs in type 1 DM (and in **ketosis prone type 2DM\***)
  - \* Type 2 DM with serious infection, trauma and cardiovascular or other emergencies
- May be the initial presentation of type 1 DM in 25% of patients
- **Hyperglycemia (> 250 mg/dL), ketosis and metabolic acidosis are features**
- Sometimes DKA can occur in relatively lower or even normal blood sugar (**Euglycemic DKA**)
- DKA and HHS Occur together in 30% of patients
- **Ketonemia** is a consistent finding in DKA and distinguishes it from simple hyperglycemia.
- Ketones, should be measured in individuals with type 1 DM when
  - The plasma glucose is > 250 mg/dL
  - During a concurrent illness, or
  - With symptoms such as nausea, vomiting, or abdominal pain

- The differential diagnosis of DKA includes
  - Starvation ketosis
    - Hyperglycemia rarely presents
  - Alcoholic ketoacidosis (AKA)
    - bicarbonate usually >15 meq/L
    - total ketone bodies are much greater than in DKA
    - with a higher  $\beta$ -OHB to acetoacetate ratio of 7:1 versus 3:1 in DKA
    - hyperglycemia seldom presents
  - Other forms of increased anion-gap acidosis
    - Lactic acidosis
    - Toxins (salicylate, Methanol, Ethylene glycol, ...)
    - Renal failure (acute and chronic)

## PATOPHYSIOLOGY

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- DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (**glucagon, catecholamines, cortisol, and growth hormone**)
- **Insulin deficiency and glucagon excess** are necessary for DKA to develop
- Ketosis results from
  - Insulin deficiency resulting mobilization and oxidation of fatty acids,
  - Increased substrate for ketogenesis,
  - Increased ketogenic state of the liver,
  - Decreased ketone clearance
- Metabolic acidosis ensues,
  - When bicarbonate stores are depleted, which neutralize ketone bodies
  - Increased lactic acid production
- The major cause of water deficit in DKA and HHS is glucose-mediated osmotic diuresis

## CONDITIONS PRECIPITATING DKA

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- Inadequate insulin administration
- Infection (pneumonia/UTI/ gastroenteritis/sepsis)
- Infarction (cerebral, coronary, mesenteric, peripheral)
- Drugs (cocaine)
- Pregnancy
- In up to 20-30% of cases no precipitant factors could be identified

## CLINICAL FEATURES

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- Symptoms and signs of DKA usually develop over 24 h
- Symptoms
  - Nausea/vomiting (**often prominent**)
  - Thirst/polyuria
  - Abdominal pain
  - Shortness of breath
- Signs
  - Tachycardia
  - Dehydration/hypotension (2ry to volume depletion and peripheral vasodilation)
  - Kussmaul respirations and fruity odor breath (2ry to metabolic acidosis and increased acetone) **are classic signs**
  - Abdominal tenderness (may resemble acute pancreatitis or ruptured viscus)
  - Lethargy/obtundation/cerebral edema/possibly coma (**usually in children**)

## DIAGNOSIS

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The three important laboratory abnormalities to diagnosis DKA

- Hyperglycemia (serum glucose  $> 250 \text{ mg/dL}$ ),
- ketones
  - Acetoacetate (**urine**, Nitroprusside reagent based), **commonly used**
  - Acetone (**urine**)
  - $\beta$ -hydroxybutyrate (**serum** form is most preferred)
- Metabolic acidosis (serum bicarbonate  $< 15 \text{ mmol/L}$  with increased anion gap)

## Electrolyte and renal function

- Sodium
  - In hyperglycemic crises, glucose becomes osmotically effective and
  - causes water shifts from intracellular space to the extra cellular space
  - resulting in dilution of sodium concentration – **dilutional or hyperosmolar hyponatremia**
  - As a result, corrected serum sodium concentration could be calculated as:
    - $[\text{Na}^+] + (1.6 \text{ mEq/L of Na for every } 100\text{mg/dl serum glucose that is above } 100\text{mg/dl})$

E.g., Let's say: serum Na<sup>+</sup> is 136 mEq/l and blood glucose is 450 mg/dl

Corrected Na<sup>+</sup> concentration will be:

$$136 + (1.6 \times 3) = 140.8$$

- **Potassium**
  - Normal or elevated (despite a total body deficit)
- **Magnesium**
  - Typically, low (due to osmotic diuresis)
- **BUN and Creatinine**
  - Elevated due to osmotic diuresis and dehydration
  - Typically responds to fluid resuscitation
  - If it doesn't respond to fluid resuscitation, needs prompt further investigation

## TREATMENT

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- DKA is a medical emergency

### Objectives of treatment

- Attention to ABC immediately on arrival
- Replace fluid losses
- Replace deficient insulin
- Replace electrolyte losses and restore acid-base balance
- Seek the precipitating cause and treat appropriately

#### 1. Replace fluids

- Total body water deficit is approximately 6 L (9L in HHS)
- The goal is to replace half of the estimated water and sodium deficit over a period of 12-24 hours
- Give **2–3 L of 0.9% saline** over first **1–3 h** (10–20 mL/kg/hr.)
- Subsequently, 0.45% saline at 250–500 mL/hr.
- Change to 5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches **≤ 250 mg/dL** and **≤ 300mg/dl in HHS**.
- Intravascular volume expansion reduces serum blood glucose
  - Through Osmotic diuresis and modulation of counter-regulatory hormone release
- Fluid is given with the intent of reducing glucose at a rate of **50 to 75 mg/dL**

## 2. Administer short-acting regular insulin

- 10 units IV- and 10-units IM, stat, then
- If there is perfuser: 0.1units/kg per hour by continuous IV infusion (**usually preferred**)
  - It ensures rapid distribution and allows adjustment of the infusion rate
- If there is no perfuser: 5 units **preferentially I.V.**, every hour.
  - **Goal**, reduce serum glucose by **50 to 70 mg/dl in the 2-3 hours**
    - If the drop is <50mg/dl in 2-3 hours, double the regular insulin.
    - If the drop is faster, reduce the dose by half for continuous infusion and give the IM insulin every 2 hour.
- **Long-acting plus SC short-acting insulin**, as soon as the patient resumes eating, b/c it
  - facilitates transition to an outpatient insulin regimen and
  - reduces length of hospital stay

### NOTE

- The rapid decline in the plasma glucose within the first 1–2 h is related to volume expansion
- Rapid correction of the serum glucose could lead to cerebral edema
- So, fluid should be given cautiously

## 3. Replace K+

- **10 meq/h** when plasma **K+ <5.0–5.2 meq/L** (or 20–30 meq/L of infusion fluid),
  - With ECG, urine flow and normal creatinine documented
- Administer **40–80 meq/h** when plasma **K+ <3.5 meq/L** or if bicarbonate is given
- If **K+>5.2 mmol/L (5.2 meq/L)**, do not supplement K+ until the potassium is corrected
- If **K+ <3.3 mmol/L (3.3 meq/L)**, **do not administer insulin** until the potassium is corrected.
- The goal is to maintain the serum potassium at **>3.5 mmol/L (3.5 meq/L)**

## 4. Assess for precipitant factors

## 5. Follow-up of response

- Blood glucose every 1–2hrs
- Urine ketones every 4hr
- Electrolytes (especially K+) every 6 h for first 24 h
- V/S, fluid intake and output every 1-4hr

## 2. HYPERGLYCEMIC HYPEROSMOLAR STATE

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- The prototypical patient with HHS is
  - An elderly individual with type 2 DM
  - With a several-week history of **polyuria, weight loss, and deprived of water intake**
- Progresses relatively slowly
  - There is sufficient amount of insulin present to prevent lipolysis and ketogenesis
  - The major features are
    - Severe hyperglycemia (**often 600mg/dl to 1200 mg/dl**) and
    - Profound dehydration

### TREATMENT

- Is like the management of DKA, but
  - Needs high (**up to 8-10 L**) fluid replacement
  - Potassium replacement is not usually needed (unless indicated by low K<sup>+</sup> level)

### COMPLICATIONS OF DKA AND HHS

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- hypoglycemia and hypokalemia (**most common**)
- Cerebral edema
- Hypoxemia and
- rarely non-cardiogenic pulmonary edema

## 3. HYPOGLYCEMIA

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- Hypoglycemia is defined as blood sugar values  $\leq 70 \text{ mg/dl}$ 
  - Except during pregnancy, and during prolonged fasting ( $>24 \text{ h}$ )
- Commonly caused by drugs used to treat diabetes mellitus, and alcohol
  - insulin, sulfonylurea, or glinides
- commonly occurs in patients with type 1 diabetes
- Because the number of T2DM is increasing the prevalence of hypoglycemia is now greater in T2DM
- Whipple's triads of hypoglycemia
  - I. Symptoms consistent with hypoglycemia,
  - II. A low plasma glucose, and
  - III. Relief of symptoms after the plasma glucose level is raised
- Estimated **6–10%** of people with T1DM die because of hypoglycemia
- Frequent hypoglycemia may cause **hypoglycemia unawareness**

- **Hypoglycemia unawareness**

- Is loss of the warning adrenergic and cholinergic symptoms
- Caused by attenuated sympathoadrenal response
- Patients will have **6x** risk of **severe iatrogenic hypoglycemia** during intensive glycemic therapy of their diabetes

**Common risk factors for hypoglycemia**

- Fasting or missed meals
- Insufficient meals
- Overdose of hypoglycemic agents or insulin
- Exercise
- Chronic kidney disease, sepsis
- Hepatic failure
- Other drugs and alcohol consumption

**CLINICAL MANIFESTATIONS**

- Autonomic manifestations (“**You are hungry**”)
  - Anxiety
  - Tremor
  - Palpitations
  - Sweating
  - Hunger and
  - Paresthesia
- Neuroglucopenic manifestations (“**Your nerves are hungry**”)
  - headache
  - Extreme Fatigue
  - cardiac arrhythmias
  - Confusion
  - Seizure
  - drowsiness
  - lethargy and
  - coma

## TREATMENT

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- Hypoglycemia is a medical emergency
- Do not wait for confirmation if test is not readily available
- change in mental status in a diabetic is considered to indicate hypoglycemia until proven otherwise
- If the patient is able and willing give oral treatment with
  - Table sugar solution,
  - Mirinda,
  - Other glucose-containing fluids,
  - 3-4 candy bars, or food
- If the patient is unable or unwilling (because of neuroglycopenia)
  - IV administration of 50ml of 40% dextrose (~25 g)
  - Followed by a 10% glucose infusion with serial plasma glucose measurements
- Start oral feeding as soon as possible
- Follow the patient 24/48 hr if the cause is sulfonylurea

## CHRONIC COMPLICATIONS OF DIABETES MELLITUS

- Are related to hyperglycemia
- Usually do not appear until the second decade of hyperglycemia
- In type 2 DM, both glucose-related and insulin resistance-related complications appear at the time of diagnosis
  - This is because of long asymptomatic period of hyperglycemia

### CLASSIFICATION

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- **Microvascular complications (retinopathy, neuropathy, nephropathy)**
  - Are diabetes-specific,
  - Result from chronic hyperglycemia
- **Macrovascular complications (CHD, peripheral arterial disease [PAD], cerebrovascular disease)**
  - Are both shared with the general population and diabetes-specific

### MECHANISMS OF COMPLICATIONS

- Chronic hyperglycemia is the important etiologic factor, though the mechanism is unknown
- Emerging hypothesis is that
  - **Hyperglycemia** leads to epigenetic changes and
  - Influence gene expression in affected cells
  - **Chronic hyperglycemia** leading to formation of glycation end products, and
  - Cell surface receptor and/or nonenzymatic glycation mediated intra- and extracellular proteins cross-linking, resulting
    - Accelerated atherosclerosis,
    - Glomerular dysfunction,
    - Endothelial dysfunction, and
    - Altered extracellular matrix composition

## DIABETIC RETINOPATHY (DR)

- Individuals with DM are **25 times** more likely to become legally blind than those without DM
- The individual lifetime risk of DR
  - 50–60% in patients with type 2 diabetes and
  - over 90% in patients with type 1 diabetes
- common cause of blindness in adults between 20-74 years of age in developed countries
- At least minimal retinopathy is almost 100% after 20 years

### RISK FACTORS

1. Hyperglycemia (elevated HbA1c levels)
  - According to Diabetes Control and Complications Trial (DCCT), intensive glucose control
    - Reduced the risk of developing retinopathy **by 76% and**
    - In patients with pre-existing retinopathy, slowed progression of the DR **by 54%**
2. Rapid Improvement in Glycemic Control
  - can worsen DR
  - Worsening can occur as soon as **3 months** after initiating intensive glycemic control
  - But usually occur during the first **6–12 months** of improved glycemic control
  - Risk factor for early worsening are
    - higher HbA1c level and reduction during the first 6 months of treatment (**most important**)
    - type 2 diabetes treated with insulin or GLP-1 agonists
    - post bariatric surgery
    - pregnant women with diabetes
    - following pancreatic transplants in patients with type 1 diabetes
3. Hypertension
  - There is no specific data that suggests lowering BP has direct effect on DR
  - But consider RAS inhibitor to control BP in those with or at high risk of DR
    - As it has beneficial effects on renal disease, has also for DR
4. Hyperlipidemia

- Fibrates (fenofibrate and etofibrate) have beneficial effects on the progression of diabetic retinopathy
  - The data on the benefit of statin therapy on DR are not very strong
5. Pregnancy
- Diabetic retinopathy may progress during pregnancy and up to one year postpartum
6. Genetics
- There is familial r/ship

## PATHOGENESIS

Histopathologic analysis shows

- Thickening of capillary basement membranes,
- Microaneurysm formation (outpouchings of the capillary wall)
  - serve as sites of fluid and lipid leakage, leading to the development of **diabetic macular edema**
- Loss of pericytes
- Capillary acellularity and
- Neovascularization

Biochemical theories

- Toxic effects from sorbitol accumulation
- with subsequent cellular and biochemical changes leading to
  - increased vascular permeability and endothelial cell proliferation

## CLINICAL FEATURES

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### NONPROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

- The earliest clinical sign of diabetic retinopathy is **microaneurysm**,
  - A red dot seen on ophthalmoscopy that varies from 15 to 60 microns in diameter

Figure. Microaneurysms and intraretinal hemorrhages in Nonproliferative retinopathy. (UCSF Department of Ophthalmology)



### The severity of NPDR can be graded as

1. **Mild:** microaneurysms with hemorrhage or hard exudates (lipid transudates)
2. **Moderate:** cotton-wool spots (focal infarcts of the retinal nerve fiber layer or areas of axoplasmic stasis) or intraretinal microvascular abnormalities (dilated and tortuous retinal vessels, or intraretinal neovascularization)
3. **Severe:** we dx if **one of the 4-2-1 rule** is met
  - Hemorrhages and microaneurysms are present in **4 quadrants**
  - Venous beading is present in **2 quadrants**
  - Moderate intraretinal microvascular abnormalities are present in **1 quadrant**
4. **very severe:** if two of the **4-2-1 rule** is met

**NB:** As the grade increases the chance of evolution to proliferative retinopathy within 5 years also increases

The above grading is required for management purpose

- Very severe NPDR had a **60x** risk of developing high-risk proliferative retinopathy after 1 year compared with eyes with mild NPDR
- Early treatment with laser is useful for very severe NPDR (not for mild or moderate)

### DIABETIC MACULAR EDEMA (DME)

- The most common cause of vision loss in NPDR
- Caused by swelling of the center of macula, the fovea

### PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

- Changes in NPDR plus **neovascularization** occurs

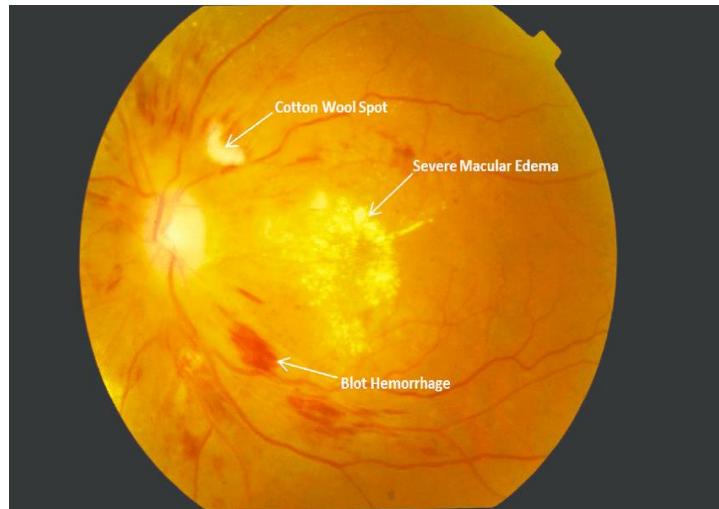
**Figure.** Active neovascularization in PDR. Fibrovascular proliferation overlies the optic disc (white arrow). Loops of new vessels are especially prominent superior to the disc and extending into the macula, where leakage of fluid has led to deposition of a ring of hard exudate around the neovascular net (black arrow). (UCSF Department of Ophthalmology)



- Vision loss in proliferative diabetic retinopathy results from three main causes
  1. Vitreous hemorrhage
  2. Retinal detachment
  3. Macular nonperfusion or coexisting diabetic macular edema

### TREATMENT

- The most effective therapy is prevention
- Intensive glycemic and blood pressure control will delay the development and slow the progression of retinopathy
- Laser photocoagulation and/or anti-VEGF therapy (intravitreous injection) in
  - Severe Nonproliferative
  - Proliferative retinopathy
  - Macular edema
- Surgical vitrectomy is indicated for:
  - Severe proliferative retinopathy
  - Vitreous hemorrhage and/or traction involving the macula



### DIABETIC NEPHROPATHY

- Leading cause of chronic kidney disease (CKD), ESRD, and CKD requiring renal replacement therapy
- Occur in **20 – 40 %** of DM patients
- If a patient is on dialysis, shows poor prognosis
- Albuminuria, increase risk of cardiovascular disease and CKD
- Smoking accelerates the decline in renal function
- usually accompanied by retinopathy; lack of retinopathy suggests another cause
- Known risk factors include
  - Race (African Americans, Native Americans, and Hispanic) and
  - Family history of diabetic nephropathy
- DM patients are predisposed to radiocontrast-induced nephrotoxicity
- So, in patients having contrast exposure
  - hydrate before and after dye exposure,
  - monitoring serum creatinine for 24–48 h following the procedure and

- Metformin should be held until postintervention confirmation of preserved kidney function

## NATURAL HISTORY

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- **At 1<sup>st</sup> year of DM;** Glomerular hyperperfusion and renal hypertrophy occurs
  - GFR will increase
- **Within the first 5 years;** thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur
  - The GFR returns to normal
- **After 5–10 years of type 1 DM;** microalbuminuria usually ensues

Nephropathy in type 2 DM differs from that of type 1 DM

1. Albuminuria may present at the time of diagnosis
2. Hypertension may accompany albuminuria
3. Nonalbuminuric diabetic kidney disease is more common

## DIAGNOSIS

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- Is mainly clinical
- Gold standard is kidney biopsy
- Presence of albuminuria is not a must to diagnose Diabetic Kidney Disease
- **Persistent albuminuria and/or decreased GFR for at least 3 months is diagnostic**
  - 3 months is b/c, transient abnormalities could give us these abnormal parameters
- Albuminuria is defined as
  - $\geq 30 \text{ mg/day}$  (if measured by timed collection)
  - $\geq 30 \text{ mg/g}$  (if using spot urine albumin to Cr ratio), **recommended for diagnosis**
- Decrease GFR is defined as
  - $\text{GFR} < 60 \text{ ml/min}/1.73 \text{ m}^2$
- “**Rapid GFR decline**” is of greatest prognostic importance than albuminuria, b/c
  - Albuminuria may regress even from the severely increased range.
  - Also advanced stage of CKD may occur before the onset of albuminuria or without albuminuria

## NONALBUMINURIC DIABETIC KIDNEY DISEASE

- Is defined as reduced GFR without albuminuria
- Prevalence, women > men
- Has slower progression to ESRD than albuminuric ones
- Type 1 DM (eGFR < 60) 7 to 24 % are nonalbuminuric (urine albumin < 30 mg/day)

- Type 2 DM with reduced GFR, 39 to 52 % are nonalbuminuric

## SCREENING

- Type 1 DM after 5 years
- Type 2 DM at the time of diagnosis
  - **Because of their long asymptomatic period**

## TREATMENT

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- optimal therapy is prevention by control of glycemia
- So, management is mainly slowing the progression, by: -
  1. Improving glycemic control
  2. Strict BP control
    - **<140/90 mmHg** in DM patient
    - **<130/80** in those with risk of CVD and CKD progression
  3. Administration of an ACE inhibitor or ARB
    - used to reduce albuminuria and associated decline in GFR
  4. Treating dyslipidemia
- GLP-1 receptor agonists and SGLT2 Inhibitors **have evidence of cardiac or kidney benefit**
- As compared with nondiabetic individuals, hemodialysis in patients with DM
  - Have frequent complications, such as hypotension (due to autonomic neuropathy or loss of reflex tachycardia),
  - more difficult vascular access, and

## DIABETIC NEUROPATHY

- It is a clinical syndrome that affect regions of nervous system either singly or combined
- Occurs in ~50% of individuals
- Both myelinated and unmyelinated nerve fibers are lost
- It is the primary risk factor for foot ulceration
  - which is responsible for **50-75% non-traumatic amputation**
- It is critically important to annually (at least) examine the feet
  - 5 years after diagnosis of type 1 DM and
  - At the time of diagnosis of type 2 DM

## SYMPTOMS

- Loss of thermal and pain sensation
  - loss of small fiber-mediated sensation (**anterior spinothalamic tract**)
- Loss of touch and vibration sensation
  - large fiber impairment (**posterior column**)
- Paresthesia and pain
  - sensory fiber involvement

## CLASSIFICATION

Diabetic neuropathies			
A. Diffuse Neuropathy	B. Mononeuropathy (mononeuritis multiplex) (atypical forms)	C. Radiculopathy or polyradiculopathy (atypical forms)	D. Non diabetic neuropathies common in diabetes
1. Distal symmetric polyneuropathy (DSPN) <ul style="list-style-type: none"> <li>▪ 1° small fiber neuropathy</li> <li>▪ 1° large fiber neuropathy</li> <li>▪ Mixed small and large fiber neuropathy (<b>most common</b>)</li> </ul> 2. Autonomic <ul style="list-style-type: none"> <li>– Cardiovascular</li> </ul>	1. Isolated cranial or peripheral nerve (Eg. CNIII ( <b>Most common</b> ), Ulnar, median, femoral, peroneal) 2. Mononeuritis multiplex (if confluent may	1. Lumbosacral polyradiculopathy 2. Thoracic radiculopathy	

<ul style="list-style-type: none"> <li>○ Reduced HRV</li> <li>○ Resting tachycardia</li> <li>○ Orthostatic hypotension</li> <li>○ Sudden death (malignant arrhythmia)</li> </ul> <p>3. Gastrointestinal</p> <ul style="list-style-type: none"> <li>○ Diabetic gastroparesis (gastropathy)</li> <li>○ Diabetic enteropathy (diarrhea)</li> <li>○ Colonic hypomotility (constipation)</li> </ul> <p>4. Urogenital</p> <ul style="list-style-type: none"> <li>○ Diabetic Cystopathy (neurogenic bladder)</li> <li>○ Erectile dysfunction</li> <li>○ Female sexual dysfunction</li> </ul> <p>5. Sudomotor dysfunction</p> <ul style="list-style-type: none"> <li>○ Distal hypohydrosis/anhedrosis</li> <li>○ Gustatory sweating</li> </ul> <p>6. Hypoglycemia unawareness</p> <p>7. Abnormal pupillary function</p>	<p>resemble polyneuropathy)</p>	<ul style="list-style-type: none"> <li>- Pressure palsies</li> <li>- Chronic inflammatory demyelinating polyneuropathy</li> <li>- Radiculoplexus neuropathy</li> <li>- Acute painful small fiber neuropathies (treatment induced)</li> </ul>
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## PREDISPOSING FACTORS

- Duration of diabetes and glycemic control
- Greater BMI
- Smoking
- Presence of cerebrovascular disease
- Elevated triglycerides, and
- Hypertension

## DISTAL SYMMETRIC POLYNEUROPATHY (DSPN)

Most common form of diabetic neuropathy

It occurs in both type 1 and type 2 DM with similar frequency

It may already be present at the time of diagnosis of type 2 DM

Characteristically

- **symmetric, glove and stocking distribution**

- length dependent sensorimotor polyneuropathy
- result from chronic hyperglycemia and cardiovascular risk

In the absence of painful symptoms, the onset of DPN is insidious

- Usually discovered by a detailed neurological examination

Although around 50% do not have symptoms of neuropathy

- **distal sensory loss and pain** are frequently encountered presentation

Painful DPN occurs in up to 34% of patients

- and interferes significantly with quality of life

## **CLINICAL PRESENTATION**

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Symptoms begin in the toes

Progressing in a stocking and then a glove distribution as the disease progresses

### **Sensory symptoms**

- Numbness (“dead feeling”)
- Paresthesia, and
- Neuropathic pain (hyperalgesia, allodynia, deep aching, burning and sharp stabbing sensations)

### **In advanced neuropathy**

- Loss of proprioception,
- Foot deformity, and
- Abnormal muscle sensory function

### **On Physical examination**

- A symmetrical **stocking like** distribution of **sensory abnormalities in both lower limbs**
- Hands may be involved (**in more severe cases**)
- All sensory modalities can be affected
  - Vibration (**earliest to be lost**), touch and position perceptions
    - large A $\alpha$ /B fiber damage
  - Pain, with abnormal heat and cold temperature perception
    - small thinly myelinated A $\delta$  and unmyelinated C fiber damage
- Deep tendon reflexes: absent/reduced
- Small muscle wasting **of the foot and extensor hallucis longus**

**Peripheral neuropathy**



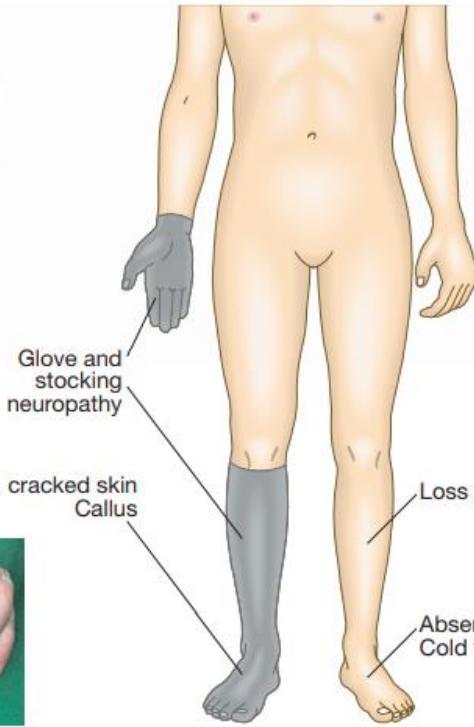
▲ Charcot foot



▲ Neuropathic ulcer



▲ Clawing of toes



**Peripheral vascular disease**



▲ Proximal arterial occlusion



▲ Digital gangrene

**Diabetic foot disease.** Patients with diabetes can have neuropathy, peripheral vascular disease or both.

Clawing of the toes is thought to be caused by intrinsic muscle atrophy and subsequent imbalance of muscle function, and causes greater pressure on the metatarsal heads and pressure on flexed toes, leading to increased callus and risk of ulceration.

A Charcot foot occurs only in the presence of neuropathy, and results in bony destruction and ultimately deformity (this X-ray shows a resulting 'rocker bottom foot').

The angiogram reveals disease of the superficial femoral arteries (occlusion of the left and stenosis of the right). Insets (Proximal arterial occlusion)

From <http://emedicine.medscape.com/article/460178-overview#a0104>

## FOCAL AND MULTIFOCAL NEUROPATHIES

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Focal limb neuropathies are usually due to entrapment

### ENTRAPMENT SYNDROMES

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- Has gradual onset (start slowly)
- occur at entrapment sites such as **carpal tunnel**
- Median, ulnar, radial, lateral femoral cutaneous, fibular, and plantar nerves are vulnerable
- **Carpal tunnel syndrome**
  - **Three times** common in diabetes patients than healthy population
  - Found in up to **one third** of patients with diabetes
  - Its increased prevalence in diabetes may be related to
    - Repeated undetected trauma
    - Metabolic changes
    - Accumulation of fluid or edema
  - Diagnosis is confirmed by electrophysiological studies.
  - Treatment consists of
    - Rest
    - Placement of a wrist splint in a neutral position to avoid repetitive trauma
    - Anti-inflammatory medications and steroid
    - Surgery should be considered if weakness appears and medical treatment fails

### MONONEUROPATHY

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- Often occur in the older population
- Have an **acute (sudden) onset**, associated with pain
- Have a self-limiting course resolving in 6–8 weeks
- Peripheral nerve involvement
  - Median (5.8% of all diabetic neuropathies)
  - Ulnar (2.1%)
  - Radial (0.6%), and
  - Common peroneal nerves
- Cranial neuropathies (extremely rare)
  - Ischemia is a proposed etiology
  - occur in older individuals with a long duration of diabetes

- third nerve palsy with spared pupillary response to light

### PROXIMAL MOTOR NEUROPATHY (DIABETIC AMYOTROPHY)

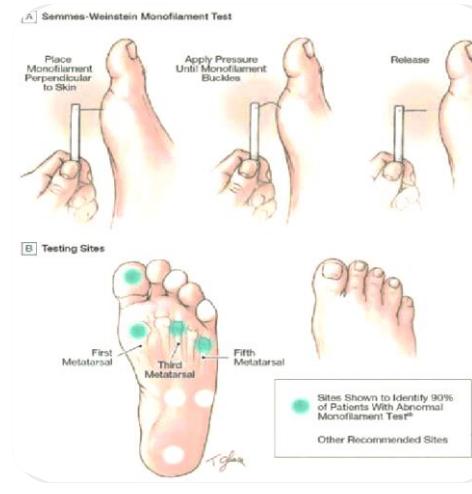
- Asymmetric involvement with severe pain in the distribution of one or more nerves over thorax, abdomen, hip and thigh.
  - Mainly proximal group of muscle is involved.
  - Most evident weakness seen in muscle innervated by femoral and obturator nerve (diabetic Amyotrophy) involving quadriceps, iliopsoas and adductor magnus.
- Clinically described based on the following common features
  - 1) common in 50 to 60 years old patients with type 2 diabetes
  - 2) with gradual or abrupt onset
  - 3) Severe pain in the thighs, hips and buttocks with significant weakness of the proximal muscles of the lower limbs and inability to rise from the sitting position (positive Gower's maneuver)
  - 4) can start unilaterally and then spread bilaterally
  - 5) often coexists with DSPN
  - 6) characterized by spontaneous or induced muscle fasciculation

### DIAGNOSIS OF DIABETIC NEUROPATHIES

- General medical and neurological history
- Neurological examination of sensation
  - 10g semmes-weinstein monofilament
  - Calibrated Rydel-Seiffer tuning fork (vibration),
  - Pin-prick (pain)
  - Tendon reflexes (knee and ankle) ... etc.
- Joint position and motor power should also be assessed

#### Toronto Classification of DPN (in short)

1. **Possible DSN:** The presence of symptoms or signs of DPN
2. **Probable DPN:** Presence of symptoms and signs of neuropathy plus 2 or more of the following
  - neuropathic symptoms,
  - decreased distal sensation, or
  - unequivocally decreased or absent ankle reflexes
3. **Confirmed DPN:** abnormality of nerve conduction and a symptom or symptoms, or a sign or signs



4. **Subclinical DPN:** The presence of no signs or symptoms of neuropathy are confirmed with abnormal nerve conduction
5. **Small fiber neuropathy (SFN)**

### TREATMENT OF DIABETIC NEUROPATHY

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Treatment of diabetic neuropathy is less than satisfactory

Prevention is critical through

- Improved glycemic control
- Lifestyle modifications (exercise, diet) in type 2 DM
- Treating hypertension and hypertriglyceridemia
- Avoid neurotoxins (including alcohol) and smoking
- consider supplementation with vitamins for possible deficiencies (B12, folate), because:
  - Metformin may reduce intestinal absorption of vitamin B12 in type 2 DM
  - Pernicious anemia is more common in type 1 DM

### Chronic, painful diabetic neuropathy

- Only symptomatic treatment available
- Duloxetine and pregabalin, or gabapentin first line
- Tricyclic antidepressants, venlafaxine, carbamazepine, tramadol, or topical capsaicin products and
- Tapentadol, a centrally acting opioid may also be used
- ***It is reasonable to switch agents if there is no response or if side effects develop***

### Autonomic neuropathy

- Orthostatic hypotension
  - Nonpharmacologic maneuvers offer some benefit
    - adequate salt intake
    - avoidance of dehydration and diuretics
    - lower extremity support hose, and
    - physical activity
  - pharmacologic
    - Midodrine and droxidopa
    - Beta blocker (in those with resting tachycardia)
  - In patients with type 1 DM Consider also the possibility Addison's disease

## DIABETIC FOOT ULCER

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- DM is the leading cause of nontraumatic lower extremity amputation in the United States
- Life time risk of foot ulcer in both type 1 and 2 DM patient is around 34%
- Foot ulcer, commonly occur at **great toe or metatarsophalangeal areas**
- Around 14-24% of ulceration will ultimately undergo amputation
- The plantar surface of the foot is the most common site of ulceration
- The following interaction of pathogenic factors in DM are responsible for diabetic foot

### 1. Neuropathy

- **Sensory neuropathy:** predispose to major or repeated minor trauma to the foot, b/c of loss of protective sensation
- **Disordered proprioception:** causes abnormal weight bearing, resulting in formation of callus or ulceration
- **Autonomic neuropathy:** results in anhidrosis and altered superficial blood flow, resulting in drying of the skin and fissure formation

### 2. Abnormal foot biomechanics (2ry to motor and sensory neuropathy)

- Leading to structural changes in the foot, hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint

### 3. Peripheral arterial disease (PAD), and Poor wound healing

- impede resolution of minor breaks in the skin
- predispose for infection

## RISK FACTORS

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- Previous foot ulceration
- Neuropathy (present in over 80% of Diabetic foot ulcer)
- Foot deformity
- Vascular disease (PAD)
- Male sex
- Diabetes for >10 years
- Smoking
- Visual impairment
- Poor glycemic control, and
- Diabetic nephropathy, especially dialysis

## RISK CLASSIFICATION

- Used to design preventive and monitoring strategies

Table showing Risk classification based on the comprehensive foot examination

Risk category	Definition	Treatment recommendation	Suggested follow-up
0	No LOPS, no PAD, no deformity	Patient education including advice on appropriate footwear	Annually (by generalist and or specialist)
1	LOPS ± deformity	Consider prescriptive or accommodative footwear	Every 3 to 6 months (by generalist and or specialist)
		If not accommodated in shoes, consider prophylactic surgery Continue patient education	
2	PAD ± LOPS	Consider prescriptive or accommodative footwear	Every 2 to 3 months (by specialist)
		Consider vascular consultation for combined follow-up	
3	History of ulcer	Same as category 1	Every 1 to 2 months (by specialist)
		Consider Consider vascular consultation for combined follow-up if PAD present	

**Key:** LOPS-Loss of protective sensation, diagnosed if monofilament or other tests are abnormal.

## EXAMINATION

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### key components of diabetic foot examination

#### 1. Inspection

- Dermatologic
  - Skin status: color, thickness, dryness, crackling
  - Sweating
  - Infection: check between toes for fungal infection
  - Ulceration
  - Calluses/blistering
- Musculoskeletal
  - Deformity (eg, claw toes, prominent metatarsal heads, Charcot joint)
  - Muscle wasting (guttering between metatarsals)

#### 2. Neurologic assessment

- 10 g monofilament + 1 of the following 4
  - Vibration using 128 Hz tuning fork
  - Pinprick sensation
  - Ankle reflexes
  - Vibration perception threshold (VPT)

#### 3. Vascular assessment

- Foot pulses
- ABI, if indicated

## ASSESSMENT OF PEDAL PULSES

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- Peripheral artery disease examination
  - Symptom
    - Claudication (leg pain usually during exercise)
  - Sign
    - Assessing pedal pulses (if absent assess for popliteal and femoral)
    - Temperature
    - Check for dependent rubor (erythematous discoloration of the limb in dependent positions)
  - Ankle brachial index testing
    - ABI is calculated by measuring SBP (by Doppler) in the brachial, posterior tibial and dorsalis pedis arteries.
    - The higher of the measurement at ankle and foot (in that limb) is divided by the higher brachial (either left or right) measurement

- **Normal ABI is 0.9 to 1.3**
- Generally, ABI is usually  $> 1$  because ankle pressure is higher than arm
- **An ABI  $<0.9$  has 95% sensitivity for detecting PAD**
- We screen for asymptomatic PAD in individuals  $>50$  years of age who have diabetes and other risk factors using ABI

## PREVENTIVE FOOT CARE

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Recommended in patients with existing neuropathy

- Avoid smoking
- Avoid going barefoot, even at home, especially on hot decks and hot sand
- Trim toenails to shape of the toe and remove sharp edges with a nail file; don't cut cuticles
- Wash in lukewarm (tepid) water, dry thoroughly (including between the toes) and check feet daily
- Shoes should be snug, but not tight, and customized if feet are misshapen or have ulcers
- Socks should fit and be changed daily

## CARDIOVASCULAR COMPLICATION

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- In DM patients marked increase in the following diseases has been observed (Framingham Heart study)
  1. PAD
  2. Coronary artery disease
    - Have worse prognosis than nondiabetics
    - more likely to involve multiple vessels
  3. MI
    - Silent ischemia (no chest pain) is common in DM
  4. CHF (risk increase 1-5x)
    - common in long-standing DM
  5. cerebrovascular disease (3x increase in stroke)
- In both type 1 and 2 DM cardiovascular death rate is twofold in men and fourfold in women
- Elevated HbA1c is predictive of risk of CHD, stroke, and all-cause mortality
- The increase in cardiovascular morbidity and mortality rates in diabetes is related to the synergism of hyperglycemia with
  - Dyslipidemia
    - **hypertriglyceridemia and reduced HDL** are most common form
    - LDL particles are more atherogenic because they are more easily glycated and susceptible to oxidation
  - Hypertension
    - Accelerates complications of DM, particularly CVD, nephropathy, and retinopathy
  - Obesity
  - Reduced physical activity
  - Cigarette smoking
  - CKD (albuminuria, reduced GFR)
  - Abnormal platelet function
  - Increased markers of inflammation, and
  - Endothelial dysfunction

## GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

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- Usually occur in Long-standing type 1 and 2 DM
- **Gastrointestinal dysfunction**
  - Gastroparesis
    - delayed gastric emptying
    - caused by parasympathetic dysfunction secondary to chronic hyperglycemia
    - with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating
    - **Nocturnal diarrhea, alternating with constipation**, is a feature
    - retinopathy and neuropathy are usually present
- **Genitourinary dysfunction**
  - Cystopathy
    - inability to sense a full bladder and
    - a failure to void completely
    - exposed for recurrent urinary tract infections
  - Female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication)
  - Erectile dysfunction and retrograde ejaculation are very common
    - may be one of the earliest signs of diabetic neuropathy

## TREATMENT

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### Gastroparesis

- Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber
  - may minimize symptoms of gastroparesis
- Avoid medications that slow gastric emptying
  - opioids, GLP-1 receptor agonists
- Metoclopramide may be used in case of severe symptoms
- Treat symptoms of GERD with antihistamine or PPI
- Diabetic diarrhea in the absence of bacterial overgrowth
  - Treat symptomatically

### Cystopathy

- scheduled voiding or self-catheterization

## Erectile dysfunction

- 5 phosphodiesterase inhibitors are effective
  - Sildenafil, tadalafil, avanafil

## INFECTIONS

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- More frequent and severe in DM, because:
  1. Abnormalities in cell mediated immunity
  2. Phagocyte dysfunction associated with hyperglycemia and
  3. Diminished vascularization
- Fungal infection is more common in DM because
  - Hyperglycemia aids the colonization and growth these species (*Candida* and others)
- Infections exclusive in the diabetic population include
  - **Rhinocerebral mucormycosis**
  - Emphysematous infections of the gallbladder and urinary tract
  - Malignant or invasive otitis externa
    - usually secondary to *Pseudomonas aeruginosa* infection
    - pain and discharge are initial symptoms
    - may progress to osteomyelitis and meningitis
- Pneumonia
  - The organisms are similar with non-diabetic population
  - However, *S. aureus*, and ***Mycobacterium tuberculosis*** are more frequent
- Urinary tract infections
  - Commonly bacterial (*E. coli*) as the general population
  - yeast species (*Candida albicans* and *Candida glabrata*) are commonly observed
- Furunculosis, superficial candidal infections, and vulvovaginitis are common
- Increased rate of colonization of *S. aureus* in the skinfolds and nares

## DERMATOLOGIC MANIFESTATIONS

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- Xerosis and pruritus (most common)
  - usually relieved by skin moisturizers
- Vitiligo and alopecia areata in type 1 DM
- Acanthosis nigricans (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces)
- Generalized or localized granuloma annulare (erythematous plaques on the extremities or trunk)
- lichen planus (violaceous papules on the cutaneous surface with or without erosions in the mouth and genitalia),
- scleredema (areas of skin thickening on the back or neck at the site of previous superficial infections)

## DIABETES MELLITUS MANAGEMENT AND THERAPIES

### OVERALL GOALS

1. Eliminate symptoms related to hyperglycemia,
2. Reduce or eliminate the long-term complications of DM
3. Allow the patient to achieve as normal a lifestyle as possible

Symptoms of diabetes usually resolve when the plasma glucose is < 200 mg/dL,

- Thus, most DM treatment focuses on achieving the second and third goals.

### COMPREHENSIVE DIABETES CARE

- Individualized glycemic goal and therapeutic plan
- Self-monitoring of blood glucose, **short term glycemic control** (individualized frequency)
- HbA1c testing (2–4 times/year) by the provider, **long term glycemic control**
  - Shows the **nonenzymatic glycation of hemoglobin** as glucose concentration elevates
  - Reflects the glycemic history over the past **2-3 months** (50% in last 1 month)
  - Is primary predictor of long-term complications of DM
  - **Glycated albumin or 1,5-anhydroglucitol** measurement used as an alternative when the HbA1c is inaccurate (e.g., **In malaria, hemoglobinopathies...**)
  - The **fructosamine assay** (measuring glycated albumin) reflects the glycemic status over the prior 2 weeks
- Lifestyle management in the care of diabetes, including:
  - Diabetes-self-management education and support
  - Nutrition therapy
    - Increase intake of fibers (wholegrain bread, cereals, lentils, and beans)
    - Reduce intake of fat and unsaturated fat
    - Choose fish and lean meat instead of fatty meat
    - Reduce portion size particularly if overweight
    - Include fruit and vegetable
  - Physical activity
    - Regular moderate-intensity aerobic physical activity
      - could be walking/ cycling/swimming for 150 min/week
    - Resistance exercise at least 2x per week
      - Free weight or weight lifting
  - Psychosocial care, including evaluation for depression, anxiety

- Detection, prevention, or management of diabetes-related complications, including:
  - Diabetes-related eye examination (**annual or biannual**)
  - Diabetes-related foot examination (**1–2 times/year by provider; daily by patient**)
  - Diabetes-related neuropathy examination (**annual**)
  - Diabetes-related kidney disease testing (**annual**)
- Manage or treat diabetes-relevant conditions, including:
  - Blood pressure (**assess quarterly**)
  - Lipids (**annual**)
  - Consider antiplatelet therapy
  - Influenza/pneumococcal/hepatitis B immunizations

Treatment goals for adults with Diabetes	
INDEX	GOAL
Glycemic Control	
HbA1c	<7.0%
Pre-prandial capillary plasma glucose	4.4–7.2 mmol/L ( <b>80–130 mg/dL</b> )
Postprandial capillary plasma glucose	<10.0 mmol/L ( <b>&lt;180 mg/dL</b> )
Blood pressure	<b>&lt;140/90 mmHg</b>

## PHARMACOLOGIC TREATMENT OF DIABETES

- The goal is to achieve an HbA1c as close to normal as possible without significant hypoglycemia
- The target HbA1c should be **<7%**
- Higher HbA1c target is required in the following patients
  - With impaired awareness of hypoglycemia (**<7.5 or 8%**) and
  - Very young or old or with comorbid conditions (**higher, > 8 or 8.5%**)

## TYPE 1 DIABETES MELLITUS

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- Insulin is the main pillar for management of Type-I DM
- Apart from insulin two other agents can be used for treatment of Type-I DM patient
  - Amylin analog—Pramlintide
  - $\alpha$ -glucosidase inhibitor—Acarbose, voglibose and miglitol.
- Goal is to design and implement insulin regimens that mimic physiologic insulin secretion
- Sources of insulin
  - human insulin and/or analogs of human insulin
  - insertion of the human proinsulin gene into **yeast and non-pathogenic E. coli**
  - They serve as the production organism
- **Intensive insulin therapy**
  - It has the goal of achieving near normal glycemia
  - It requires combined effort of
    - Patient education
    - comprehensive recording of plasma glucose measurement and nutrition intake
    - Appropriate insulin dose, that matches CHO intake
  - Benefits
    - Reduces the risks of microvascular complication by **35% to 90%** compared with conventional treatment
    - Reduction in the acute metabolic complication
    - During or prior to pregnancy reduces the risk of fetal malformations and morbidity
    - Is most effective when begun early, before complications were detectable
    - **Despite its impressive benefits, it is also accompanied by significant personal and financial costs and is therefore not appropriate for all individuals.**

## INSULIN PREPARATIONS

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Two types of insulin are currently in use

- Standard Human Insulin (NPH and regular)
- Insulin Analogues (Aspart, Glulisine, Lispro, Glargine and Determine)

Properties of Insulin Preparations			
PREPARATION	TIME OF ACTION		
	ONSET, h	PEAK, h	EFFECTIVE DURATION, h
<b>Short-acting</b>			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro	<0.25	0.5–1.5	2–4
Regular ( <i>Human insulin</i> )	0.5–1.0	2–3	3–6
Inhaled human insulin	0.5–1.0	2–3	3
<b>Long / intermediate acting</b>			
Degludec	1–9	-	42
Detemir	1–4	-	12–24
Glargine	2–4	-	20–24
NPH ( <i>intermediate acting, Human insulin</i> )	2–4	4–10	10–16

## BASIC PHYSICAL AND CHEMICAL PROPERTIES

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- **Regular human insulin**
  - crystalline zinc insulin dissolved in a clear solution
  - can be administered by any parenteral route
  - injected **pre-meal** to **blunt the postprandial rise** in glucose levels
  - delayed onset of action of 30-60 minutes
  - so, should be injected approximately 30 minutes before the meal
- **NPH (neutral protamine Hagedorn)**
  - suspension of regular insulin complexed with protamine
  - **protamine used to delay its absorption**
  - should not be administered intravenously
  - onset of action is approximately 2 hours, peak effect is 6-14 hours
  - duration of action of 10-16 hours (depending on the size of the dose)
  - serve as a basal insulin when administered at bedtime
  - basal and prandial insulin when dosed in the morning
- **Insulin aspart, glulisine and lispro**
  - crystalline zinc insulin dissolved in a clear solution 23
  - intended for subcutaneous (SQ) route

## ELIMINATION

- Insulin released by the pancreas (**into the portal vein**)
  - 50-60% degraded in liver
  - 35-45% by kidney

- insulin injected exogenously (as **not delivered into portal vein**)
  - 60% degraded by kidney
  - 30-40% by liver
  - **Clinical significance:** If renal function is altered, insulin administration will have deleterious effect on the patient, so we must have to do RFT before administering insulin.

## INSULIN REGIMENS

1. Basal standard (conventional) Regimen
  - Intermediate acting insulin (NPH) twice per day
  - With or Without Short-acting Insulin
  - Once daily dose is no more acceptable
  - BID dosing recommended even for a small dose
  - Commonly used in Ethiopia
2. Bi-Phasic “split-mixed” Regimen
  - Is simple and has only two injections per day
  - Disadvantages, due to the Dawn Phenomenon
    - nocturnal hypoglycemia (from midnight to 4:00 a.m.)
    - early morning hyperglycemia (from 4:00 to 8:00 a.m.)
3. Basal-Bolus Regimen (Intensive Insulin Therapy)
  - Also called “ideal insulin replacement therapy”
  - **Basal Insulin** – intermediate/ long-acting insulins
    - Nearly constant day-long insulin level
    - Suppress hepatic glucose production
    - Cover 50% of daily needs
  - **Bolus Insulin** – short/ rapid acting insulins (Prandial)
    - Immediate rise and sharp peak at 1 hr
    - Limit postprandial hyperglycemia
    - Cover 10-20% of total daily insulin requirement at each meal.

## DESIGNING INSULIN THERAPY

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- Total insulin dose per day Initiation, **0.2 to 0.6 units/kg/day**
  - because remaining beta cells still produce some insulin
- Maintenance – highly variable roughly 0.5 to 1 units/kg/day
  - You can go up to 1.5 unit/kg/day
- Regimen options-with NPH and regular insulin
- **Preferred regimen: NPH with premeal regular insulin**

- NPH before breakfast and at bedtime **PLUS**
- Regular Insulin three times daily injection: before breakfast, lunch, and dinner
- **Other options:** if the patient couldn't do preferred regimen
- NPH with pre-breakfast and pre-dinner regular insulin
- Mixed NPH and regular insulin -70/30 (70% NPH & 30% regular)
- Twice daily NPH injections only: Before breakfast and before bedtime

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### Example

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- Let's initiate a 60kg adult with insulin therapy (NPH and regular)
    - Initial total insulin must be **0.2-0.6 IU/kg/day**
    - So, if we start him with 0.5 IU/Kg/day, total insulin dose will be **30 IU/day**
    - Then we divide this dose into **½ NPH (15 IU/day)** and **½ regular (15 IU/day)**
    - Then administer NPH (**2/3 before breakfast and 1/3 at bedtime**)
    - Administer regular insulin (**1/2 before breakfast, 1/2 before lunch and ½ before dinner**)
- 

### METHODS OF INSULIN ADMINISTRATION

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- Calculate the initial dose as Insulin 0.2-0.6 U/kg/day
- Adjust dose by ~ 4 U every 3-5 days
- Initial Regimen should be Simple
- Insulin therapy requires a structured program employing active insulin dose titration that encompasses:
  - injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites
  - self-monitoring
  - dose titration to target levels
  - dietary understanding
  - Management of hypoglycemia

## COMPLICATIONS OF INSULIN THERAPY

1. Hypoglycemia
2. Weight Gain, Possible causes
  - Improvement in glycemic control
  - Increased food intake to treat or prevent hypoglycemia
  - Insulin itself may stimulate appetite.
3. Worsening Retinopathy
4. Insulin Allergy
5. Dawn Phenomenon
  - Blood glucose levels increase in the early morning
  - Caused by overnight growth hormone secretion and increased insulin clearance
  - It is a normal physiologic process in non-diabetic individuals
6. Somogyi Phenomenon
  - Blood glucose levels increase in the early morning
  - Thought to be from an exaggerated counterregulatory response
7. Lipodystrophy (hypertrophy /atrophy)
  - Secondary to insulin's trophic effects (lipohypertrophy)
  - Try to immune-mediated condition resulting in loss of fat at insulin injection sites (lipoatrophy)
  - Repeated single site injection
  - Easily accessible sites commonly affected
  - Forms lump at injection site
  - Less painful so patient tends to choose it for injection.
  - **Insulin absorption from this site is not reliable**

Factors	Comment
Exercise of injected area	Strenuous exercise of a limb within 1 hour of injection will speed insulin absorption.  Clinically significant for regular insulin analogs
Local massage	Vigorously rubbing or massaging the injection site will speed absorption
Temperature	Heat can increase absorption rate, including use of a sauna, shower, or hot bath soon after injection. Cold has the opposite effect

Site of injection	Insulin is absorbed faster from the abdomen.  Less clinically relevant with rapid-acting insulins, insulin glargine, and insulin detemir.
Lipohypertrophy	Injection into hypertrophied areas delays insulin absorption
Jet injectors	Increase absorption rate
Insulin mixtures	Absorption rates are unpredictable when suspension insulins are not mixed adequately (i.e., they need to be resuspended).
Insulin dose	Larger doses delay insulin action and prolong duration
Physical status (soluble vs. suspension)	Suspension insulins must be sufficiently resuspended prior to injection to reduce variability.

Table showing factors Affecting Insulin Absorption

## PATIENT EDUCATION OF INSULIN THERAPY

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1. Insulin storage
  - Store insulin preferably at 2-8 °c, in a fridge (do not freeze)
  - check expiry date
  - If fridge not available, can be kept in a cool, dark, well-ventilated place
  - A vial in use is stable at 25 °c for 6 weeks at 37°c for 4 weeks
2. To mix cloudy insulin, roll between hands
3. Transporting insulin
  - carry insulin in a handbag
  - avoid keeping insulin in direct contact with ice pack
4. Mixing Insulins
  - Inject air into the vials before drawing insulin
  - Draw soluble insulin first, then the intermediate
  - Avoid contaminating short acting insulin with the intermediate acting one
  - Should be injected with in 5 minutes of mixing
  - If there is difficulty mixing, better inject separately
5. Injection sites
  - Abdomen, thighs, buttock, arms
    - fast absorption from abdomen, slow from thigh
  - preferred sites for soluble insulin
    - **Abdomen** (good blood flow)
  - For longer acting insulin - **the thighs**
  - Use one area for a particular time of the day

- Rotate injection areas
- Avoid injecting into lipodystrophy site

6. Injection techniques

- No need of cleaning with alcohol
- If need be, clean with water
- Make a skin fold - inject at 90° in most with long needles or very thin pt. at 45°
- Slight bleeding is ok
- Never give intermediate insulin IV

7. Before changing insulin dosages

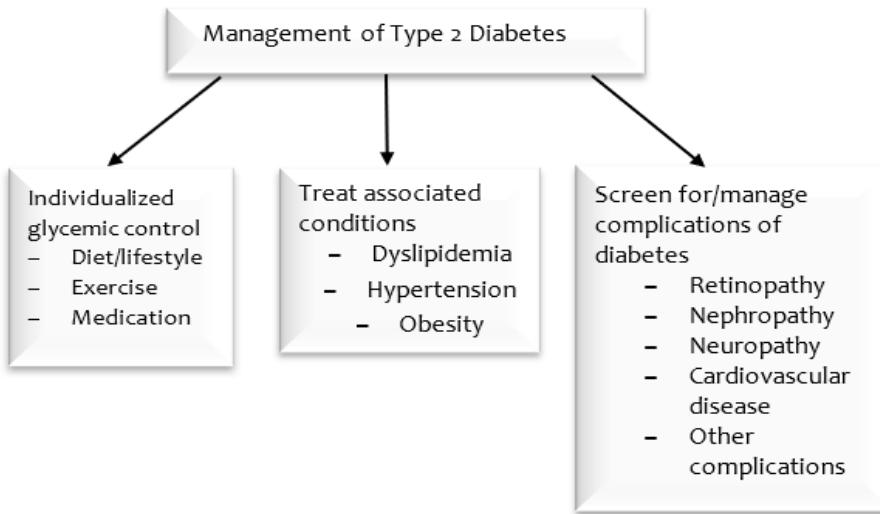
Check

- Insulin storage
- Patient compliance
- Injection techniques (resuspension, dosages, mixing procedures, & injecting)
- Injection sites
- eating plans, exercise, BG monitoring compliance
- other factors e.g., stress, infection, other illnesses

**N. B: If food is not readily available, be cautious in dose escalation**

## TYPE 2 DIABETES MELLITUS MANAGEMENT

Essential elements in comprehensive care of type 2 diabetes



The two important components of type 2 DM management are

- ↳ Lifestyle Modifications and
- ↳ medications

Type 2 DM is a complex disease:

- Patients often fail to reach treatment goals
- There are associated disturbances:
  - Over 45% are obese ( $BMI \geq 30 \text{ kg/m}^2$ )
  - As many as 75–80% have hypertension
  - Over half of patients have hypercholesterolemia
  - Atherothrombotic changes
- Effective management of Type 2 diabetes is beyond glycemic control
- Need to address BP, Lipids, Obesity and others

## PHARMACOLOGIC MANAGEMENT

Patients typically require multiple glucose lowering agents over time to maintain glycemic control

- As type 2 diabetes is a progressive disease with ongoing beta cell failure
- And eventually became insulin dependent

### The goal of diabetes management

- To improve glycemic control
- Minimizing hypoglycemia and weight gain
- Mitigating cost

### SETTING A TARGET

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The target HbA1c needs to be individualized.

HbA1c goal of **< 7%** (**glucose ~155mg/dl**) is appropriate and can be achieved safely.

A goal A1c **< 8.0-8.5%** in patients with **short life expectancy** for any reason (severe comorbidities, very old age, etc.) b/c

- The risks of tight control outweigh the long-term benefits in reduction of complications that may never be realized
- Reasonable to avoid hypoglycemia but also avoid the acute complications of hyperglycemia

### INITIATING THERAPY

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Before considering pharmacologic treatment

- Education on diet and lifestyle interventions,
- At least 150 minutes of Moderate exercise per week and
- A reduction in body weight by > 7%

In order to initiate therapy knowing the level of HbA1C is pivotal

- A1c of **6.5-7%**
  - If younger and/or obese patients (Age < 60 y, BMI > 35 kg/m<sup>2</sup>) **start metformin**
  - or allow a period of 3-6 months to assess the effects of lifestyle changes
- with an A1c **> 7%**,
  - start metformin provided no contraindications exist (eGFR < 30 ml/min/1.73 m<sup>2</sup>)
- with an initial A1c **> 9%**
  - started on combination oral therapy if they are **asymptomatic**
  - started on insulin (at least temporarily, to relieve glucose toxicity) if **symptomatic**

#### 1) Metformin

- Can be started at **500mg once daily (With evening meal)**
- Titrated (after 1-2 week, to BID) up slowly to avoid gastrointestinal (GI) side effects
- patient can stay with BID dose until 3-month A1c assessment

- If not still at goal, the dose can be further titrated to **1000mg BID (maximum dose)**  
\*Some references also say maximum dose can be 3000mg/day

Metformin is preferred as initial therapy because

- Good glycemic efficacy
- Absence of weight gain and hypoglycemia
- Tolerability and
- Favorable cost
- Has effect of decreasing cardiovascular events

### Combination Therapy

- Reviewed here based on cost and availability
- After metformin failure, we favor starting
  - Daily sulfonylurea such as glimepiride

#### 2) Glimepiride

- A1c of 7-7.5%,
  - starting a low dose of **1mg daily**
- with an A1c > 7.5%,
  - we start at **2mg**
- titrated up in 1 to 2 mg increments based on either the A1c or a FPG goal of roughly **140mg/dl**
- maximum dose of 8mg daily
- **works much more rapidly**
- common side effect weight gain and hypoglycemia

Add another agent if A1c climbs **above 7** while treating with both metformin and Glimepiride of max. dose

- **Remember**, agents should be added and not substituted

#### 3) Add pioglitazone (TZD) as a third agent

- **Pioglitazone**
  - Mechanism involves changes in gene activation
  - It can take weeks to months to see the full effect
  - start with 15mg/day and assessing the A1c change at 3 months
  - can be titrated up to 30mg once daily
  - common side effect weight gain (average 3-4 kg)

Contraindicated in

- Heart failure,

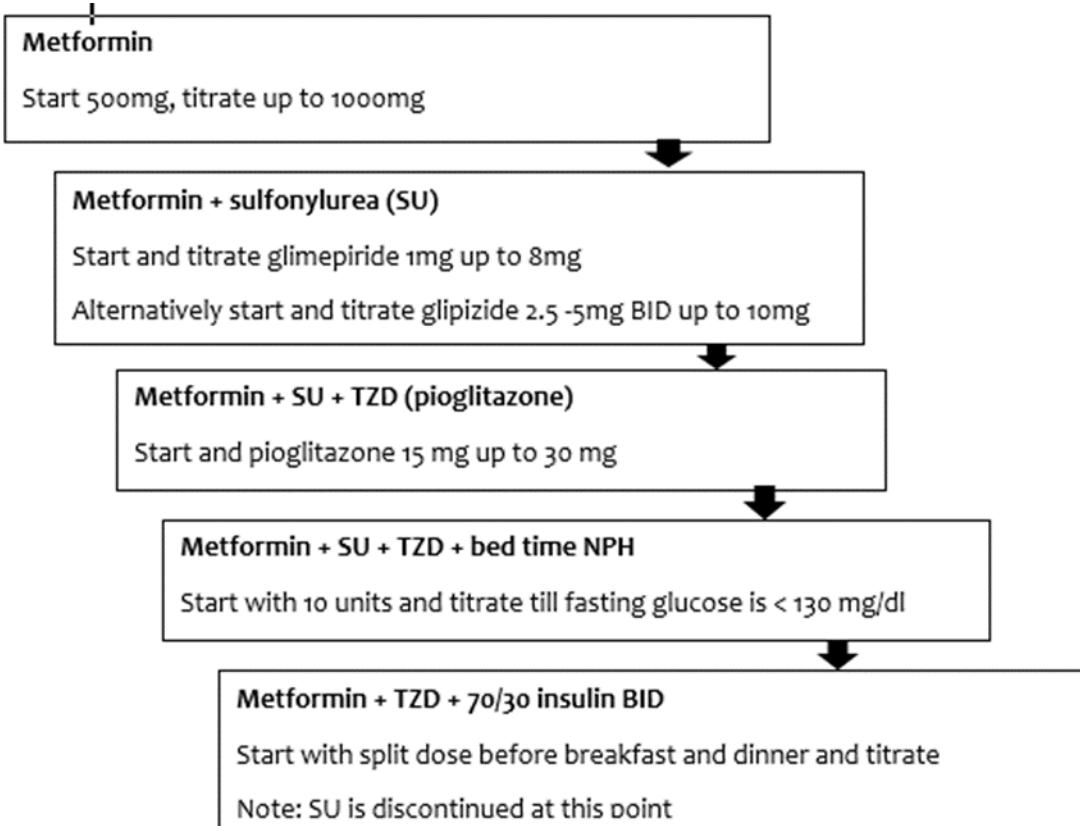
- Severe edema, and
- High risk of fractures or known osteoporosis.

4) If hyperglycemia is not still controlled with the above three combination

- Adding one injection of NPH insulin at bedtime is favored
- 10 units (0.2 U/kg) of NPH at bedtime to avoid nocturnal hypoglycemia
- Expected to lower **HbA<sub>1c</sub> 1.2-1.5%**
- Measure FBG each morning and titrate by 1 unit/day until they are consistently < 130mg/dl

Over time, despite controlling fasting hyperglycemia if postprandial glucose levels rise along with A1c

- start prandial insulin and discontinue Sulfonylurea therapy
- 70/30 combination of NPH/Regular insulin



Cost effective management algorithm of Type 2 DM

## INDICATIONS FOR INSULIN THERAPY IN T2DM

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- Patients whose glycemic target are not met despite sufficient antidiabetic treatment
- Patients with contraindication for noninsulin antidiabetic drugs, like
  - Patients with end stage renal failure
- Pregestational and gestation DM
- Hyperglycemic crisis
- **Consider in newly diagnosed patients with any of the following**
  - Hyperglycemia is severe ( $>300\text{mg/dl}$ ), especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present
  - A1C  $>10\%$
  - If the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss)

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## CHAPTER SIX

# Disorders of kidney & urinary system

Presenting problems

Acute Kidney injury

Chronic kidney disease

Glomerular disease

Polycystic Kidney disease

Tubulointerstitial kidney disease

Nephrolithiasis

### PRESENTING PROBLEMS

- Patients with kidney disease may have a variety of presentations. These features may be referable either:
  - Directly to the kidney (gross hematuria, flank pain) or
  - Extra renal symptoms (edema, hypertension, signs of uremia).
- Many patients, however, are asymptomatic and are noted on routine examination to have an abnormal renal function test or urinalysis.
- Once kidney disease is discovered, the presence or degree of kidney dysfunction and rapidity of progression are assessed, and the underlying disorder is diagnosed.
- Although the Hx and PEx can be helpful, the most useful information is initially obtained from estimation of the GFR and examination of the urinary sediment.
- The following are some of the presenting problems in renal and urinary tract disease:

#### Oliguria/anuria:

- Oliguria refers to a 24-h urine output <400 mL,
- Anuria is the complete absence of urine formation (<100 mL).
- Causes of anuria include:
  - complete bilateral urinary tract obstruction;
  - a vascular catastrophe (dissection or arterial occlusion);
  - renal vein thrombosis;
  - renal cortical necrosis;
  - severe ATN;

- combined therapy with NSAIDs, ACE inhibitors, and/or ARBs; and
  - shock (be hypovolemic, cardiogenic, or septic)
- 1) Oliguria is never normal, since at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load.
  - 2) *Nonoliguria* refers to urine output >400 mL/d in patients with acute or chronic azotemia.
  - 3) Compared with oliguric ATN, nonoliguric ATN patients have less severe potassium and hydrogen balance derangements, and recovery to normal renal function is usually more rapid.

**Hematuria:**

- Occasionally up to 12 500 cells/mL RBCs may be found in healthy individuals
- Visible (macroscopic) hematuria or non-visible hematuria (microscopic, only detectable on dipstick testing) is indicative of significant bleeding from somewhere in the urinary tract.

**Proteinuria:**

- very small amounts of high-molecular-weight (HMW) proteins and moderate amounts of low-molecular-weight (LMW) proteins pass through the healthy GBM.
- In healthy individuals, less than 150 mg of protein is excreted in the urine each day, much of which is derived from tubular cells.
- This includes Tamm–Horsfall protein (*uromodulin*) that has recently been linked to tubulo-interstitial disease.
- Larger amounts of protein are usually indicative of significant renal disease.
- Proteinuria is usually asymptomatic and is often picked up by urinalysis, although large amounts of protein may make the urine frothy.
- Testing for proteinuria is best done on an early morning sample, as some individuals exhibit orthostatic proteinuria.
- Isolated proteinuria — is defined as proteinuria without abnormalities in the urinary sediment, i.e., no:
  - hematuria, or
  - reduction in GFR
  - Hypertension or diabetes.
- In most cases the patient is asymptomatic
- It is discovered incidentally by use of a dipstick during routine urinalysis.
- The urine sediment is unremarkable (fewer than three RBCs per high-power field and no casts), protein excretion is less than 3.5 g/day (non-nephrotic),

serologic markers of systemic disease are absent, and there is no hypertension, diabetes, and also no edema or hypoalbuminemia.

- This benign presentation of isolated non-nephrotic proteinuria is different from that in patients with more prominent renal disease.
- Types of proteinuria — there are four basic types of proteinuria:
  1. Glomerular proteinuria
  2. Tubular proteinuria
  3. Overflow proteinuria
  4. Post-renal proteinuria

Classification of proteinuria	Clinical setting	Typical level of proteinuria
<b>Transient proteinuria</b>	Fever, heavy exercise, vasopressor infusion, albumin infusion	<1 g/day
<b>Persistent proteinuria – orthostatic proteinuria</b>	Uncommon over age 30 years, may occur in 2 to 5 percent of adolescents	<1 to 2 g/day
<b>Persistent proteinuria – overflow proteinuria</b>	Myeloma (monoclonal light chains), Hemolysis (hemoglobinuria), Rhabdomyolysis (myoglobinuria)	Variable, could be nephrotic range
<b>Persistent proteinuria – glomerular proteinuria</b>	Primary glomerular diseases, secondary glomerular diseases, diabetic nephropathy, hypertensive nephrosclerosis	Variable, often nephrotic range
<b>Persistent proteinuria – tubulointerstitial proteinuria</b>	Heavy metal intoxications, autoimmune or allergic interstitial inflammation, medication-induced interstitial injury	<3 g/day
<b>Post-renal proteinuria</b>	Urinary tract infections, nephrolithiasis, genitourinary tumor	<1 g/day

- Normal rate of albumin excretion is less than 20mg/day
- Moderately elevated albuminuria (previously referred to as microalbuminuria):
  - Is persistent albumin excretion 30 – 300 mg/day
  - In healthy individuals, there is virtually no urinary excretion of LMW serum proteins, such as albumin, in contrast to modest urinary excretion of tubule-derived proteins.
  - The presence of even moderate amounts of albuminuria is therefore abnormal, and
  - It may indicate early glomerular pathology, at a time when the standard dipstick test remains negative.
- Overt (dipstick-positive) proteinuria:

- The standard urine dipstick primarily detects albumin but is relatively insensitive to non-albumin proteins.
- Thus, a positive dipstick usually reflects glomerular proteinuria.
- The dipstick is very specific but not sensitive to low levels of albumin excretion.
- The lower limit of detection is a urine albumin concentration of approximately 10 to 20 mg/dL.
- Typically, standard dipsticks test positive for protein once the urinary protein exceeds approximately 0.5 g/24 hrs.
- Trace to 1+ on dipstick may be observed in very concentrated urine from individuals with no evidence of renal pathology.
- Hence, all patients with persistent proteinuria on dipstick should have the amount of protein quantified to guide further investigations.
- Since quantification by 24-hour urine collection is often inaccurate, the protein: creatinine ratio (PCR) in a spot sample of urine is preferred.
- Normally of 8–10 mg/24 h of albumin appears in the urine in the absence of kidney disease.
- Frank proteinuria: (300 mg/24 h of albuminuria) represents more advanced renal disease.
- Sustained proteinuria: (>1–2 g/24 h) is also commonly associated with glomerular disease.
- Benign proteinuria: (<1 g/24 h) is nonsustained, and is sometimes called functional or transient proteinuria & found in normal population.
- Transient proteinuria: can be explained by: fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure, UTI
- Orthostatic proteinuria: proteinuria only seen with upright posture; it has a benign prognosis.
- Nonselective: (contain albumin and a mixture of other serum proteins) – is seen in most adults with glomerular disease)
- Selective: (composed largely of albumin)- is seen in children

with minimal change disease (MCD).

**Edema:**

- Caused by an excessive accumulation of fluid within the interstitial space
- Clinically, this can be detected by persistence of an indentation in tissue following pressure on the affected area (pitting edema).
- It tends to accumulate in the ankles during the day and improves overnight as the interstitial fluid is reabsorbed.
- Facial edema on waking is common. Dependent areas, such as the ankles and lower legs, are typically affected.
- Ascites and pleural effusion are also common, but frank pulmonary edema is rare.
- Features of intravascular volume depletion (tachycardia, postural hypotension) may occur.

**Hypertension:**

- very common feature of renal disease
- Its presence identifies a population at risk of developing CKD

**Loin pain:**

- is often caused by musculoskeletal disease but can be a manifestation of renal tract disease;
- in the renal disease, it may arise from renal or ureteric stones, renal tumors, acute pyelonephritis and urinary tract obstruction.

**Dysuria:**

- Refers to painful urination, often described as burning, scalding or stinging, and commonly accompanied by suprapubic pain
- It is often associated with frequency of micturition and a feeling of incomplete emptying of the bladder.
- By far the most common cause is urinary tract infection.
- Other diagnoses that need to be considered in patients with dysuria include sexually transmitted infections and bladder stones.

**Bladder pain:**

- patients perceive pain as coming from the urinary bladder if it is suprapubic in location,
  - alters with bladder filling or emptying, and/or
  - associated with urinary symptoms such as urgency and frequency.
  - Bladder pain occurring acutely (i.e., over hours or a day or two) is helpful in distinguishing bacterial cystitis from urethritis, vaginitis, and other

genital infections.

- Chronic or recurrent bladder pain may accompany
  - Lower urinary tract stones;
  - Bladder, uterine, cervical, vaginal, urethral, or prostate cancer;
  - Urethral diverticulum;
  - Cystitis induced by radiation or certain medications;
  - Tuberculous cystitis;
  - Bladder neck obstruction;
  - Neurogenic bladder;
  - Urogenital prolapse; or BPH.
  - In the absence of these conditions, the diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) should be considered.

**Frequency:**

- describes daytime micturition more often than a patient would expect
- may be a consequence of polyuria, when urine volume is normal or high
- also found in patients with dysuria and prostatic diseases, when the urine volume is normal

**Polyuria:**

- Is defined as a urine volume in excess of 3 L/24 hrs (or 40mL/Kg)
- Underlying conditions, both renal and extrarenal, may be responsible.

**Nocturia:**

- Is defined as waking up at night to void urine; clinically meaningful if a patient voids two or more times nightly
- may be result of:
  - polyuria
  - increased fluid intake
  - diuretic use in the late evening (including caffeine)
  - CKD
  - prostatic enlargement when it is associated with poor stream, hesitancy, ...
  - sleep disturbance without any functional abnormalities of the urinary tract

### Urinary incontinence:

- is defined as any involuntary leakage of urine
- may occur in patients with a normal urinary tract, as the result of dementia or poor mobility
- may occur transiently during an acute illness or hospitalization, especially in older people

### DISEASE DURATION

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- Useful to narrow the differential diagnosis and provide prognostic information to guide management,
- Can be acute, subacute, or chronic
- There's usually overlap, and at times, it's not exactly clear
- Acute exacerbations of chronic renal disease are common presentations
- Best assessment is best performed by comparing the current serum creatinine and/or urinalysis with previous results
  - E.g., a patient with a current serum creatinine of 4 mg/dL and a value of 0.6 mg/dL one month previously has acute or rapidly progressive disease.
  - In contrast, the same patient with a prior serum creatinine concentration of 3.5 mg/dL two years ago almost certainly has slowly progressive CKD.
- If a previous laboratory and/or radiographic study are unavailable, Hx and PEx may suggest the duration of disease. As examples:
  - Acute process is suggested by:
    - recent onset of symptoms or signs, such as sudden onset of anasarca and discolored urine
    - Marked oliguria (urine output <500 mL/day) or anuria in a patient not on maintenance dialysis
    - A progressive increase in the serum creatinine on a daily basis after the initial evaluation
  - Chronicity (CKD) is suggested by:
    - stable values of SCr after initial evaluation
    - Imaging showing small kidneys (definitive evidence of chronicity)
    - Increased echogenicity combined with relatively small kidneys
    - Radiologic evidence of renal osteodystrophy such as subperiosteal bone resorption or loss of bone density at the distal third of the clavicles suggests CKD.
  - However, the presence of normal-sized kidneys does **not** exclude chronicity
  - Some causes of CKD are associated with preserved kidney size (see CKD below: Ix-

*Imaging studies)*

- Renal parenchyma echogenicity (normally less echogenicity than of healthy liver parenchyma), if markedly increased, suggests nonspecific diffuse renal disease.
- Other less helpful findings are:
  - *anemia* due to erythropoietin deficiency is a common (though not absolute) finding in CKD,
  - *hyperphosphatemia* commonly affects CKD patients, it may also be seen in AKI
  - The absence of anemia or hyperphosphatemia does not exclude the presence of CKD.
- **Useful Features that Suggest Acute or chronic kidney disease**

Feature	Acute Kidney Injury	Chronic Kidney Disease
Previous history	Normal renal function	History of elevated blood urea nitrogen or creatinine
Kidney size	Normal	Small, with exception of multiple myeloma, DM, amyloid, PCKD
Bone film	No evidence of renal osteodystrophy	Possible evidence of renal osteodystrophy
Hemoglobin, hematocrit	Anemia possible, but normal Hb level in a patient with advanced azotemia is presumptive evidence of acute renal failure	Anemia common

- Segment or component of kidney involved
  - The traditional approach to kidney disease has been to categorize the clinical etiology as
    - prerenal (decreased renal perfusion pressure)
    - intrinsic renal (pathology of the vessels, glomeruli, or tubules-interstitium)
    - postrenal (obstructive)
  - Kidney disease may result from disease processes in any of these categories.

## ACUTE KIDNEY INJURY (AKI)

### DEFINITION

- The KDIGO guidelines define AKI as follows:
  - Increase in serum creatinine by  $\geq 0.3$  mg/dL ( $\geq 26.5$  micromol/L) within 48 hours, or
  - Increase in serum creatinine to  $\geq 50\%$  than baseline within 7 days, or
  - Urine volume  $< 0.5$  mL/kg/hour for greater than six hours

### EPIDEMIOLOGY

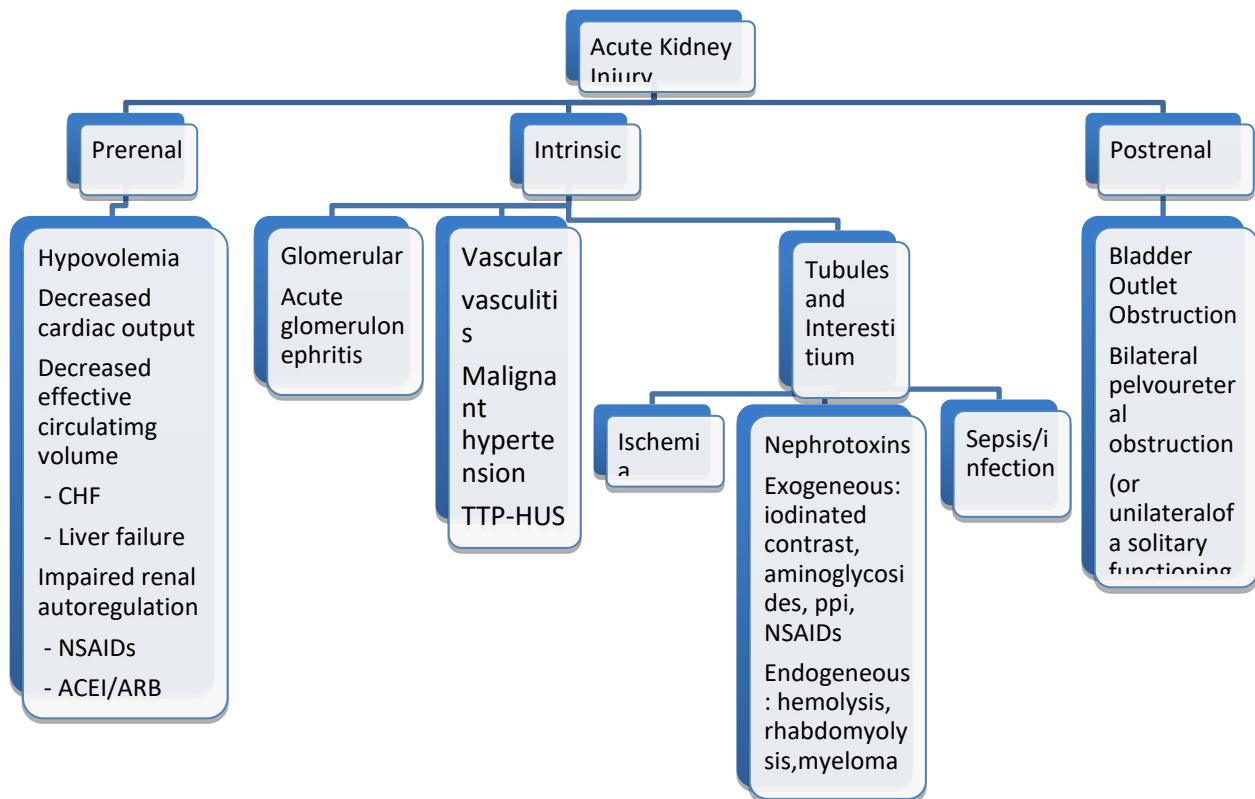
- complicates 5–7% of acute care hospital admissions and up to 30% of admissions to the intensive care unit
- increases the risk for the development or worsening of CKD
- may be community-acquired or hospital-acquired
- Common causes of community-acquired AKI include
  - volume depletion,
    - heart failure
    - adverse effects of medications,
    - obstruction of the urinary tract,
    - malignancy
- The most common clinical settings for hospital-acquired AKI are
  - sepsis,
  - major surgical procedures,
  - critical illness involving heart or liver failure,
  - nephrotoxic medication administration
- Many etiologies for AKI are region-specific
  - envenomation from snakes, spiders, caterpillars, and bees
  - infectious causes such as malaria and leptospirosis
  - crush injuries and resultant rhabdomyolysis from earthquakes

### ETIOLOGY AND PATHOPHYSIOLOGY

- The causes of AKI have traditionally been divided into three broad categories:
  - prerenal azotemia,
  - intrinsic renal parenchymal disease, and
  - postrenal obstruction

**PRERENAL AZOTEMIA** (“azo,” meaning nitrogen, and “-emia,” meaning in the blood)

- Is the most common form of AKI
- It is the designation for a rise in SCr or BUN due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration
- most common associated clinical conditions are listed in the above table
- may coexist with other forms of intrinsic AKI
- If prolonged periods of it may lead to ischemic injury, often termed acute tubular necrosis (ATN)
- By definition, prerenal azotemia involves no parenchymal damage to the kidney and...
- It is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored.



## INTRINSIC AKI

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- Involves pathology of vessels, glomeruli, or tubules-interstitium
- The most common causes of intrinsic AKI are
  - sepsis,
  - ischemia, and
  - nephrotoxins, both endogenous and exogenous
- In many cases, prerenal azotemia advances to tubular injury.
- Although classically termed “acute tubular necrosis,” human biopsy confirmation of tubular necrosis is, in general, often lacking in cases of sepsis and ischemia;
- inflammation, apoptosis, and altered regional perfusion may be important contributors pathophysiologically
- ATN is also often diagnosed clinically without biopsy confirmation in settings such as sepsis with multiple alternate potential diagnoses
- These and other causes of intrinsic AKI are considered to be less common

## POSTRENAL AKI

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- occurs when the normally unidirectional flow of urine is acutely blocked either partially or totally,
  - leading to increased retrograde hydrostatic pressure and interference with glomerular filtration.
- Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra.
- Normal urinary flow rate does not rule out the presence of partial obstruction,
  - because the GFR is normally two orders of magnitude higher than the urinary flow rate and
  - hence a preservation of urine output may be misleading in hiding the postrenal partial obstruction
- For AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr.
- Unilateral obstruction may cause AKI in the setting of
  - significant underlying CKD
  - from reflex vasospasm of the contralateral kidney (rarely)
- Bladder neck obstruction is a common cause of postrenal AKI which impacts both kidneys. This can be due to
  - prostate disease (benign prostatic hypertrophy or prostate cancer),
  - neurogenic bladder, or

- therapy with anticholinergic drugs
- Obstructed Foley catheters can cause postrenal AKI if not recognized and relieved.
- Other causes of lower tract obstruction are
  - blood clots,
  - calculi, and
  - urethral strictures
- Ureteric obstruction can occur from
  - intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae),
  - infiltration of the ureteric wall (e.g., neoplasia), or
  - external compression (e.g., retroperitoneal fibrosis, neoplasia, abscess, or inadvertent surgical damage)

## DIAGNOSTIC EVALUATION

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- Diagnosis: is clinical (see definition above)
- The distinction between AKI and CKD is important for proper diagnosis and treatment.
- Although some features can help (See above: *disease duration*), no set of tests, can rule out AKI superimposed on CKD
- **NB:** AKI is a frequent complication in patients with CKD, further complicating the distinction.
- Serial blood tests showing a continued substantial rise of SCr represents clear evidence of AKI.
- Once the diagnosis of AKI is established, its cause needs to be determined.

## EVALUATION

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### HISTORY

- **Symptoms**
  - Prerenal (most common form)
    - Thirst, decreased urine output, dizziness (hypovolemia)
    - Elders may present with vague change in mental status.
    - Patients with CHF may have orthopnea and PND
  - Renal/intrinsic
    - Hematuria, edema and hypertension (nephritic syndrome) indicates glomerular etiology.
    - Hemorrhage/bleeding/, sepsis, drug overdose or surgery- suspect acute tubular necrosis
    - Muscle pain, recent coma- in pigment induced AKI e.g. Rhabdomyolysis or hemolysis.

- Fever, arthralgia, pruritic erythematous rash
- Postrenal
  - Urgency, frequency, hesitancy in older men with prostatic obstruction
  - Flank pain and haematuria should raise concern about renal calculi or papillary necrosis as source of obstruction.
  - Abdominal fullness and suprapubic pain can accompany bladder enlargement.

## RISK FACTORS

- Prerenal
  - Volume restriction (e.g. low fluid intake, gastroenteritis: vomiting and diarrhea)
  - Glycosuria causing polyuria, hemorrhage, sweating.
  - Medications including diuretics, NSAIDs, ACEI, and ARBs
  - CKD
  - Most common clinical causes for hospital-acquired AKI
    - sepsis,
    - major surgical procedures,
    - critical illness involving heart or liver failure, and
    - nephrotoxic medication administration
- Intrinsic
  - Glomerular: query about throat or skin infections
  - Tubulointerstitial: exposure to nephrotoxins: current medications, recent radiologic examinations/contrast/,
  - Excessive exercise, trauma, seizure, intoxication – in pigment induced AKI or recent blood transfusion (hemolysis)
  - In pregnancy preeclampsia should be considered
  - If there's history of autoimmune disease, e.g. SLE, AKI may be due to its worsening
- Postrenal
  - History of prostatic disease, nephrolithiasis, or pelvic or Para aortic malignancy
  - History of prior gynecologic surgery or abdominopelvic malignancy often can help to get clues to the level of obstruction.
  - Crystals of acyclovir, methotrexate, triamterene, indinavir or sulfonamides can cause obstruction.

## COMPLICATIONS

- Uremia: elevated BUN is a hallmark of AKI. At levels ( $>100$  mg/dL) mental status changes and bleeding complications can arise.
- Hypervolemia and hypovolemia: can result in raised JVP, & pulmonary edema; it may

also induce or exacerbate acute lung injury. Recovery can sometimes be accompanied by polyuria-> if un Rx hypovolemia occurs.

- Hyponatremia: Administration of excessive hypotonic crystalloid or isotonic dextrose solutions; if severe neurologic abnormalities can occur.
- Hyperkalemia: marked one is common in hemolysis, rhabdomyolysis, & TLS. It can lead to muscle weakness and fatal arrhythmias.
- Acidosis: Metabolic acidosis can further complicate acid-base and potassium balance in individuals with other causes of acidosis, including sepsis, DKA, or respiratory acidosis.
- Hyperphosphatemia and hypocalcemia: Hypocalcemia is often asymptomatic, but can lead to perioral paresthesia, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on ECG.
- Hematologic: bleeding and anemia
- Infections: are also common precipitant of AKI
- Cardiac complications: major ones include arrhythmias, pericarditis, and pericardial effusion
- Malnutrition: AKI is often a severely hypercatabolic state.

## PHYSICAL EXAMINATION

- **General appearance:** can be acute sick looking
- **Vital signs**
  - Blood pressure and Pulse rate recordings measured in the supine and the standing position (Orthostatic hypotension)
  - Hypotension: from hypovolemia, severe heart failure
  - Pulse rate: tachycardia; irregular rhythms (i.e. atrial fibrillation) – Thromboemboli
- **HEENT:**
  - Eye
    - Keratitis, iritis, uveitis, dry conjunctivae → Autoimmune vasculitis
    - Icterus → Liver diseases; Band keratopathy (i.e., hypercalcemia), Multiple myeloma
  - Ear
    - Hearing loss - Alport disease and aminoglycoside toxicity
    - Mucosal or cartilaginous ulcerations - Wegener granulomatosis
  - Mouth
    - Dry mucous membranes

- **Chest**
  - Rales - Goodpasture syndrome, Wegener granulomatosis
  - Hemoptysis - Wegener granulomatosis
- **Cardiovascular system**
  - Reduced jugular venous pressure (may be not in CHF?)
  - Murmurs – Endocarditis;
  - Pericardial friction rub - Uremic pericarditis;
  - Hypovolemia leads to hypotension; however, hypotension may not necessarily indicate hypovolemia.
  - Although patients with HF may have low BP, volume expansion is present and effective renal perfusion is poor, which can result in AKI.
  - Severe hypertension with renal failure suggests one of the following disorders:
    - Renovascular disease
    - Glomerulonephritis
    - Vasculitis
    - Atheroembolic disease
- **Abdomen**
  - Pulsatile mass or bruit – Atheroemboli
  - Epigastric bruit suggests renal vascular hypertension, which may predispose to AKI.
  - Tense abdomen should prompt consideration of acute abdominal compartment syndrome: elevated intra-abdominal pressure that can retard renal venous return & => AKI.
  - PRE/DRE: Pelvic, rectal masses; prostatic hypertrophy; distended bladder – Urinary obstruction
- **Genitourinary**
  - CVAT - Nephrolithiasis, papillary necrosis, renal artery thrombosis, renal vein thrombosis;
  - Suprapubic tenderness(obstruction)
- **Integumentary:**
  - Decreased skin turgor
  - Livedo reticularis, digital ischemia, butterfly rash, palpable purpura, pulmonary hemorrhage, or sinusitis - Systemic vasculitis/Atheroemboli
  - Maculopapular rash - Allergic interstitial nephritis
  - Track marks (i.e., intravenous drug abuse) – Endocarditis
  - Petechiae, purpura, ecchymosis, & livedo reticularis can provide clues to inflammatory & vascular causes of AKI.
  - Infectious diseases, TTP, DIC, and embolic phenomena can produce typical

cutaneous changes.

- **Musculoskeletal:**
  - Assessment for peripheral edema; Limb ischemia, edema - Rhabdomyolysis
- **Nervous system:**
  - confusion, loss of consciousness

## INVESTIGATIONS

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### RFT(Scr); see definition

- Anuria is uncommon
- Red or brown urine-color
- Proteinuria
- If the dipstick is positive for hemoglobin but few red blood cells are evident in the urine sediment, then rhabdomyolysis or hemolysis should be suspected.

### Serum electrolytes (Na+, K+, BUN)

- AKI often leads to hyperkalemia, hyperphosphatemia, and hypocalcemia

### CBC

- Anemia is common in AKI

### Renal failure indices

- The FeNa is the fraction of the filtered sodium load that is reabsorbed by the tubule.
- With prerenal azotemia, the FeNa may be <1%;
- In patients with CKD, a FeNa significantly >1% can be present despite a superimposed prerenal state.
- The FeNa may also be >1% despite hypovolemia due to treatment with diuretics.
- NB: Low FeNa is suggestive, but not synonymous, with effective intravascular volume depletion.
- In ischemic AKI, the FeNa is frequently >1% because of tubular injury and resultant inability to reabsorb sodium.
- The other one is osmolality/see table below/.

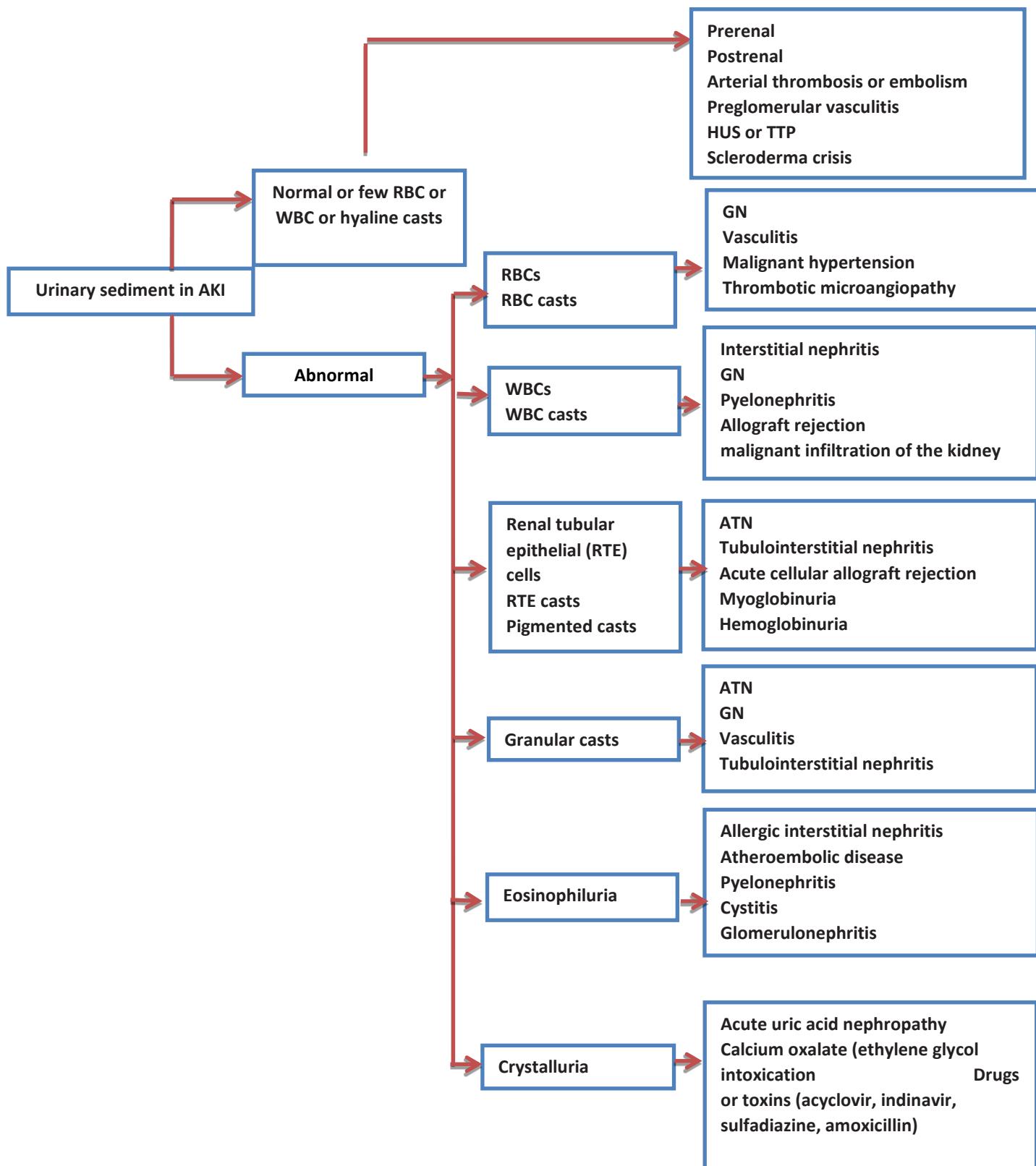
### Radiologic evaluation

- Bladder catheterization to rule out obstruction (diagnostic and therapeutic)
- Renal ultrasound to look for obstruction
- Normal sized kidneys are expected in AKI. Enlarged kidneys in a patient with AKI suggest the possibility of acute interstitial nephritis or infiltrative diseases.

### Kidney Biopsy:

- considered if the cause of AKI is not apparent based on the methods mentioned above

Diagram showing Interpretation of urinary sediment findings in acute kidney injury (AKI)



### Novel Biomarkers:

- Kidney injury molecule-1 (KIM-1) is abundantly expressed in proximal tubular cells injured by ischemia or nephrotoxins such as cisplatin.
- Neutrophil gelatinase associated lipocalin (NGAL, also known as lipocalin-2 or siderocalin) is another novel biomarker.

### Classic laboratory findings in AKI

Type	$U_{osm}$	$U_{Na}$	$F_{e_{Na}}$	BUN/Cr
Prerenal	>500	<10	<1%	>20
Intrinsic	<350	>20	>2%	<15
Postrenal	<350	>40	>4%	>15

### Staging of AKI

	RIFLE <sup>[1]</sup>	AKIN <sup>[2]</sup>	KDIGO <sup>[3]</sup>
<b>Diagnostic criteria*</b> (See definition )			
<b>Staging criteria</b>			
Risk (RIFLE) or <b>stage 1</b> (AKIN/KDIGO)	Increase in SCr to 1.5 times baseline  OR  OUP of <0.5mL/kg/hour for 6 to 12 hours	Increase in SCr of $\geq 0.3$ mg/dL or 150 to 200% baseline  OR  OUP of <0.5 mL/kg/hour for 6 to 12 hours	Increase in SCr of $\geq 0.3$ mg/dL or 1.5–1.9 times baseline)  OR  UOP of <0.5 mL/kg/hour for 6 to 12 hours
Injury (RIFLE) or <b>stage 2</b> (AKIN/KDIGO)	Increase in SCr of to 2 times baseline  OR  UOP of <0.5 mL/kg/hour for 12 to 24 hours	Increase in SCr to 200 to 300% baseline  OR  UOP of <0.5 mL/kg/hour for 12 to 24 hours	Increase in SCr to 2.0 to 2.9 times baseline  OR  UOP of <0.5mL/kg/hour for 12 to 24 hours
Failure (RIFLE) or <b>stage 3</b> (AKIN/KDIGO)	Increase in SCr to 3 times baseline  OR  Increase in SCr by >0.5 mg/dL	Increase in SCr of 300% baseline  OR  Increase in SCr by >0.5 mg/dL to $\geq 4.0$	Increase in SCr to $\geq 3.0$ times baseline  OR  Increase in SCr of $\geq 0.3$

	to >4.0 mg/dL  OR  UOP of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours  OR  Initiation of renal replacement therapy	mg/dL  OR  UOP of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours  OR  Initiation of renal replacement therapy	mg/dL to ≥4.0 mg/dL <sup>¶</sup>  OR  UOP of <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours  OR  Initiation of renal replacement therapy
Loss (RIFLE)	Need for renal replacement therapy for >4 weeks		
End stage (RIFLE)	Need for renal replacement therapy for >3 months		

RIFLE: risk, injury, failure, loss, ESRD; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; ESRD: end-stage renal disease. SCr= Serum creatinine; UOP= Urine output

\* AKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria.

¶ In patients <18 years, stage 3 AKI is also defined by KDIGO as a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m<sup>2</sup>.

## MANAGEMENT PRINCIPLES

- The management is mainly supportive and the objectives includes:
  - Correct reversible causes of AKI
  - Avoid worsening of kidney injury
  - maintenance of homeostasis and correction of biochemical abnormalities (volume & electrolytes)
  - Avoid overdoses of medications with renal clearance
 

In hospitalized patients, accurate daily records of fluid intake and urine output, as well as daily measurements of patient weight, are important.
- **Pharmacologic treatment**
  - There is no specific pharmacologic treatment for AKI caused by ischemic or nephrotoxic ATN
  - The specific treatment depends on the cause of the AKI.
  - **Intravenous fluids**

- Indicated only in patients who are hypotensive or dehydrated on clinical evaluation.
- In patients with hypovolemia or clinical dehydration, fluids should be given to keep the fluid balance in the positive side.
- Do not give (challenge ' ) fluid for all patients unless there is evidence of volume depletion)
- Urine output and fluid balance should be closely followed as oliguric patients can easily develop pulmonary edema.
- **Furosemide:**
  - Indicated in patients with signs of fluid overload (edema, evidence of pulmonary congestion or high BP)
  - Starting dose 40mg, intravenously. If no response increases the dose every 1-2 hour till adequate response.
  - Do not go beyond 200mg/dose.
  - Doses above 100mg should be given diluted (1-2mg/ml of fluid) and given slowly (4mg/min). E.g. 200mg in 100ml NS/01 hr, 160mg in 100mL NS/ 40min
  - Response can be considered adequate, if the urine output is 50-100ml in 01 hour, or 100-200ml in 02 hours.
- **Surgical intervention:**
  - For obstructive uropathy
- **Dialysis:**
  - If the patients live far from a hospital with dialysis service, referral should be made before the indications for dialysis develop.
    - ↳ **Indications for dialysis**
      - Pulmonary edema and anuria.
      - Intractable metabolic acidosis.
      - Severe hyperkalemia ( $> 6.5 \text{ mmol/L}$ ).
      - Uremic complications-pericarditis, encephalopathy and bleeding

## Management of Acute Kidney Injury

### General Issues

1. Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
2. Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides) if possible
3. Initiation of renal replacement therapy when indicated

### Specific Issues

#### 1. Nephrotoxin-specific

- a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis
- b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase

#### 2. Volume overload

- a. Salt and water restriction
- b. Diuretics
- c. Ultrafiltration

#### 3. Hyponatremia

- a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose
- b. Hypertonic saline is rarely necessary in AKI. Vasopressin antagonists are generally not needed.

#### 4. Hyperkalemia

- a. Restriction of dietary potassium intake
- b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs
- c. Loop diuretics to promote urinary potassium loss
- d. Potassium binding ion-exchange resin (sodium polystyrene sulfonate)
- e. Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly
- f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly
- g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium

#### 5. Metabolic acidosis

- a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L)
- b. Administration of other bases, e.g., THAM
- c. Renal replacement therapy

#### 6. Hyperphosphatemia

- a. Restriction of dietary phosphate intake
- b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)

#### 7. Hypocalcemia

- a. Calcium carbonate or calcium gluconate if symptomatic

#### 8. Hypermagnesemia

- a. Discontinue Mg<sup>2+</sup> containing antacids

**9. Hyperuricemia**

- a. Acute treatment is usually not required except in the setting of tumor lysis syndrome

**10. Nutrition**

- a. Sufficient protein and calorie intake (20–30 kcal/kg per day) to avoid negative nitrogen balance. Nutrition should be provided via the enteral route if possible.

**11. Drug dosing**

- a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure
- b. Note that serum creatinine concentration may overestimate renal function in the non-steady state characteristic of patients with AKI

Abbreviation: THAM, tris (hydroxymethyl) aminomethane.

## PREVENTION

- A significant proportion of AKI is preventable.
  - Rapid and adequate fluid replacement in volume depleted patients
  - Early detection and management of sepsis, malaria, pre-eclampsia
  - Avoiding nephrotoxic medications in high-risk patients, whenever possible e.g. NSAIDS, aminoglycosides, iodinated intravenous contrast agents.
  - Close monitoring of renal function and urine output in hospitalized patients
  - Dose adjustment of drugs with renal clearance.

## CHRONIC KIDNEY DISEASE (CKD)

### DEFINITION

- CKD is defined by the presence of *kidney damage or decreased kidney function for three or more months*, irrespective of the cause.
- The persistence of the damage or decreased function for at least three months is necessary to distinguish CKD from acute kidney disease.

Criteria	Comment
<i>Duration ≥3 months, based on documentation or inference</i>	Duration is necessary to distinguish chronic from acute kidney diseases. <ul style="list-style-type: none"> <li>• Clinical evaluation can often suggest duration</li> <li>• Documentation of duration is usually not available in epidemiologic studies</li> </ul>
<i>Glomerular filtration rate (GFR) &lt;60 mL/min/1.73 m<sup>2</sup></i>	GFR is the best overall index of kidney function in health and disease. <ul style="list-style-type: none"> <li>• The normal GFR in young adults is approximately 125 mL/min/1.73 m<sup>2</sup>;</li> <li>• GFR &lt;15 mL/min/1.73 m<sup>2</sup> is defined as kidney failure</li> <li>• Decreased GFR can be detected by current estimating equations for GFR based on SCr (estimated GFR) but not by SCr alone</li> <li>• Decreased estimated GFR can be confirmed by measured GFR, measured Cr clearance, or estimated GFR using cystatin C</li> </ul>
<i>Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR</i>	Pathologic abnormalities (examples). Cause is based on underlying illness and pathology. Markers of kidney damage may reflect pathology. <ul style="list-style-type: none"> <li>• Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia)</li> <li>• Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy)</li> <li>• Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity)</li> <li>• Cystic disease (polycystic kidney disease)</li> </ul> History of kidney transplantation. In addition to pathologic abnormalities observed in native kidneys, common pathologic abnormalities include the following: <ul style="list-style-type: none"> <li>• Chronic allograft nephropathy (non-specific findings of tubular atrophy, interstitial fibrosis, vascular and glomerular sclerosis)</li> <li>• Rejection</li> <li>• Drug toxicity (calcineurin inhibitors)</li> <li>• BK virus nephropathy</li> <li>• Recurrent disease (glomerular disease, oxalosis, Fabry disease)</li> </ul>
	Albuminuria as a marker of kidney damage (increased glomerular permeability, urine albumin-to-creatinine ratio [ACR] >30 mg/g).* <ul style="list-style-type: none"> <li>• The normal urine ACR in young adults is &lt;10 mg/g.</li> <li>• NB: Urine ACR categories:</li> <li>• 10-29 - mildly increased,</li> </ul>

	<ul style="list-style-type: none"> <li>• 30-300 - moderately increased and</li> <li>• &gt;300 mg - severely increased</li> <li>• Urine ACR &gt;2200 mg/g is accompanied by signs and symptoms of nephrotic syndrome (low serum albumin, edema and high serum cholesterol).</li> <li>• Threshold value corresponds approximately to urine dipstick values of trace or 1+, depending on urine concentration</li> <li>• High urine ACR can be confirmed by urine albumin excretion in a timed urine collection</li> </ul>
	<p>Urinary sediment abnormalities as markers of kidney damage, for example:</p> <ul style="list-style-type: none"> <li>• RBC casts in proliferative glomerulonephritis</li> <li>• WBC casts in pyelonephritis or interstitial nephritis</li> <li>• Oval fat bodies or fatty casts in diseases with proteinuria</li> <li>• Granular casts and renal tubular epithelial cells in many parenchymal diseases (non-specific)</li> </ul>
	<p>Imaging abnormalities as markers of kidney damage (ultrasound, computed tomography and magnetic resonance imaging with or without contrast, isotope scans, angiography).</p> <ul style="list-style-type: none"> <li>• Polycystic kidneys</li> <li>• Hydronephrosis due to obstruction</li> <li>• Cortical scarring due to infarcts, pyelonephritis or vesicoureteral reflux</li> <li>• Renal masses or enlarged kidneys due to infiltrative diseases</li> <li>• Renal artery stenosis</li> <li>• Small and echogenic kidneys (common in later stages of CKD due to many parenchymal diseases)</li> </ul>

## EPIDEMIOLOGY

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- CKD is a worldwide public health problem.
- In many countries, estimates of the prevalence of CKD stages 3–5 (eGFR < 60 mL/min/1.73 m<sup>2</sup>) are around 5–7%, mostly affecting people aged 65 years and above.
- The prevalence is higher in patients with hypertension, diabetes and vascular disease
- The prevalence of end-stage renal disease (ESRD) is growing
- Reasons for the increasing prevalence of ESRD include
  - improved survival from nonrenal diseases (particularly cardiovascular disease [CVD])
  - relaxed criteria for entry into ESRD programs
- Striking racial and ethnic differences rates of ESRD: The highest incidence is reported for African Americans; followed by American Indians
- There is variability in the causes of ESRD among the various racial and ethnic groups.
- Diabetic nephropathy remains the most common cause of ESRD in all racial/ethnic groups.
- Both early stages of CKD and ESRD are associated with high morbidity and increased health care utilization.

- The comorbid conditions and causes of hospitalization are strikingly similar between patients with early stages of CKD and ESRD,
  - suggesting that the complications of ESRD manifest themselves well before the onset of ESRD
- The risk of hospitalization and cardiovascular events in patients with CKD progressively increase as GFR declines.

## ETIOLOGY

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CKD may result from (chronic) disease processes involving any of the components of kidney: prerenal, intrinsic renal or postrenal.

### PRERENAL DISEASE

- occurs in patients with ongoing heart failure or cirrhosis with persistently decreased renal perfusion,
  - which increases the propensity for intrinsic kidney injury, such as acute tubular necrosis (ATN)

### INTRINSIC DISEASE

- can be renal vascular, glomerular or tubular and interstitial disease
- **Intrinsic renal vascular disease**
  - the most common is nephrosclerosis, which initially involves the blood vessels but ultimately damages the glomeruli and tubulointerstitium
  - renal artery stenosis from atherosclerosis or fibromuscular dysplasia
- **Intrinsic glomerular disease**
  - may be classified as nephritic or nephrotic
  - A *nephritic pattern* is suggested by an abnormal urine microscopy with red blood cell (RBC) casts and dysmorphic red cells, occasionally white blood cells (WBCs), and a variable degree of proteinuria.
  - A *nephrotic pattern* is associated with proteinuria, usually in the nephrotic range ( $>3.5$  g per 24 hours), and an inactive urine microscopic analysis with few cells or casts. Some patients cannot be easily assigned to one of these two categories.
- **Intrinsic tubular and interstitial disease**
  - the most common is polycystic kidney disease (PKD)
  - Other chronic etiologies include
  - nephrocalcinosis (most often due to hypercalcemia and/or hypercalciuria),
  - sarcoidosis,
  - Sjögren's syndrome,
  - reflux nephropathy in children and young adults, and

- medullary cystic kidney disease in families with a pattern of autosomal dominant inheritance

### POSTRENAL (OBSTRUCTIVE NEPHROPATHY)

- Chronic obstruction may be due to
- prostatic disease
- abdominal/pelvic tumor with mass effect on ureter(s)
- Retroperitoneal fibrosis (is a rare cause of chronic ureteral obstruction).
- If untreated, obstructive nephropathy leads to irreversible tubulointerstitial fibrosis (i.e., intrinsic disease).

### Leading Categories of Etiologies of CKD

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

### PATHOPHYSIOLOGY

- The pathophysiology of CKD involves two broad sets of mechanisms of damage:
- Initiating mechanisms specific to the underlying etiology
  - (e.g., abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium)
- Hyperfiltration and hypertrophy of the remaining viable nephrons,
  - that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology and lead to further decline in kidney function.

### EVALUATION

#### HISTORY

- **Symptoms**
  - Stages 1 and 2 CKD are usually asymptomatic, such that recognition occur by lab test
  - Stages 3 and 4, clinical and laboratory complications become more prominent.
  - Stage 5 CKD, toxins accumulate-eventuating in the *uremic syndrome*.
  - The manifestations of CKD and uremia include:
    - **Fluid, electrolyte, and acid-base disorders**
      - Sodium and Water Homeostasis:  
→ peripheral edema (due to Hypernatremia),

- SOB, coughing up blood, sweating (pulmonary edema)
- **Potassium Homeostasis:**
  - palpitations, dizziness, fainting (arrhythmia-due to hyperkalemia)
  - nausea/vomiting, intestinal colic, diarrhea
- **Metabolic Acidosis:**
  - weight loss, muscle weakness
  - (In most patients, mild; the pH is rarely <7.32)
- **Disorders of calcium and phosphate metabolism**
  - weakening of bones and possibly fractures (due to renal osteodystrophy)
  - necrotic skin lesions (**calciphylaxis**- b/c calcium & phosphate precipitate)
  - **tumoral calcinosis** (calcium precipitate in the soft tissues into large concretions)
- **Cardiovascular abnormalities**
  - *Ischemic heart disease/CHF*
    - Chest pain,
    - shortness of breath, orthopnea, PND
  - *Pericarditis (uremic)*
    - chest pain with respiratory accentuation
- **Hematologic abnormalities**
  - *Anemia* (normocytic, normochromic & is almost universal by stage 4)
    - fatigue,
    - impaired cognitive function,
    - lightheadedness, tinnitus
  - Causes of Anemia in CKD:
    - Deficiency of erythropoietin - primary cause
    - Diminished red blood cell survival
    - Bleeding diathesis
    - Iron deficiency due to poor dietary absorption and gastrointestinal blood loss
    - Hyperparathyroidism/bone marrow fibrosis
    - Chronic inflammation
    - Folate or vitamin B12 deficiency
    - Hemoglobinopathy
    - Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs
  - Abnormal Hemostasis

- Increased tendency to bleeding and bruising,
- Prolonged bleeding from surgical incisions,
- Menorrhagia, and
- GI bleeding.
- **Neuromuscular abnormalities**
  - Early manifestations of CNS complications include
    - mild disturbances in memory and concentration
    - sleep disturbance
  - Later, neuromuscular irritability, including
    - hiccups,
    - cramps, and
    - twitching, becomes evident
  - In advanced untreated kidney failure
    - involuntary jerking of hands
    - myoclonus,
    - seizures, and
    - coma can be seen
  - *Peripheral neuropathy*
    - ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement (**restless leg syndrome**)
- **Gastrointestinal and nutritional abnormalities**
  - urine-like odor on the breath (*Uremic fetor*)
  - unpleasant metallic taste (*dysgeusia*)
  - abdominal pain, nausea, vomiting, and GI bleeding (Gastritis, peptic disease, and mucosal ulcerations at any level of the GI tract occur in uremic patients + retention of uremic toxins)
  - constipation (can be worsened by the administration of calcium and iron supplements)
- **Endocrine-metabolic disturbances**
  - In women, **infertility**, and inability to carry pregnancies to term (b/c of low estrogen)
  - Glucose metabolism is impaired in CKD. However, FBG is usually normal or mildly elevated
- **Dermatologic abnormalities**
  - Pruritus is quite common and one of the most vexing manifestations of the uremic state.

- patients may become more pigmented in advanced CKD (Deposition of retained pigmented metabolites/urochromes)
- progressive **subcutaneous induration**, (esp. on the arms and legs)
  - Is called nephrogenic fibrosing dermopathy
  - skin condition unique to CKD patients
  - Seen very rarely in patients with CKD who have been exposed to the MR contrast agent gadolinium.
- Dryness and ecchymosis

## RISK FACTORS

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- Diabetes mellitus
- Hypertension
- Kidney diseases
  - Chronic glomerulonephritis
  - Interstitial nephritis,
  - Polycystic kidney disease,
  - Any of the causes of AKI may lead to CKD if prolonged and/or if treatment is delayed.
  - History of abnormal urinalyses,
- Obstructive uropathy
- Problems with pregnancy such as preeclampsia or early pregnancy loss.
- **Drugs** to consider include:
  - NSAIDS,
  - cyclooxygenase-2 (COX-2) inhibitors,
  - antimicrobials,
  - chemotherapeutic agents,
  - ART agents,
  - proton Pump Inhibitors,
  - phosphate-containing bowel cathartics, and
  - lithium
  - Warfarin treatment is considered a risk factor for calciphylaxis
- Family history of kidney disease,
  - together with assessment of manifestations in other organ systems such as auditory, visual, and integumentary, may lead to the diagnosis of a heritable form of CKD (e.g., Alport or Fabry disease, cystinosis) or
  - Shared environmental exposure to nephrotoxic agents (e.g., heavy metals, aristolochic acid).

- **Complications** (*discussed above in clinical presentation*)
  - Life-threatening Complications in CKD includes
    - Hyperkalemia—obtain an ECG
    - Pulmonary edema secondary to volume overload→look for recent weight gain.
    - Infection (e.g., pneumonia, UTI, sepsis) etc.
  - Pericarditis, can be complicated by cardiac tamponade
  - Ischemic heart disease: increased prevalence of vascular disease in CKD patients derives from both traditional (“classic”) and nontraditional (CKD-related) risk factors.
    - Traditional risk factors include
      - hypertension,
      - hypervolemia,
      - dyslipidemia,
      - sympathetic overactivity, and
      - hyperhomocysteinemia
    - The CKD-related risk factors comprise
      - anemia,
      - hyperphosphatemia,
      - hyperparathyroidism,
      - increased FGF-23,
      - sleep apnea, and
      - generalized inflammation

## PHYSICAL EXAMINATION

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### VITAL SIGNS

- BP: Hypertension; Pulsus paradoxus in pericardial tamponade
- RR: Increased respiratory rate and depth in metabolic acidosis

### HEENT:

- EYE
  - Fundoscopy is important in the diabetic patient, because it may show evidence of diabetic retinopathy, which is associated with nephropathy.
  - Pale conjunctiva

### CVS:

- Jugular venous pressure raised in fluid overload or pericardial tamponade
- Pericardial friction rub not attributable to other causes usually signifies the presence of the uremic syndrome

**ABD:** Ascites, Tenderness

I/S

- Excoriation of pruritus,
- ‘Brown line’ pigmentation of nails,
- Bruising easily
- Uremic frost esp. over forehead

**MSS**

- Edema and sensory polyneuropathy.
- Asterixis not attributable to other causes usually signifies the presence of the uremic syndrome

**NS:**

- Change in mental status
- Peripheral neuropathy:
- Absent reflexes
- Reduced sensation
- Paresthesia
- ‘Restless legs’

## INVESTIGATIONS

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### LABORATORY

- Serial measurements of **renal function**
  - to ensure that the disease is truly chronic rather than acute or subacute and hence potentially reversible
- **Serum concentrations of**
  - **Sodium and Potassium**
    - Hypernatremia; **hyponatremia is not commonly** seen in CKD patients
    - Hyperkalemia may be precipitated in certain settings. These include
      - increased dietary potassium intake,
      - hemolysis,
      - hemorrhage,
      - transfusion of stored RBCs,
      - metabolic acidosis, and
      - Medications.
    - **Hypokalemia is not common** in CKD.
  - **Calcium, phosphorus, vitamin D, ALP and PTH** should be measured to evaluate metabolic bone disease.

- Hemoglobin concentration, iron, vitamin B12, albumin and folate should also be evaluated.
- Decreased renal clearance of phosphate leads to *hyperphosphatemia*, which results in decreased renal production of 1,25-dihydroxy vitamin D. This leads to *hypocalcemia*, which causes secondary *hyperparathyroidism*.
- A **24-hr urine** collection may be helpful, because protein excretion >300 mg may be an indication for therapy with ACE inhibitors or ARBs.
- **Urinalysis**—examine sediment (see NS, Ix)
- **CBC** (anemia, thrombocytopenia)
- **Lipid profile**: patients with CKD have increased risk of cardiovascular disease.
- **Serology**: In the presence of glomerulonephritis, autoimmune diseases such as lupus and underlying infectious etiologies such as hepatitis B and C and HIV should be tested. Anti-GBM=>Goodpasture syndrome; P-ANCA & C-ANCA => GPA.
- **Serum and urine protein electrophoresis**, looking for multiple myeloma, should be obtained in all patients >35 years with unexplained CKD, especially if there is associated anemia and elevated, or even inappropriately normal, serum calcium concentration in the face of renal insufficiency.

## IMAGING STUDIES

- **Renal ultrasound** (most useful imaging study), which can:
  - Verify the presence of two kidneys,
  - Determine if they are symmetric,
  - Provide an estimate of kidney size,
  - Rule out renal masses and
  - Rule out evidence of obstruction
    - Finding of *bilaterally small kidneys supports the diagnosis of CKD of long-standing duration*.
  - If the kidney size is normal, it is possible that the renal disease is acute or subacute. The **exceptions** are:
    - *diabetic nephropathy* (where kidney size is increased at the onset of diabetic nephropathy before CKD supervenes),
    - *amyloidosis*, and
    - *HIV nephropathy*, where kidney size may be normal in the face of CKD.
  - **Polycystic kidney disease** that has reached some degree of renal failure will almost always present with enlarged kidneys with multiple cysts.
    - A discrepancy >1 cm in kidney length suggests there is some abnormality.
- **Doppler sonography, nuclear medicine studies, or CT or MRI studies:**

- to undertake the diagnosis of renovascular disease
- **Voiding cystogram**, if there is a suspicion of reflux nephropathy:
  - recurrent childhood urinary tract infection,
  - Asymmetric renal size with scars on the renal poles may be indicated.
  - However, in most cases, by the time the patient has CKD, the reflux has resolved, and even if still present, repair does not improve renal function.
- Radiographic **contrast imaging** studies **are not** particularly helpful.
  - Intravenous or intra-arterial **dye should be avoided** where possible in the CKD patient, especially with diabetic nephropathy.

### KIDNEY BIOPSY

- *Ultrasound-guided percutaneous biopsy*
  - Is the favored approach, but a surgical or laparoscopic approach can be considered
  - In the CKD patient in whom a kidney biopsy is indicated, bleeding time should be measured; if increased treat w/ desmopressin.
- In the patient with bilaterally small kidneys, renal biopsy is **not advised** because
  - it is technically difficult and has a greater likelihood of causing bleeding and other adverse consequences,
  - there is usually so much scarring that the underlying disease may not be apparent, and
  - The window of opportunity to render disease-specific therapy has passed.
- Other contraindications to renal biopsy include
  - uncontrolled hypertension,
  - active urinary tract infection,
  - bleeding diathesis (including ongoing anticoagulation), and
  - severe obesity

### STAGING OF CKD

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- To stage CKD, it is necessary to estimate the GFR rather than relying on SCr concentration.
  - The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m<sup>2</sup>) attained during the third decade of life is ~1 mL/min per year per 1.73 m<sup>2</sup>,
    - reaching a mean value of 70 mL/min per 1.73 m<sup>2</sup> at age 70, with considerable inter-individual variability
  - Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases.
  - The cumbersome 24-h urine collection has been replaced by measurement of urinary

albumin to creatinine ratio (UACR) in one and preferably several spot first-morning urine samples as a measure pointing to glomerular injury.

- Even in patients with negative conventional dipstick tests for elevated total protein excretion, UACR above 17 mg albumin/g creatinine in men and 25 mg albumin/g creatinine in women
  - serves as a marker not only for early detection of primary kidney disease, but for systemic microvascular disease as well
- Once the diagnosis of CKD is established cause identification and staging should be made based on the CAG system (C-cause A-albuminuria level and G-GFR level).
  - Example if a patient with CKD presumed to be due to diabetic kidney disease has eGFR of 40m/min and 24hr protein is 1200mg. C= Diabetes G=G3b A= A3 (Stage: G3b A3 CKD due to diabetic kidney disease)

Prognosis of CKD by GFR and albuminuria categories:  
KDIGO 2012

GFR categories (ml/min/1.73 m <sup>2</sup> ) description and range	Persistent albuminuria categories description and range		
	A1	A2	A3
	Normal to mildly increased	Moderately increased	Severely increased
	<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1 Normal or high	≥90		
G2 Mildly decreased	60-89		
G3a Mildly to moderately decreased	45-59		
G3b Moderately to severely decreased	30-44		
G4 Severely decreased	15-29		
G5 Kidney failure	<15		

Kidney Disease Improving Global Outcome (KDIGO), classification of chronic kidney disease (CKD). Gradation of color from green to red corresponds to increasing risk and progression of CKD. GFR= glomerular filtration rate.

## MANAGEMENT PRINCIPLES

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The medical care of patients with CKD should focus on the following:

1. Delaying or halting the progression of CKD: treatment of the underlying condition, if possible, is indicated.

- **Treatment and control of hypertension**
  - Target blood pressure < 130/80 mmHg
  - First line: ACE inhibitors or angiotensin receptor blockers (ARBs)
  - Avoid ACE inhibitors/ARBs if patient has hyperkalemia.
    - Serum creatinine and potassium should be followed one to two weeks following initiation or dose increment.
    - If serum potassium or creatinine can't be followed, don't start ACE inhibitors/ARBs in patients with CKD.
    - Up to 20-30% increment in creatinine is expected
  - Add-on and Alternatives:
    - Long acting calcium channel blocker(CCB),
    - Loop diuretics (if eGFR is <30ml/min) or
    - thiazide diuretics ( if GFR>30ml/min) or
    - combinations of the three
    - if still uncontrolled beta blocker can be added
- **Treatment and control of proteinuria**
  - First line: ACE inhibitors or angiotensin receptor blockers (ARBs).
    - ACE inhibitors (particularly Enalapril) are preferred over ARBs due to their low cost and wide availability.
    - Enalapril: starting dose 5mg BID, Maximum dose 20mg BID
  - Alternatives
    - Lisinopril: starting dose 5mg/day, Maximum dose 40mg/day
    - Losartan: Starting dose 50mg/day maximum dose 100mg/day
    - Valsartan: Starting dose 80 -160mg/day, maximum dose 320mg/day
- **Control of hyperglycemia in Diabetes**
  - In early CKD good blood sugar control is essential and helps to decrease progression of CKD.
  - In advanced CKD (Stage G4 and above or in patients on dialysis) the risk of hypoglycemia is very high and tight glycemic control should be avoided.
  - Although individualization based on age, expected survival, rates of hypoglycemia, additional comorbidities is need, in patients with eGFR<30ml/min a HbA1C target of about 7.5% is acceptable ( if achieved

without significant hypoglycemia)

- In patients with advanced CKD eGFR <30ml/min o Metformin should be discontinued. o Long acting sulfonylureas (particularly the commonly used Glibenclamide) should be avoided. o Insulin based therapy is preferred.

**2. Diagnosing and treating the pathologic manifestations of CKD:**

- **Anemia:** Rx with erythropoiesis agents e.g., Epoetin alpha
  - Indications to start treatment: Hemoglobin < 10g/dl or symptomatic.
- Preferred: Intravenous iron
- **Iron sucrose**
  - **for patients not on hemodialysis:**
    - **Iron sucrose** 200mg, IV, over 5 minutes, every 3 days for a total of 5 doses (a total of 1000mg).
    - This dose is usually sufficient but if hemoglobin is not corrected, additional doses can be given. OR
    - **Iron sucrose** 200mg diluted in 100ml NS; administer over 30 minutes.
  - **For patients on hemodialysis**
    - **Iron sucrose** 100mg, IV, over 2-5 minutes, given early during dialysis sessions (within the first hour) until iron deficiency is corrected
    - It needs to be given again, if iron deficiency persists or recurs.
  - Alternative: Options o **Ferrous sulfate**, 325mg (65mg elemental iron) before meal
- **Epoetin (alpha/beta)**
  - **Initiate if Hemoglobin is < 10g/dl after iron therapy.**
    - CKD patients **on hemodialysis**
      - Initial dose: 4000IU, IV, 3 times a week
    - CKD patients **not on dialysis**
      - Initial dose: 4000IU, SC, 3 times a week
    - Dosage adjustments for CKD patients (either on dialysis or not on dialysis):
      - Do not increase dose more frequently than every 4 weeks (dose decreases may occur more frequently).
        - If hemoglobin does not increase by >1 g/dl after 4 weeks: Increase dose by 25%
        - If hemoglobin increases >1 g/dl in any 2-week period: Reduce dose by

25-50%

- **Hyperphosphatemia:** treatment with dietary phosphate binders and dietary phosphate restriction
  - Phosphate binders are indicated if serum phosphorus is > 5.5mg/dl
  - **First line:** Sevelamer (as hydrochloride or carbonate)
    - Initial dose 800mg, PO, TID with meal. If serum phosphorus >9mg/dl, 1600mg, PO TID can be started.
    - Adjust the dose to target to a target serum phosphorus near normal (< 5.5mg/dl)
  - **Alternative:** Calcium carbonate : starting dose 500 – 1000mg, PO, TID, chew, with meal
- **Hypocalcemia:** Rx with calcium supplements with or without calcitriol
- **Hyperparathyroidism:** Rx with calcitriol or vitamin D analogues or calcimimetics
  - The main stay of treatment is correcting phosphorus and serum calcium
  - Serum PTH (preferably intact PTH) should not be overcorrected: 2-9 times the upper limit of normal is acceptable.
  - If PTH level is above nine times the upper limit after correction of phosphorus and calcium use either of the following: Calcitriol or synthetic vitamin D analog (alfacalcidol or paricalcitol).
    - Alfacalcidol: starting dose 2.5 to 5 microgram/day. OR
    - Paricalcitol: starting dose 1microgram/day or 2 microgram 3x/week. OR
    - Calcitriol: 0.25 – 0.5 microgram/day
- **Volume overload:** treat with loop diuretics or ultrafiltration
  - Furosemide 40-120mg, PO/IV, two –three times per day
  - higher dose and more frequent dosing intervals are required in advanced CKD
- **Metabolic acidosis:** treat with oral alkali supplementation
- **Uremic manifestations:** treat with long term renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation).
  - Indications for renal replacement therapy includes:
    - severe metabolic acidosis
    - hyperkalemia
    - pericarditis
    - encephalopathy, peripheral neuropathy
    - intractable volume overload
    - failure to thrive and malnutrition

- intractable gastrointestinal symptoms in asymptomatic patients, a GFR of 5-9 mL/min/1.73m<sup>2</sup>, irrespective of the cause of the CKD or the presence or absence of other comorbidities

**3. Timely planning for long term renal replacement therapy**

## GLOMERULAR DISEASES

- The glomerulus is the basic filtering unit of the kidney.
- Diseases of the glomerulus can result in three different urinary and clinical patterns: focal nephritic; diffuse nephritic; and nephrotic.

## TERMINOLOGIES

- On a pathological basis, glomerular lesions can be:
  - **diffuse** (all glomeruli are involved) or
  - **focal** (only some glomeruli are involved [typically less than 50 percent])
- At the level of the individual glomerulus, a process can be:
  - **global** (the whole glomerular tuft is involved) or
  - **segmental** (only a portion is involved (less than 50 percent))
- Histologic descriptions:
  - **proliferative** (an increase in the number of cells in the glomerulus),
  - **sclerosing** (presence of scarring), and
  - **necrotizing** (areas of cell death)
- Proliferation may occur predominantly in:
  - **mesangium** (mesangial proliferative glomerulonephritis),
  - **capillary wall** (endocapillary hypercellularity), and
  - **extracapillary** location
- Extracapillary proliferation (also known as **crescents**)

are lesions associated with accumulations of macrophages, fibroblasts, proliferating epithelial cells, and fibrin within Bowman's space

- represent rupture of the glomerular membrane, signifying severe injury to the glomerular capillary wall
- Some examples of how this terminology is used include "focal and segmental necrotizing glomerulonephritis" and "diffuse global proliferative glomerulonephritis".
- Lastly, interstitial fibrosis, which accompanies uncontrolled glomerular disease, is a poor prognostic sign.

## PATHOGENESIS OF GLOMERULAR DISEASES

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- are variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus
- Even after careful study, however, the cause often remains unknown, and the lesion is called idiopathic.

## APPROACH TO THE PATIENT

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### HEMATURIA AND PYURIA

- Patients with glomerular disease usually have some hematuria (asymptomatic) with varying degrees of proteinuria.
- The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria* (exception: in IgA nephropathy and sickle cell disease *gross hematuria* is present).
- Microscopic hematuria may also appear:
  - anatomic lesions, such as malignancy of the urinary tract, particularly in older men,
  - with the onset of benign prostatic hypertrophy,
  - interstitial nephritis,
  - papillary necrosis,
  - hypercalciuria,
  - renal stones,
  - cystic kidney diseases
  - renal vascular injury
  - glomerulonephritis (is likely esp. when RBC casts/dysmorphic RBCs are found in the sediment)

### PYURIA

- presence of considerable numbers of leukocytes; in some patients with inflammatory glomerular disease, such as acute PSGN or MPGN. It has to be distinguished from urine infected with bacteria.

### CLINICAL SYNDROMES

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- Various forms of glomerular injury can also be parsed into several distinct syndromes (Six, listed below) on clinical grounds which are not always mutually exclusive:
  - Acute nephritic syndrome features:
    - produce 1–2 g/24 h of proteinuria,
    - hematuria with red blood cell casts,
    - pyuria,
    - hypertension,

- fluid retention, and
- a rise in serum creatinine associated with a reduction in glomerular filtration.
- E.g., Poststreptococcal glomerulonephritis, subacute bacterial endocarditis, Lupus nephritis
- *Rapidly progressive glomerulonephritis (RPGN)*: acute nephritis in which serum creatinine rises quickly, particularly over a few days,
- *Crescentic glomerulonephritis* (the histopathologic term) is the pathologic equivalent of the clinical presentation of RPGN.
- *Pulmonary-renal syndrome*: when patients with RPGN present with lung hemorrhage from e.g.
  - Goodpasture's syndrome,
  - antineutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis,
  - lupus erythematosus, or
  - cryoglobulinemia.
- *Nephrotic syndrome* refers to:
  - onset of heavy proteinuria ( $>3.0 \text{ g}/24 \text{ h}$ ),
  - hypertension,
  - hypercholesterolemia,
  - hypoalbuminemia,
  - edema/anasarca, and
  - microscopic hematuria
  - E.g., Minimal change disease, FSGS, Diabetic nephropathy, ...
  - *Nephrotic-range proteinuria*: when only large amounts of proteinuria are present without clinical manifestations
- *Basement membrane syndrome*: abnormal basement membranes associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine.
  - It can be genetic (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome)
- *Glomerular–vascular syndrome* describes patients with vascular injury producing hematuria and moderate proteinuria. Patients can have vasculitis, or systemic disease such as atherosclerosis, hypertension autoimmunity ...
- *Infectious disease–associated syndrome*: some most important causes include:
  - Subacute bacterial endocarditis (SBE)
  - Malaria,
  - Schistosomiasis

- HIV
- Chronic hepatitis B and C.
  - These infections can cause reactions ranging from nephrotic syndrome to acute nephritic injury.
  - After history, physical examination and baseline tests done, further diagnostic workup that typically involves testing of the serum for the presence of various
- proteins (HIV and hepatitis B and C antigens),
- antibodies (antiGBM, APLS, antistreptolysin O [ASO], anti-DNAse, antihyaluronidase, ANCA, anti-DNA, cryoglobulins, anti-HIV, and anti-hep. B and C antibodies) or
- complement components (C3 and C4) depletion
- Hx and PEx can also help determine whether the glomerulonephritis is isolated to the kidney (*primary GN*) or is part of a systemic disease (*secondary glomerulonephritis*).
- Once glomerulonephritis is considered whether it is *acute* or *chronic* must be determined.
- The following can help differentiation
  - Careful Hx (last known urinalysis or serum creatinine during pregnancy, evidence of infection, or use of medication or recreational drugs);
  - the size of the kidneys on renal ultrasound examination; and
  - how the patient feels at presentation
  - Chronic glomerular disease often presents with decreased kidney size.
  - Patients who quickly develop renal failure are fatigued and weak and often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence.
- Primary glomerulonephritis presenting with renal failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis without much loss in renal function.
- Once this initial information is collected, selected patients who are clinically stable, have adequate blood clotting parameters, and are willing and able to receive treatment are encouraged to have a renal biopsy.

## ACUTE NEPHRITIC SYNDROMES

**Acute nephritic syndromes** classically present with hypertension, hematuria, red blood cell casts, pyuria, and mild to moderate proteinuria.

- **Features of suggesting the underlying causes (systemic diseases)**

- Hair loss/diffuse non-scarring alopecia – SLE
- Malar rash, photosensitive rash, non-pruritic rash over the body– SLE
- Joint pain, evidence of arthritis (swelling and tenderness of joints) – SLE
- Hemoptysis, cough and dyspnea – Vasculitis, Anti-GBM disease or pulmonary edema
- Petechiae/purpura – Vasculitis or SLE
- Pleural effusion – Part of the complication or SLE associated
- Pericarditis (friction rub or distant heart sound) – SLE or uremic pericarditis
- Cardiac murmurs – Infective endocarditis or SLE
- Focal neurologic deficit – SLE( Lupus cerebritis) or vasculitis

- **Features related to marked decrement in the kidney function**

- Pulmonary crackles – pulmonary congestion
- Nausea and vomiting – uremic gastropathy
- Change in mental status – uremic or hypertensive encephalopathy
- Mucocutaneous bleeding – uremic bleeding

## POSTSTREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

### Definition

- immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell mediated injury
- prototypical for *acute endocapillary proliferative glomerulonephritis*

### Epidemiology

- In underdeveloped countries it is epidemic and usually affects children between the ages of 2 and 14 years.
- In developed countries it is more typical in the elderly. It is more common in males.

### Etiology and pathophysiology

- Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease;
  - M types 47, 49, 55, 2, 60, and 57 are seen following impetigo and
  - M types 1, 2, 4, 3, 25, 49, and 12 with pharyngitis.
- PSGN due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.
- The renal biopsy in PSGN demonstrates

- hypercellularity of mesangial and endothelial cells,
- glomerular infiltrates of polymorphonuclear leukocytes,
- granular subendothelial immune deposits of IgG, IgM, C3, C4, and C5–9, and
- subepithelial deposits (which appear as “humps”)
- Among candidate antigens from nephritogenic streptococci: a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) and NAP1r, the nephritis-associated plasmin receptor.
- These two antigens have biochemical affinity for plasmin, bind as complexes facilitated by this relationship, and activate the alternate complement pathway.

### CLINICAL MANIFESTATIONS

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- The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN.
- Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases.

### LAB FINDINGS

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- Proteinuria in the nephrotic range (5% of children and 20% of adults)
- In the first week of symptoms, 90% of patients will have a depressed CH50 and decreased levels of C3 with normal levels of C4.
- Positive rheumatoid factor (30–40%),
- cryoglobulins and circulating immune complexes (60–70%), and
- ANCA against myeloperoxidase (10%) are also reported
- Positive cultures for streptococcal infection are inconsistently present (10–70%),
- increased titers of ASO (30%), anti-DNAse (70%), or antihyaluronidase antibodies (40%) can help confirm the diagnosis
  - Consequently, the **diagnosis** of poststreptococcal glomerulonephritis **rarely** requires a renal biopsy. (Findings: see above **Etiology and pathophysiology**)
- A subclinical disease is reported in some series to be 4–5 times as common as clinical nephritis
- These latter cases are characterized by asymptomatic microscopic hematuria with low serum C3 complement levels.

## TREATMENT

- Treatment is supportive, with control of hypertension, edema, and dialysis as needed.
  - **Non-pharmacologic**
    - Salt and fluid restrictions
  - **Pharmacologic treatment**
    - **Loop diuretics** are the preferred antihypertensive
    - **Oral Furosemide:** for patients with mild peripheral edema.
      - Starting dose 40mg PO BID.
      - Follow every 2-3 days, increase the dose to higher dose (Max. dose 600mg/day)
      - admit for IV diuresis, if response is suboptimal or there is worsening
    - **IV Furosemide:** for patients with pulmonary congestion or sever edematous state
      - Start with 40mg IV, stat. See response every 2 hours. If urine output of 150ml and above is achieved in 2 hours and give the 40mg IV BID or TID.
      - If urine output is <150ml in 2 hours, increase the dose by 40mg and reassess the urine output in another 2 hours.
      - Give the dose which resulted in adequate once diuresis (>150ml/2hour) as standing e.g. 80mg or 120 IV BID or TID. Maximum bolus dose 200mg.
      - IV Furosemide above 100mg should be given slowly(over 15-20minutes)
    - **Additional antihypertensive:** If BP is not well controlled with loop diuretics alone
    - **Add Calcium channel blocker on loop diuretics:**
      - Amlodipine 5-10mg PO once daily OR
      - Nifedipine 20-40mg PO BID.
    - **If a third agent is needed,** add a beta-blockers: **Alternatives**
      - Carvedilol 6.25 to 25mg BID
      - Bisoprolol 2.5 to 10mg/day or
      - Metoprolol 25-100mg/day or
      - Atenolol 25-100mg/day
    - **Avoid ACE inhibitors, Angiotensin receptor blockers (ARBs):** due to the risk of hyperkalemia and potential for deterioration in kidney function.
    - **Avoid Spironolactone prophylactic potassium tablet** in patients with AGN/RPGN: due to risk of hyperkalemia and worsening kidney function
  - **Management of hyperkalemia**
    - Start shifting treatment with regular insulin < if serum potassium is >6.0mmol/l
      - **Regular Insulin:** 10IU regular insulin IV, immediately followed by 03vials

(60ml) of 4% dextrose IV, to be given every 6 hour. Monitor blood sugar every 4-6 hourly.

- If potassium is >7mmol/l or there are ECG changes hyperkalemia start IV calcium
  - **Calcium gluconate (10%) 10ml**, IV, to be given over 5 minutes followed by regular insulin (as above).
- **Antibiotic** treatment for streptococcal infection should be given to all patients and their cohabitants.
- There is no role for immunosuppressive therapy, even in the setting of crescents.
- Recurrent PSGN is rare despite repeated streptococcal infections.
- Overall, the prognosis is good, with permanent renal failure being reported as very uncommon in the past (<1%) but with recent reports of an increased risk of CKD in adulthood.
- Complete resolution of the hematuria and proteinuria in the majority of children occurs within 3–6 weeks of the onset of nephritis
- Three–10% of children may have persistent microscopic hematuria, nonnephrotic proteinuria, or hypertension.
- The prognosis in elderly patients is worse with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and ESRD.

## LUPUS NEPHRITIS

- Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents.

### PATHOGENESIS

- Lupus nephritis results from the deposition of circulating immune complexes
  - which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines.
- In situ immune complex formation following glomerular binding of nuclear antigens, particularly necrotic nucleosomes, also plays a role in renal injury.
- The presence of antiphospholipid antibodies may also trigger a thrombotic microangiopathy in a minority of patients.

### CLINICAL MANIFESTATIONS

- Thirty to 50% of patients will have clinical manifestations of renal disease at the time of diagnosis.
- Sixty percent of adults and 80% of children develop renal abnormalities at some point in the course of their disease.

- The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure, and active urine sediment with RBC casts can all be present.
- The extra renal manifestations of lupus are important in establishing a firm diagnosis of systemic lupus
  - because, while serologic abnormalities are common in lupus nephritis, they are not diagnostic.

### DIAGNOSIS

- In patients with SLE, the presence of nephritis is **suspected by** an abnormal urinalysis and/or elevation of the serum creatinine.
- The **diagnosis is** confirmed by histopathologic findings on *renal biopsy*, which is also the only reliable method of identifying the morphologic variants of lupus nephritis (see table below).
- Anti-dsDNA antibodies that fix complement correlate best with the presence of renal disease.
- *Hypocomplementemia* is common in patients with acute lupus nephritis (70–90%) and declining complement levels may herald a flare.
- *Elevated serum creatinine* is present in 25% of patients.

### TREATMENT AND PROGNOSIS

- Patients with crescents on biopsy often have a rapidly progressive decline in renal function.
- Without treatment, this aggressive lesion has the worst renal prognosis.
- However, if a remission—defined as a return to near-normal renal function and proteinuria  $\leq 330$  mg/dL per day—is achieved with treatment, renal outcomes are excellent.
- Current evidence suggests that inducing a remission with administration of
  - highdose steroids and
  - either cyclophosphamide or mycophenolate mofetil for 2–6 months,
  - followed by maintenance therapy with lower doses of steroids and mycophenolate mofetil or azathioprine, best balances the likelihood of successful remission with the side effects of therapy

Classification for Lupus Nephritis		
<b>Class I</b>	<b>Minimal mesangial</b>	Normal histology with mesangial deposits
<b>Class II</b>	<b>Mesangial proliferation</b>	Mesangial hypercellularity with expansion of the mesangial matrix
<b>Class III (A, A/C, C subclass) *</b>	<b>Focal nephritis</b>	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
<b>Class IV (S, G &amp; A, C)</b>	<b>Diffuse nephritis</b>	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
<b>Class V</b>	<b>Membranous nephritis</b>	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
<b>Class VI</b>	<b>Sclerotic nephritis</b>	Global sclerosis of nearly all glomerular capillaries

Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study

Group. \*A= acute, C= Chronic; S =Segmental, G= global pattern of glomerular injury

- Both class I and II lesions are typically associated with minimal renal manifestation and normal renal function; nephrotic syndrome is rare.
- Class III lesions have the most varied course.
  - Patients with mild proliferation involving a small percentage of glomeruli respond well to therapy with steroids alone, and fewer than 5% progress to renal failure over 5 years.
- Patients with more severe proliferation involving a greater percentage of glomeruli have a far worse prognosis and lower remission rates.
- Treatment of those patients is the same as that for class IV lesions.

## IgA NEPHROPATHY

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### DEFINITION

- IgA nephropathy is an immune complex–mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity.

### EPIDEMIOLOGY

- It is one of the most common forms of GN worldwide (esp. in developed countries; rare in blacks).
- There is a peak incidence in the second and third decades of life and male preponderance.

### ETIOLOGY AND PATHOGENESIS

- The etiology of primary immunoglobulin A (IgA) nephropathy is generally unknown.
- The initiating event in the pathogenesis of IgA nephropathy is the mesangial deposition

of IgA, which is predominantly polymeric IgA of the IgA1 subclass (polymeric IgA1).

- The factors that lead to development of disease are poorly understood but are thought to include dysregulation in IgA production by plasma cells; in IgA clearance, by the liver and in mesangial IgA clearance and receptors for IgA.
- Environmental factors including *dietary antigens* and *mucosal infections* may drive the generation of pathogenic IgA immune complexes due to a dysregulated mucosal immune system.
- IgA nephropathy is predominantly a sporadic disease but susceptibility to it has been shown uncommonly to have a *genetic component*.
- It is a complex polygenic disease that involves both major histocompatibility complex (MHC) and non-MHC susceptibility alleles.

### CLINICAL MANIFESTATIONS

- Approximately 40 to 50 percent present with one or recurrent episodes of gross (visible) hematuria, often accompanying an upper respiratory infection, sometimes been called "synpharyngitic hematuria."
- Another 30 to 40 percent have microscopic hematuria and usually mild proteinuria and are incidentally detected on a routine examination or during a diagnostic evaluation for CKD.
- Less than 10 percent present with either nephrotic syndrome or an acute, RPGN
- Rarely, IgA nephropathy may present with malignant hypertension.
- Rarely, patients develop acute kidney injury with or without oliguria.
- **Associations:** Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic bronchiectasis, dermatitis herpetiformis, leprosy, ankylosing spondylitis, and Sjögren's syndrome.
- IgA deposition in these entities is not usually associated with clinically significant glomerular inflammation or renal dysfunction and thus **is not called** IgA nephropathy.

### DIAGNOSIS

- The suspicion of a diagnosis of IgA nephropathy is generally based upon the clinical history and laboratory data. The diagnosis can be confirmed **only** by kidney biopsy.
- *Indications for renal biopsy:* only if there are signs suggestive of more severe or progressive disease, such as persistent urine protein excretion of at least 500 mg/day (which may increase over time) or an elevated serum creatinine.
- A number of other tests have been proposed for the evaluation of possible IgA nephropathy, but none are recommended

## DIFFERENTIAL DIAGNOSIS

- The renal disease in IgA vasculitis (Henoch-Schönlein purpura)
  - Clinical and laboratory evidence suggests close similarities between Henoch-Schönlein purpura and IgA nephropathy. Histologically they're identical.
  - Henoch-Schönlein purpura is distinguished clinically from IgA nephropathy by
    - prominent systemic symptoms,
    - younger age (<20 years old),
    - preceding infection,
    - abdominal complaints
- Hereditary nephritis (Alport syndrome)
- Thin basement membrane nephropathy
  - These are the two other major glomerulopathies that present with persistent isolated hematuria.
  - The diagnosis of any of these disorders can only be made by renal biopsy, or by inference in hereditary nephritis
- Membranoproliferative glomerulonephritis
- IgA-dominant Staphylococcus-associated glomerulonephritis

## TREATMENT AND PROGNOSIS

- IgA nephropathy is a benign disease for the majority of patients, and 5–30% of patients may go into a complete remission, with others having hematuria but well-preserved renal function.
- Several analyses found persistent proteinuria for 6 months or longer to have the greatest predictive power for adverse renal outcomes.
- There is no agreement on optimal treatment.
- Angiotensin converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function.
- Tonsillectomy and fish oil have also been suggested in small studies to benefit select patients.
- When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

### **OTHERS TYPES**

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- Subacute bacterial endocarditis
- Antiglomerular basement membrane disease
- Anca small-vessel vasculitis
  - Granulomatosis with Polyangiitis
  - Microscopic Polyangiitis
  - Churg-Strauss Syndrome
  - C3 Glomerulopathies
- Membranoproliferative glomerulonephritis
- Mesangioproliferative glomerulonephritis

## NEPHROTIC SYNDROME

### DEFINITION

- The nephrotic syndrome is defined by the presence of
  - heavy proteinuria (protein excretion greater than 3.5 g/24 hours in an adult),
  - hypoalbuminemia (less than 3 g/dL), and
  - peripheral edema
  - Hyperlipidemia and thrombotic disease may be present.

### ETIOLOGY

- Heavy proteinuria with or without the nephrotic syndrome may occur in association with a wide variety of primary and systemic diseases.
- Minimal change disease is the predominant cause in children.
- In adults, approximately 30 % have a systemic disease such as DM, amyloidosis, or SLE
- The remaining cases are usually due to primary renal disorders such as minimal change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy.

#### Major causes of nephrotic syndrome in adults

A. Major cause of primary nephrotic syndrome	B. Major causes of secondary nephrotic syndrome
<ol style="list-style-type: none"> <li>1. Primary Focal segmental glomerulosclerosis (FSGS)</li> <li>2. Minimal change disease (MCD)</li> <li>3. Primary membranous nephropathy (MN)</li> <li>4. Primary membranoproliferative glomerulonephritis (MPGN)</li> </ol>	<ul style="list-style-type: none"> <li>• Diabetes</li> <li>• Autoimmune disease: SLE</li> <li>• Infectious: HBV, HCV, HIV, Syphilis, Schistosomiasis</li> <li>• Amyloidosis: primary or secondary amyloidosis</li> <li>• Drugs: NSAIDS</li> <li>• Preeclampsia</li> <li>• Malignancy: Multiple myeloma, lymphoma, carcinomas</li> </ul>

## MINIMAL CHANGE DISEASE (MCD)

- MCD is also known as *nil lesion* sometimes
- causes 70–90% of nephrotic syndrome in childhood but only **10–15% of NS in adults**
- usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of NSAIDs
- The pathophysiology of this lesion is uncertain. Most agree there is a circulating cytokine, perhaps related to a T cell response that alters capillary charge and podocyte integrity.

## CLINICAL MANIFESTATIONS

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- MCD presents clinically with the abrupt onset of edema and nephrotic syndrome accompanied by acellular urinary sediment.
- Average urine protein excretion reported in 24 h is 10 g with severe hypoalbuminemia.
- Less common clinical features include hypertension (30% in children, 50% in adults), microscopic hematuria (20% in children, 33% in adults), atopy or allergic symptoms (40% in children, 30% in adults), and decreased renal function (<5% in children, 30% in adults).

## DIAGNOSIS

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- In children esp. <10yrs, a presumptive diagnosis of MCD is usually made based upon the clinical findings, because of its highest prevalence
- In adults
  - the diagnosis of MCD cannot be predictably made from the clinical presentation,
  - So a **renal biopsy** is almost always performed in to both establish the diagnosis and guide therapy.
  - MCD on renal biopsy shows no obvious glomerular lesion by light microscopy.
  - Electron microscopy demonstrates an effacement of the foot processes supporting the epithelial podocytes with weakening of slit-pore membranes.

## TREATMENT AND OUTCOME

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(See “management” section below for general management issues)

- Nonimmunosuppressive therapies — First-line therapy for edema and hypertension is a low-sodium diet and diuretics for fluid removal. Others: ACEI/ARBs
- Immunosuppressive therapy — **Glucocorticoid** therapy
- Glucocorticoids may have a specific, beneficial antiproteinuric effect on the glomerular filtration barrier in addition to their immunosuppressive effect.
- The mainstay of initial therapy of MCD is prednisone or prednisolone.
- Ninety to 95% of children will develop a complete remission after 8 weeks of steroid therapy, and 80–85% of adults will achieve complete remission, but only after a longer course of 20–24 weeks.
- Based on response to treatment:
  - **Primary responders** are patients who have a complete remission (<0.2 mg/24 h of proteinuria) after a single course of prednisone
  - **Steroid-dependent** patients relapse as their steroid dose is tapered
  - **Frequent relapsers** have two or more relapses in the 6 months following taper
  - **Steroid-resistant** patients fail to respond to steroid therapy. Adults are not considered steroid-resistant until after 4 months of therapy.
- Patients with steroid resistance may have FSGS on repeat biopsy.

- Relapses occur in 70–75% of children after the first remission, and early relapse predicts multiple subsequent relapses, as do high levels of basal proteinuria.
- The frequency of relapses decreases after puberty.
- There is an increased risk of relapse following the rapid tapering of steroids in all groups. Relapses are less common in adults but are more resistant to subsequent therapy.
- **Prednisone** is first-line therapy, either given daily or on alternate days.
- Other immunosuppressive drugs, such as cyclophosphamide, chlorambucil, and mycophenolate mofetil, are saved for frequent relapsers, steroid-dependent patients, or steroid-resistant patients.
- The long-term prognosis in adults is less favorable when acute renal failure or steroid resistance occurs.

## FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- FSGS refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli;
- The incidence of this disease is increasing, and it now represents up to **one-third of cases of nephrotic syndrome in adults**
- There are two types: primary and secondary FSGS

### Causes of FSGS

Primary FSGN: considered once secondary causes are ruled out

Secondary FSGN:

Viruses: HIV/hepatitis B/parvovirus  
Hypertensive nephropathy  
Reflux nephropathy  
Cholesterol emboli  
Drugs: Heroin/analgesics/bisphosphonates/ecstasy  
Oligomeganephronia  
Renal dysgenesis  
Alport's syndrome  
Sickle cell disease  
Lymphoma  
Radiation nephritis  
Familial podocytopathies

- The pathogenesis of FSGS is probably multifactorial.
- Possible mechanisms include a T cell-mediated circulating permeability factor, increased soluble urokinase receptor levels, TGF- $\beta$ -mediated cellular proliferation and matrix synthesis, and podocyte abnormalities associated with genetic mutations.
- The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction.

- So, if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD.
- The histologic variants of FSGS include:
  - FSGS not otherwise specified (NOS), formerly called classic FSGS, is the most common
  - Collapsing variant,
  - Tip variant
  - Perihilar variant
  - Cellular variant

### CLINICAL MANIFESTATIONS

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- FSGS largely manifest as proteinuria.
- It can present with hematuria, hypertension, any level of proteinuria, or renal insufficiency.
- Nephrotic-range proteinuria, African-American race, and renal insufficiency are associated with a poor outcome, with 50% of patients reaching renal failure in 6–8 years.
- FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis.

### TREATMENT

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(See “management” section below for general management issues)

- Treatment of patients with primary FSGS should include inhibitors of the renin-angiotensin system.
- Patients with nephrotic-range proteinuria can be treated with steroids but respond far less often and after a longer course of therapy than patients with MCD.
- Limited evidence suggests the use of cyclosporine. Relapse frequently occurs after its cessation.
- The treatment of secondary FSGS typically involves treating the underlying cause and controlling proteinuria.
- There is no role for steroids or other immunosuppressive agents in secondary FSGS.

## MEMBRANOUS GLOMERULONEPHRITIS (MGN)

- MGN, aka membranous nephropathy sometimes
- accounts for ~20% of cases of nephrotic syndrome in adults
- peak incidence between the ages of 30 and 50 years and a male to female ratio of 2:1
- rare in childhood and the most common cause of nephrotic syndrome in the elderly
- In 20–30% of cases, MGN is secondary and is associated with:
  - malignancy (solid tumors of the breast, lung, colon),
  - infection (hepatitis B, syphilis, malaria, schistosomiasis),
  - rheumatologic disorders like lupus, rheumatoid arthritis, IgG4 diseases or
  - drug exposure (Gold, mercury, penicillamine, NSAIDs, probenecid).

### CLINICAL MANIFESTATIONS

- Eighty percent of patients with MGN present with nephrotic syndrome and nonselective proteinuria.
- Microscopic hematuria is seen but less commonly than in IgA nephropathy or FSGS.
- Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy;
- this thickening needs to be distinguished from that seen in diabetes and amyloidosis.
- Immunofluorescence demonstrates diffuse granular deposits of IgG and C3
- electron microscopy typically reveals electron-dense subepithelial deposits

### TREATMENT AND PROGNOSIS

(See “management” section below for general management issues)

- Spontaneous remissions occur in 20–33% of patients and often occur late in the course which makes treatment decisions difficult.
- One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome.
- Male gender, older age, hypertension, and the persistence of proteinuria are associated with worse prognosis.
- Although thrombotic complications are a feature of all nephrotic syndromes, MGN has the highest reported incidences of renal vein thrombosis, pulmonary embolism, and deep-vein thrombosis.
- Prophylactic anticoagulation is controversial but has been recommended for patients with severe or prolonged proteinuria in the absence of risk factors for bleeding.
- In addition to the treatment of edema, dyslipidemia, and hypertension, inhibition of the renin-angiotensin system is recommended.

- Therapy with immunosuppressive drugs is also recommended for patients with primary MGN and persistent proteinuria ( $>3.0$  g/24 h).
- The choice of immunosuppressive drugs for therapy is controversial
- current recommendations are to treat with steroids and cyclophosphamide, chlorambucil, mycophenolate mofetil, or cyclosporine or rituximab, an anti-CD20 antibody directed at B cells

## **DIABETIC NEPHROPATHY**

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Refer under chronic complication of DM

## MANAGEMENT

**General management issues:** management of edema, proteinuria, hyperlipidemia, and hypercoagulability

### EDEMA

- **Loop diuretics**
  - **Oral Furosemide:**
    - Starting dose 40mg, PO, BID -TID.
    - Increase the dose to 80 mg PO BID-TID, then 120mg. PO, BID-TID.
    - **Aim:** decrease weight by 0.5 to 1kg/day.
  - **IV Furosemide:** If no adequate weight loss with increasing dose, admit for IV Furosemide
    - Start with 40mg, IV, TID.
    - Increase the dose to 80 mg IV TID, then 120mg. PO, TID
    - If no adequate response with IV Furosemide, add **hydrochlorothiazide 12.5 to 25mg BID** (to be given 30 minutes before the IV Furosemide)
    - Add prophylactic **KCl tablets (600mg BID-TID) or Spironolactone 25-50mg PO/daily** and monitor serum electrolytes every 2-3days.

### PROTEINURIA

- **ACE inhibitors or Angiotensin receptor blockers (ARBs)**
  - Start after adequate diuresis.
  - The kidney function must be stable before starting.
  - The dose should be escalated gradually with monitoring of serum Cr and potassium.
  - Monitoring should be done within 2 weeks of initiation and dose escalation.
  - ACE inhibitors (particularly Enalapril) are preferred over ARBs due to their low cost and wide availability.

#### ↳ Preferred

- **Enalapril:** starting dose 5mg BID, Maximum dose 20mg BID
  - **Alternatives**
    - Lisinopril: starting dose 5mg/day, Maximum dose 40mg/day
    - Perindopril: starting dose 5mg/day. Maximum dose 15mg/day
    - Telmisartan: Starting dose: 40mg/day maximum dose 80mg/day
    - Irbesartan : Starting dose: 75-150mg/day, maximum dose 300mg/day
    - Losartan: Starting dose 50mg/day maximum dose 100mg/day
    - Valsartan: Starting dose 80 -160mg/day, maximum dose 320mg/day

### HYPERCOAGULABILITY

- **Prophylactic anticoagulation:** Indicated if serum albumin is <2g/dl and patient is hospitalized
  - Unfractionated heparin 5,000IU, BID until discharge Or
  - Enoxaparin 40mg, SC, daily until discharge
- **Therapeutic (Full dose) anticoagulation**
  - **Indications**
    - If there is active venous thromboembolic disease (e.g. DVT/PE, renal vein thrombosis)
    - If their albumin is low and the following risk factors are found: Pregnancy, active malignancy, recent major surgery, NYHA class III or IV heart failure or morbid obesity –
  - **Unfractionated heparin 17,500 SC, BID or Enoxaparin 1mg/kg/dose BID + Warfarin** (dose to be adjusted according to INR) - **Overlap heparin with warfarin** until two therapeutic INRs (2-3) achieved, and then followed by Warfarin alone.
    - **Duration of anticoagulation:** Until the nephrotic syndrome resolves or 6-12 months (if it does not resolve).
  - **Hyperlipidemia:** Many patients require statins due to severe hyperlipidemia.

#### NON-PHARMACOLOGIC TREATMENTS

- Salt restriction
- Fluid restriction (less than 1 - 1.5 liter/day)
- Encourage ambulation
- Protein should not be restricted rather encourage patients to take adequate protein and high calorie diet

#### Treatment of the specific cause of the nephrotic syndrome

- Empiric steroid or any immunosuppressive should not be started for adults with nephrotic syndrome without doing renal biopsy.
- Please refer “etiology” above for treatment overview.

## POLYCYSTIC KIDNEY DISEASE (PKD)

- The polycystic kidney diseases are a group of genetically heterogeneous disorders and a leading cause of kidney failure.
- The autosomal dominant form of polycystic kidney disease (ADPKD) is the most common life-threatening monogenic disease, affecting 12 million people worldwide.
- The autosomal recessive form of polycystic kidney disease (ARPKD) is rarer but affects the pediatric population. Kidney cysts are often seen in a wide range of syndromic diseases.
- Recent studies have shown that defects in the structure or function of the primary cilia may underline this group of genetic diseases collectively termed ciliopathies.

## AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

- ADPKD is characterized by progressive formation of epithelial lined cysts in the kidney.
- Although cysts only occur in 5% of the tubules in the kidney, the enormous growth of these cysts ultimately leads to the loss of normal surrounding tissues and loss of renal function.
- ADPKD is caused by mutations in *PKD1* and *PKD2* which, respectively, code for polycystin-1 (PC1) and polycystin-2 (PC2).
- ADPKD is inherited as an autosomal dominant trait with complete penetrance, but variable expressivity. The disease affects all ethnic groups worldwide with an estimated prevalence of 1:1000 to 1:400.
- Only half of the patients with ADPKD are clinically diagnosed during their lifetime.

## CLINICAL MANIFESTATIONS

- ADPKD is characterized by the progressive bilateral formation of renal cysts. Focal renal cysts are typically detected in affected subjects aged <30 years.
- Hundreds to thousands of cysts are usually present in the kidneys of most patients in the fifth decade.
- Enlarged kidneys can each reach a fourfold increase in length, and weigh up to 20 times the normal
- The clinical presentations of ADPKD are highly variable.
- Many patients are asymptomatic until the fourth to fifth decade of life and are diagnosed by incidental discoveries of hypertension or abdominal masses
- Back or flank pain is a frequent symptom in ~60% of patients with ADPKD. The pain may result from renal cyst infection, hemorrhage, or nephrolithiasis.
- Gross hematuria resulting from cyst rupture occurs in ~ 40% of patients during the course of their disease, and many of them will have recurrent episodes.

- Proteinuria is usually a minor feature of ADPKD.
- *Infection* is the second most common cause of death for patients with ADPKD. Up to half of patients with ADPKD will have one or more episodes of renal infection during their lifetime.
- An infected cyst and acute pyelonephritis are the most common renal infections often due to gram-negative bacteria, which are associated with fever and flank pain, with or without bacteremia.
- Kidney stones occur in ~20% of patients with ADPKD (more than half of the stones are of uric acid)
- *Renal cell carcinoma* is a rare complication of ADPKD with no apparent increased frequency
- *Cardiovascular complications* are the major cause of mortality in patients with ADPKD.
- *Hypertension* (RAAS, increased sympathetic activity,..) is common, and typically occurs before any reduction in GFR. It is a risk factor for both cardiovascular and kidney disease progression.
- Notably, some normotensive patients with ADPKD may also have *left ventricular hypertrophy*.
- The progression of ADPKD has striking inter- and intrafamilial variability. The disease can present as early as *in utero*, but end-stage renal disease (ESRD) typically occurs in late middle age.
- Liver cysts derived from the biliary epithelia are the most common extrarenal complication.
- Polycystic liver disease associated with ADPKD is different from autosomal dominant polycystic liver disease (ADPLD).
- *Intracranial aneurysm (ICA)* occurs four to five times more frequent in ADPKD patients than that seen in the general population and cause high mortality. Family history of ICA is a risk factor of aneurysm rupture in ADPKD.
- Other vascular abnormalities in ADPKD patients include *diffuse arterial dolichoectasias* of the anterior and posterior cerebral circulation, which can predispose to arterial dissection and stroke.
- *Mitral valve prolapse* occurs in up to 30% of patients with ADPKD, and tricuspid valve prolapse is less common. Others: insufficiency of the mitral, aortic, and tricuspid valves.
- The prevalence of *colonic diverticulae* and *abdominal wall hernias* are also increased in ADPKD patients.

## DIAGNOSIS

- Diagnosis is typically made from a positive family history consistent with autosomal dominant inheritance and multiple kidney cysts bilaterally.
- **Ultrasound** demonstrates cysts in approximately 95% of affected patients over the age of 20 and is the screening method of choice, but may not detect small developing cysts in younger subjects.
- The following criteria exist for an ultrasound diagnosis of PKD among at-risk subjects:
  - 15 - 29 years of age: presence of at least two renal cysts (unilateral or bilateral) is sufficient (sensitivity value of 96% and specificity value of 100 %.)
  - 30–59 years of age: presence of at least two cysts in each kidney (SN & SP 100%)
  - ≥60 years of age: presence of *at least four cysts in each kidney* (SN & SP 100%)
- Because there is an increased frequency of developing simple renal cysts with age.
- Conversely, in subjects aged between 30 and 59 years the absence of *at least two cysts in each kidney*, which is associated with a false negative rate of 0%, can be used for disease exclusion.
- CT scan and T2-MRI, with and without contrast enhancement, are more sensitive than ultrasonography and can detect cysts of smaller size.

## TREATMENT

- **No specific treatment** to prevent cyst growth or the decline of renal function has been approved
- **Blood pressure control:** to a target of 140/90 mmHg is recommended for reducing cardiovascular complications and renal disease progression.
- More rigorous blood pressure control does not equal greater clinical benefits.
- **Cyst infection:** Lipid-soluble antibiotics against common gram-negative organisms include SMX-TMP, quinolones, and chloramphenicol are preferred. Treatment often requires 4-6 weeks.
- **Kidney stones:** treatment includes standard measures such as analgesics for pain relief, and hydration to ensure adequate urine flow.
- **Chronic flank, back, or abdominal pain** (due to renal enlargement) management may include both
  - pharmacologic (non-narcotic and narcotic analgesics)
  - non-pharmacological (transcutaneous electrical nerve stimulation, acupuncture, and biofeedback)
- **Surgical decompression** of cysts may be necessary occasionally
- More than half of ADPKD patients eventually require **peritoneal dialysis, hemodialysis, or kidney transplantation.**

## AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

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- ARPKD is a significant hereditary renal disease in childhood, with an estimated prevalence of 1 in 20,000 live births.
- Mutations in a single gene, PKHD1, are responsible for all the clinical presentations

### CLINICAL FEATURES

- Classic ARPKD is generally diagnosed in utero or within the neonatal period, and characterized by greatly enlarged echogenic kidneys in diseased fetuses.
- Reduced fetal urine production may contribute to oligohydroamnios and pulmonary hypoplasia.
- About 30% of affected neonates die shortly after birth due to respiratory insufficiency.

### DIAGNOSIS

- Ultrasonography, CT, and MRI all can be used for diagnosis.
- Ultrasonography reveals large, echogenic kidneys with poor corticomedullary differentiation.
- The diagnosis can be made in utero after 24 weeks of gestation in severe cases.

### TREATMENT

- There is no specific therapy for ARPKD.
- Appropriate neonatal intensive care, blood pressure control, dialysis, and kidney transplantation increase survival into adulthood.
- Complications of hepatic fibrosis may necessitate liver transplantation.

## TUBULO-INTERSTITIAL DISEASES OF KIDNEY

### ACUTE INTERSTITIAL NEPHRITIS (AIN)

#### DEFINITION

- **AIN** is immune-mediated disorder characterized by acute inflammation of the tubulointerstitium of the kidney
- AIN is demonstrated in 1 to 3 percent of all renal biopsies. The percentage rises to 13 to 27 percent when biopsy analysis restricted to AKI.

#### CAUSES

- Drug-induced(commonly), with proton pump inhibitors (PPIs) fast becoming the most common cause; others NSAIDs, penicillins, rifampin, ethambutol, acyclovir, diuretics, anticonvulsants,...
- Toxins, mushrooms
- Complication of a variety of systemic diseases and infections including:
  - Systemic lupus erythematosus [SLE],
  - Sjögren's syndrome,
  - Sarcoidosis,
  - Autoimmune nephritis ± uveitis
  - Bacteria (*Streptococcus*, *Staphylococcus*, *Legionella*, *Salmonella*, *C. diphtheriae*)
  - Viruses (EBV, CMV, hantavirus, polyomavirus, HIV)
  - Miscellaneous: *Leptospira*, *Rickettsia*, *Mycoplasma*, *Histoplasma*, Tuberculosis
- In some cases, there is no identifiable cause despite features suggestive of an immunologic etiology

#### CLINICAL FEATURES

- Typically present with renal impairment
- Nonspecific signs and symptoms of acute renal dysfunction which may include acute or subacute onset of nausea, vomiting, and malaise
- Patients may present with symptoms related to the cause of the AIN
- Classic **triads** esp. in drug induced AIN with **fever**, **rash** and **eosinophilia** (in some patients with drug-induced AIN, now less commonly reported)
  - There is no typical range of onset for medication-induced AIN.
  - The onset may range from 3 to 5 days (as occurs with a second exposure to an offending drug), to as long as several weeks, to many months (as occurs following a first exposure to an offending drug).
  - The latent period may be as short as one day with rifampin or as long as 18 months with an NSAID.

- The classic features occurring after 7–10 days of treatment with methicillin or another  $\beta$ -lactam antibiotic, is the exception rather than the rule.
- Gross hematuria occurs in approximately 5 percent of individuals
- However, many patients are asymptomatic
- Proteinuria is generally modest ( $\text{PCR} < 100 \text{ mg/mmol}$ ) and tubular in type.
- The urine may contain white blood cells and white cell casts but is sterile on culture.
- Eosinophils are present in up to 70% of patients but this is a non-specific finding.
- AIN should always be considered in patients with non-oliguric AKI.
- There may be a rapid deterioration of renal function in some cases of drug-induced AIN, causing the condition to be mistaken for RPGN.

## DIAGNOSIS

- **Suspect AIN** in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria.
- **Suspect Drug-induced AIN** when the onset of characteristic lab findings is temporally related to the initiation of a new drug, particularly one that has been previously reported to cause AIN.
- A **definitive diagnosis of AIN is made by renal biopsy**.
- It is often considered unnecessary to make a definitive diagnosis, such as among patients who have clearly documented onset of renal failure after initiation of a common culprit drug and who improve immediately upon stopping the offending agent.
- Kidney biopsy may be done for:
  - Patients who have a characteristic urinalysis for AIN but are not being treated with a drug known to cause AIN.
  - Patients who are being treated with a drug known to cause AIN but do not have a characteristic urinalysis. Some of the drugs that cause AIN can also produce other forms of AKI. As an example, NSAIDs can exacerbate prerenal disease by inhibiting the production of vasodilator prostaglandins.
  - who are being considered for treatment with glucocorticoids for AIN (usually drug induced) & ...
- Biopsy typically shows evidence of intense inflammation, with infiltration of the tubules and interstitium by polymorphonuclear leucocytes and lymphocytes. Eosinophils may also be observed, especially in drug-induced AIN.
- Often granulomas may be evident, especially in drug-induced AIN or sarcoidosis.
- The degree of chronic inflammation in a biopsy is a useful predictor of long-term renal function. Eosinophiluria may be present but is not a good discriminator for AIN.

**DDx:** The differential diagnosis of AIN includes all other causes of AKI

### **MANAGEMENT**

- Potentially offending agent should be immediately discontinued
- Some patients with drug-induced AIN recover following withdrawal of the drug alone, but high-dose glucocorticoids may accelerate recovery and prevent long-term scarring
- (E.g., of high-dose glucocorticoid: (prednisolone 1 mg/kg/day (to a maximum of 40 to 60 mg) for a minimum of 1 to 2 weeks, beginning a gradual taper after the SCr has returned to or near baseline, for a total therapy duration of 2 to 3 months is one possible regimen))
- Other specific causes should be treated, if possible.
- NSAID induced AIN may not respond to corticosteroids.

## **CHRONIC INTERSTITIAL NEPHRITIS**

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**CIN** is characterized by renal dysfunction with fibrosis and infiltration of the renal parenchyma by lymphocytes, plasma cells and macrophages, in association with tubular damage.

### **CAUSES**

- It may follow on from AIN that does not resolve
- Renal ischemia or secondary to a primary glomerular disease (most often cause today)
- Developmental anomalies or inherited diseases such as reflux nephropathy or sickle cell nephropathy
- Toxins: Herbal medicines, Lead, Balkan nephropathy, Mushrooms (*Cortinarius*)
- Drugs: All drugs causing AIN, Tenofovir, Lithium toxicity, Analgesic nephropathy, Ciclosporin,...
- Metabolic and chronic inflammatory diseases (Calcium phosphate crystallisation after excessive phosphate administration (e.g. phosphate enemas in patients with CKD), Hypokalaemia, Hyperoxaluria)
- In many patients, CIN presents at a late stage and no underlying cause can be identified. Genetic causes may underlie many of these cases.

### **CLINICAL FEATURES**

- Most patients with CIN present in adult life with CKD, hypertension and small kidneys.
- Urinalysis abnormalities are non-specific.
- A minority present with salt-losing nephropathy, characterised by hypotension, polyuria and features of sodium and water depletion.
- People with CIN have an impairment of urine-concentrating ability and sodium conservation, which puts them at risk of AKI due to salt and water depletion during an

acute illness.

- Renal tubular acidosis may complicate CIN but is seen most often in myeloma, sarcoidosis, cystinosis, amyloidosis and Sjögren's syndrome.

#### **MANAGEMENT**

- Management is supportive, with correction of acidosis and hyperkalemia; replacement of fluid and electrolytes, as required.
- Renal replacement therapy if irreversible renal damage has occurred.

## NEPHROLITHIASIS

- Nephrolithiasis specifically refers to calculi/stones in the kidneys, but are often discussed in conjunction with ureteral calculi (ureterolithiasis).
- It is a common, painful, and costly condition.

### CLINICAL PRESENTATION

- It typically requires weeks to months (and often much longer) for a kidney stone to grow to a clinically detectable size.
- Although the passage of a stone is a dramatic event, stone formation and growth are characteristically clinically silent.
- A stone can remain asymptomatic in the kidney for years or even decades. Thus, the onset of symptoms, typically attributable to a stone moving into the ureter, does not provide insight into when the stone actually formed.
- The factors that induce stone movement are unknown.
- There are two common presentations for individuals with an acute stone event:
  - a) Renal colic and painless gross hematuria.
  - b) *Renal colic* is a misnomer because pain typically does not subside completely; rather, it varies in intensity. When a stone moves into the ureter, the discomfort often begins with a sudden onset of unilateral flank pain.
- The intensity of the pain can increase rapidly, and there are no alleviating factors. This pain, which is accompanied often by nausea and occasionally by vomiting, may radiate, depending on the location of the stone.
- If the stone lodges in the upper part of the ureter, pain may radiate anteriorly; if the stone is in the lower part of the ureter, pain can radiate to the ipsilateral testicle in men or the ipsilateral labium in women.
- Occasionally, a patient has gross hematuria without pain.

### DIAGNOSIS

- The diagnosis is often made on the basis of the Hx, PEx, and urinalysis. Thus, it may not be necessary to wait for radiographic confirmation before treating the symptoms.
- Serum chemistry are typically normal, WBC count may be elevated
- Urine sediment: red and white blood cells and occasionally crystals
- The absence of hematuria does not exclude a stone
- The diagnosis is confirmed by an imaging study—preferably helical computed tomography (CT)
- Typically, **helical CT** reveals:
  - a ureteral stone or

- evidence of recent passage (e.g., perinephric stranding or hydronephrosis)
- Plain **abdominal radiograph** (kidney/ureter/bladder or KUB) can miss a stone in the ureter or kidney, even if it is radiopaque, and does not provide information on obstruction.
- **Abdominal ultrasound** offers the advantage of avoiding radiation and provides information on hydronephrosis, but it is not as sensitive as CT; most ureteral stones are not detectable by US.

### DIFFERENTIAL DIAGNOSIS

- acute cholecystitis (if the stone is lodged at the right ureteral pelvic junction)
- acute appendicitis (if the stone blocks the ureter as it crosses over the right pelvic brim)
- acute diverticulitis (if blockage occurs at the left pelvic brim)
- bacterial cystitis (if the stone lodges in the ureter at the ureterovesical junction, but in stone the urine culture will be negative)
- acute pyelonephritis (stone with proximal infection )
- muscular or skeletal pain,
- *Herpes zoster*,
- duodenal ulcer,
- abdominal aortic aneurysm,
- gynecologic conditions,
- ureteral stricture, and ureteral obstruction by materials other than a stone, such as a blood clot or sloughed papilla.
- Extraluminal processes can lead to ureteral compression and obstruction; however, because of the gradual onset, these conditions do not typically present with renal colic.

### MANAGEMENT

- Nonsteroidal anti-inflammatory drugs, opioids
- Maintain euvoolemia
- If the pain can be adequately controlled and the patient is able to take fluids orally, hospitalization can be avoided
- Alpha blockers may increase the rate of spontaneous stone passage
- Urologic intervention should be postponed unless there is evidence of
  - UTI,
  - low probability of spontaneous stone passage (e.g., a stone measuring  $\geq 6$  mm or an anatomic abnormality), or
  - intractable pain.
- A ureteral stent may be placed cystoscopically
- If an intervention is indicated, the selection of the most appropriate intervention is

determined by the size, location, and composition of the stone; the urinary tract anatomy; and the experience of the urologist.

- Extracorporeal shockwave lithotripsy (ESWL) is the least invasive option.
- An endourologic approach can remove a stone by basket extraction or laser fragmentation. percutaneous nephrolithotomy
- For large upper-tract stones:
  - Open surgical procedures such as ureterolithotomy or pyelolithotomy are nearly eliminated

### **EVALUATION FOR STONE PREVENTION**

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- More than half of first-time stone formers will have a recurrence within 10 years.
- A careful evaluation is indicated to identify predisposing factors, which can then be modified to reduce the risk of new stone formation.

### **HISTORY**

- The number and frequency of episodes (distinguishing stone passage from stone formation)
- Previous imaging studies, interventions, evaluations, and treatments
- Medical history: UTIs, bariatric surgery, gout, hypertension, and diabetes mellitus
- Family history of stone disease
- Current prescription and OTC medications as well as vitamin and mineral supplements
- Review of systems (to identify possible etiologic factors related to low urine volume, and gastrointestinal malabsorption, urinary frequency)
- Dietary history should encompass information on usual dietary habits (meals and snacks), calcium intake, consumption of high-oxalate foods (spinach, rhubarb, potatoes), and fluid intake (including amount of specific beverages typically consumed).

### **PHYSICAL EXAMINATION**

- Weight, blood pressure,
- Costovertebral angle tenderness, and
- Lower-extremity edema
- Signs of other systemic conditions such as primary hyperparathyroidism and gout

### **LABORATORY EVALUATION**

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- If not recently measured, the following serum levels should be determined:
- electrolytes (to uncover hypokalemia or renal tubular acidosis),
- creatinine, and uric acid
- calcium,
- PTH level - if indicated by high-normal or elevated serum and urine calcium concentrations.

- Often, 25-hydroxy vitamin D is measured in concert with PTH (to investigate the possible role of secondarily elevated PTH levels in the setting of vitamin D insufficiency)
- Urinalysis: red and white blood cells; crystals: strong risk factor for new stone formation.
- The results from 24-h urine collections serve as the cornerstone on which therapeutic recommendations are based.
- From at least two 24-h urine samples while consuming their usual diet and usual volume of fluid, the following factors should be measured:
  - Total volume,
  - Calcium, oxalate,
  - Citrate,
  - Uric acid,
  - Sodium, potassium, phosphorus,
  - pH, and creatinine.
- Stone composition analysis is essential if a stone or fragment is available; patients should be encouraged to retrieve passed stones.
- The stone type cannot be determined with certainty from 24-h urine results.

### **IMAGING**

- The “gold standard” diagnostic test is helical CT without contrast.
- Recommendations for follow-up imaging should be tailored to the individual patient.

### **PREVENTION OF NEW STONE FORMATION**

- Recommendations for preventing stone formation depend on the stone type and the results of metabolic evaluation.
- After remediable secondary causes of stone formation (e.g., primary hyperparathyroidism) are excluded, the focus should turn to modification of the urine composition to reduce the risk of new stone formation.
- For all stone types, consistently diluted urine reduces the likelihood of crystal formation.
- The urine volume should be at least 2 L/d (advice patients to drink water until this target reached).

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# CHAPTER SEVEN

## Infectious disease

Tuberculosis

Retroviral infection

Acute rheumatic fever

Infective endocarditis

Leishmaniasis

Schistosomiasis

### TUBERCULOSIS

- TB is among the top 10 cause of death and the leading cause of deaths from a single infectious agent globally.
- Ethiopia is among the 30 High TB, HIV and MDR-TB Burden Countries, with annual estimated TB incidence of 151/100,000 populations and death rate of 22 per 100,000 populations according to Global TB Report 2019 by WHO.
- Ethiopia misses an estimated 31% (nearly 62,000 persons with TB) of TB cases each year.

### ETIOLOGY

- Tuberculosis (TB) is an airborne disease caused by the bacterium Mycobacterium tuberculosis complex (MTBC), rod-shaped “acid-fast” bacillus.
- M. tuberculosis complex is comprised of M. tuberculosis (MTB) and other closely related mycobacterial species (M. bovis, M. africanum, M. microti, M. caprae, and M. canetti) are known to cause disease in humans, though majority of TB cases are caused by M. tuberculosis organisms, also called tubercle bacilli.

## TRANSMISSION

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- M. tuberculosis is carried in airborne particles, called droplet nuclei, of 1– 5 microns in diameter.
- Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing.
- The probability of transmission depends on the dynamics of four major factors:
  - The susceptibility of the host;
  - degree of infectiousness of the person with TB disease;
  - environmental factors and
  - Level of exposure (proximity, frequency and duration).
- The risk of infection of a susceptible individual is therefore higher with **close, prolonged, indoor exposure** to a person with infectious pulmonary TB.
- Population groups with conditions that compromise the immune system, including PLHIV, Diabetics, young age groups and malnourished, are at higher risk of developing Active TB as they fail to contain the latent TB infection from progressing to active disease.
- Besides, congregated settings like prisons, refugee camps, homeless shelters and urban slums are usually overcrowded and poorly ventilated.

## PATHOGENESIS

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- Primary infection occurs in persons without previous exposure to tubercle bacilli.
- Pulmonary infection occurs when TB bacilli, contained in a small infectious aerosol droplet, reaches a terminal airway and succeeds in establishing infection.
- A localized granulomatous inflammatory process occurs within the lung and this is called the primary (Ghon) focus.
- From the Ghon focus, bacilli drain via lymphatics to the regional lymph nodes.
- The Ghon focus with associated tuberculous lymphangitis and involvement of the regional lymph nodes is called the primary (Ghon) complex.
- The development of the primary complex is asymptomatic.
- From the regional lymph nodes bacilli enter the systemic circulation directly or via the lymphatic duct.
- This occult hematogenous spread occurs during the incubation period, before adequate immune responses contain the disease.
- After dissemination, bacilli may survive in target organs for prolonged periods.

## PRIMARY DISEASE

- Occurs soon after the initial infection with tubercle bacilli.
- Commonly in persons with impaired immunity or children.
- Middle and lower lung zones most commonly involved.
- Presents with pleural effusion, hilar or mediastinal LAD, military TB.

## POST-PRIMARY TB- ADULT-TYPE, REACTIVATION, OR SECONDARY TUBERCULOSIS

- Occurs after a latent period following primary infection.
- Occur either by reactivation or by re infection.

**REACTIVATION:** means that dormant bacilli persisting in tissues for months or years after primary infection start to multiply

**RE INFECTION:** means a repeat infection in a person who has previously had a primary infection

- The characteristic features are:-
  - Extensive lung destruction with cavitations
  - Positive sputum smear; upper lobe involvement
  - Usually, no intrathoracic lymphadenopathy
  - Patients with these lesions are the main transmitters of infection in the community.
- The future course of the disease at each of these sites depends on the dynamic balance between host immunity and the pathogen.

## NATURAL HISTORY

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- In the great majority (90-95%) of persons infected with M. Tuberculosis, the immune system either kills the bacilli or perhaps more often, keeps them suppressed (silent focus) resulting in a latent TB infection (LTBI).
- In immunocompetent individuals, only 5-10% of infected persons develop active disease in their lifetime.
- Individuals with latent TB infection do not have symptoms as there is no tissue destruction by the bacilli and are not infectious.

- Active TB disease may arise from progression of the primary lesion after infection, or from endogenous reactivation of latent foci, which remained dormant since the initial infection, or from exogenous re-infection.
- The progression from LTBI to TB disease may occur at any time, from soon to many years later.
- Post primary TB usually affects the lungs though any body part can be affected after haematogenous and/or lymphatic spread of the bacilli.
- Persons who have Active TB are usually infectious and may spread the bacteria to other people.

## **CLINICAL PRESENTATION OF TUBERCULOSIS**

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- The clinical presentation of Tuberculosis is most commonly the result of involvement of the lungs (more than 80% of cases); however, organ specific presentations may be seen upon involvement of extra-pulmonary organs, most commonly lymph nodes, pleura, spine, joints, genito-urinary tract, nervous system or abdomen.

### **PULMONARY TUBERCULOSIS (PTB):**

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- Symptoms of Pulmonary tuberculosis:
  - Persistent cough for two or more weeks, (cough of any duration for HIV positives)
  - Fever for more than 2 weeks
  - Night sweats
  - Unexplained weight loss

### **EXTRA-PULMONARY TB (EPTB):**

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- Patients may present with non-specific symptoms such as unintentional weight loss, night sweats and fever for more than 2 weeks. Other symptoms depend on the site or organ affected.
- In descending order of frequency, the extra pulmonary sites most commonly involved in TB are
  - The lymph nodes,
  - Pleura,

- Genitourinary tract,
- Bones and joints,
- Meninges,
- Peritoneum, and
- Pericardium.

## LYMPH NODE TB (TUBERCULOUS LYMPHADENITIS)

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- The most common presentation of extra pulmonary TB.
- Presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula).
- Lymph nodes are usually discrete in early disease but develop into a matted nontender mass over time; a fistulous tract draining caseous material may result.
- The diagnosis is established by fine-needle aspiration biopsy (with a yield of up to 80%) or surgical excision biopsy.
- Granulomatous lesions with or without visible AFBs are typically seen.
- Cultures are positive in 70–80% of cases.

## PLEURAL TB

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- Accounts for ~20% of extra pulmonary cases.
- Isolated pleural effusion usually reflects recent primary infection, and the collection of fluid in the pleural space represents a hypersensitivity response to mycobacterial antigens.
- It may also result from contiguous parenchymal spread, as in many cases of pleurisy accompanying post primary disease.
- Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. CXR reveals the effusion.
- Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies.
  - The fluid is: -

- ↳ Straw-colored and at times hemorrhagic.
- ↳ It is an exudate with: -
  - A protein concentration >50% of that in serum,
  - A normal to low glucose concentration,
  - A pH of ~7.3 (occasionally <7.2), and
  - Detectable white blood cells (usually 500–6000/ $\mu$ L).
- Needle biopsy of the pleura is often required for diagnosis and is recommended over pleural fluid analysis;
  - ↳ It reveals granulomas and/or yields a positive culture in up to 80% of cases.
- Tuberculous empyema is a less common complication of pulmonary TB.
  - ↳ It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space.

## **GENITOURINARY TB**

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- Accounts for ~10–15% of all extra pulmonary cases.
- Urinary frequency, dysuria, nocturia, hematuria, and flank or abdominal pain are common presentations.
- Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria.
- The documentation of culture-negative pyuria in acidic urine should raise the suspicion of TB.
- Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases.
- Genital TB is diagnosed more commonly in female than in male patients.
- In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities.
- In male results in epididymitis, orchitis and prostatitis.

## **SKELETAL TB**

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- TB of the bones and joints is responsible for ~10% of extra pulmonary cases.
- Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected.
- Spinal TB (Pott's disease or tubercu

- Ilious spondylitis; often involves two or more adjacent vertebral bodies).
- Whereas the upper thoracic spine is the most common site of spinal TB in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults.
- With advanced disease, collapse of vertebral bodies results in kyphosis (gibbus).
- A paravertebral “cold” abscess may also form.
- CT or MRI reveals the characteristic lesion and suggests its etiology.
- Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical.
- A catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord.
- Paraparesis due to a large abscess is a medical emergency and requires rapid drainage.

**TABLE1: Radiology of the Spine: Differentiation of Brucellosis from Tuberculosis**

Parameters	BRUCELLOSIS	TUBERCULOSIS
<b>Site</b>	Lumbar and others	Dorsolumbar
<b>Vertebrae</b>	Multiple or contiguous	Contiguous
<b>Diskitis</b>	Late	Early
<b>Body</b>	Intact until late	Morphology lost early
<b>Canal compression</b>	Rare	Common
<b>Epiphysitis</b>	Anterosuperior (Pom's sign)	General: upper and lower disk regions, central, subperiosteal
<b>Osteophyte</b>	Anterolateral (parrot beak)	Unusual
<b>Deformity</b>	Wedging uncommon	Anterior wedge, gibbus
<b>Recovery</b>	Sclerosis, whole-body	Variable
<b>Paravertebral abscess</b>	Small, well-localized	Common and discrete loss, transverse process
<b>Psoas abscess</b>	Rare	More likely

## TUBERCULOUS MENINGITIS AND TUBERCULOMA

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- Accounts for ~5% of extra pulmonary cases.
- It is seen most often in young children but also develops in adults, especially those infected with HIV.
- The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability.
- Because meningeal involvement is pronounced at the base of the brain, paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia.
- Lumbar puncture is the cornerstone of diagnosis.
- Examination of cerebrospinal fluid (CSF) reveals:-
  - A high leukocyte count (up to 1000/ $\mu$ L), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage;
  - A protein content of 1–8 g/L (100–800 mg/dL and
  - A low glucose concentration.
- Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard.
- Real time automated nucleic acid amplification (the Xpert MTB/RIF assay) has a sensitivity of up to 80% and is the preferred initial diagnostic option.
- Treatment should be initiated immediately upon a positive Xpert MTB/RIF result.
- If unrecognized, tuberculous meningitis is uniformly fatal.
- Neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed.
- Adjunctive dexamethasone significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae.
- The dexamethasone schedule was (1) 0.4 mg/kg per day given IV with tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered; followed by (2) 4 mg/d given by mouth with tapering by 1 mg per week until the fourth week, when 1 mg/d was administered.
- The WHO now recommends that adjuvant glucocorticoid therapy with either dexamethasone or prednisolone, tapered over 6–8 weeks, should be used in central nervous system TB.

- Tuberculoma, an uncommon manifestation of TB of the central nervous system, presents as one or more space-occupying lesions and usually causes seizures and focal signs.
- CT or MRI reveals contrast enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

## GASTROINTESTINAL TB

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- It is uncommon, making up only 3.5% of extra pulmonary cases.
- The most common forms of disease include involvement of the peritoneum, intestine, and/or liver.

### INTESTINAL TUBERCULOSIS

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- Signs and symptoms in a patient with intestinal tuberculosis may include:
  - Clinical manifestations reflecting intestinal ulcero-constrictive disease; these include intestinal colic, abdominal distension, chronic diarrhea, nausea, vomiting, constipation, and bleeding.
  - Clinical manifestations reflecting adjacent tissue involvement; these include ascites, lymph node enlargement, and tubo-ovarian symptoms.
  - Clinical manifestations of chronic inflammation; these include fever, fatigue, weight loss, and night sweats
  - Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved in 75 percent of cases.
  - Forms of intestinal lesions include ulcerative and hypertrophic; these forms can coexist.

#### ↳ The ulcerative

- Presentation commonly affects the ileum and jejunum;
- It is characterized by single or multiple transverse ulcers that form strictures during the healing process and
- May perforate, bleed, or form fistulas.
- Ulcers due to TB tend to be circumferential and are usually surrounded by inflamed mucosa.

↳ **The hypertrophic**

- Presentation commonly affects the ileocecal region and
- Causes obstruction or presents as a mass.
- Ileocecal valve involvement usually includes both side's valve, leading to incompetence.
- A patulous valve with surrounding heaped-up folds or a destroyed valve with a fish mouth opening may be observed.

**Table: Difference between TB of intestine and Crohn disease**

Characteristics	Intestinal tuberculosis	Crohn disease
Endoscopic feature	The ulcer is sub mucosal, transverse and circular	Transmural and longitudinal ulcer (cobble stone appearance)
Histopathology	Caseating granuloma	Non caseating and poorly formed granuloma
Etiology	Infectious	Inflammatory
Clinical	Perianal fissure	Perianal fistula
Intestinal perforation	Not common	Common

### PERITONEAL TUBERCULOSIS

- Peritoneal TB occurs most commonly following reactivation of latent tuberculous foci in the peritoneum established via hematogenous spread from a primary lung focus.
- As the disease progresses, the visceral and parietal peritoneum become studded with tubercles.
- Ascites develop secondary to exudation of proteinaceous fluid from the tubercles.
- Clinical manifestations of peritoneal TB include
  - Ascites (93 percent),
  - Abdominal pain (73 percent), and
  - Fever (58 percent).

- Typically, symptoms have persisted for week or months before the diagnosis is established.
- Peritoneal TB occurs in several form: -

**1. Acute** - rare

- Difficult to distinguish from pyogenic

**2. Chronic** - common

↳ Four variants

**A. Ascetic (serous)**

- Nonspecific abdominal pain, fever, and abdominal swelling
- Paracentesis-
  - Exudative fluid with a high protein content.
  - Leukocytosis that is usually lymphocytic.
- AFB smear and culture -low; culture of a large volume of ascitic fluid can increase the yield
- Peritoneal biopsy

**B. Loculated (Encysted)**

- Localized inflammatory reaction
- Localized cystic swelling
- Difficult to Dx / laparotomy

**C. Fibrosis (plastic)**

- Extensive adhesions involving most of the viscera (include intestine)
- Intestinal obstruction and diarrhea
- Doughy and ill-defined mass

**D. Caseating**

- Rare also called purulent

## PERICARDIAL TB (TUBERCULOUS PERICARDITIS)

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- Develops frequently in HIV-infected patients.
- Case-fatality rates are as high as 40% in some series.
- The onset may be sub-acute, although an acute presentation, with dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible.
- An effusion eventually develops in many cases.
- The effusion is exudative in nature, with a high count of lymphocytes and monocytes.
- Hemorrhagic effusion is common.
- Culture of pericardial fluid reveals *M. tuberculosis* in up to two-thirds of cases, whereas pericardial biopsy has a higher yield.
- High levels of adenosine deaminase, lysozyme, and IFN- $\gamma$  may suggest a tuberculous etiology (ADA>40U/L, IFN 140pg/dl).
- Without treatment, pericardial TB is usually fatal. Even with treatment complications may develop, including chronic constrictive pericarditis with thickening of the pericardium, fibrosis, and sometimes calcification.
- The WHO currently recommends that, in patients with tuberculous pericarditis, initial adjuvant glucocorticoid therapy may be used.

## MILIARY OR DISSEMINATED TB

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- Is due to hematogenous spread of tubercle bacilli.
- The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds.
- Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases.
- Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy.
- Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary TB, in up to 30% of cases.
- Meningismus occurs in fewer than 10% of cases.

## POST-TB COMPLICATIONS

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- TB may cause persisting pulmonary damage in patients whose infection has been considered cured on clinical grounds.
- Chronic impairment of lung functions, bronchiectasis, aspergillomas, and chronic pulmonary aspergillosis have been associated with TB.
- Chronic pulmonary aspergillosis may manifest as simple aspergilloma (fungal ball) or chronic cavitary aspergillosis.

## DIAGNOSIS OF TUBERCULOSIS AND TB CASE FINDING

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- Diagnosis of Tuberculosis employs the use of various diagnostic methods that are organized in various algorithms for appropriate investigations of patients that are triaged for TB diagnostic evaluation.

## TUBERCULOSIS DIAGNOSTIC METHODS

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The diagnosis of TB may be reached by proper investigations using either bacteriologic examination, imaging techniques, histopathology or biochemical analysis of body parts/fluids.

### 1. CONVENTIONAL TB DIAGNOSTIC METHODS

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**A. Smear Microscopy:** is used to identify acid fast bacilli (AFB) on microscopic examination of stained sputum smears.

- It is an applicable method to directly identify mycobacterial TB bacilli to make a diagnosis and also monitor treatment response in peripheral laboratories.
- Smears may be prepared directly from clinical specimens or from concentrated preparations.
- Two staining methods can be used to identify acid-fast bacilli: Ziel-Neelsen staining (ZN) or fluorescent auramine staining (LED FM).
- Sputum-smear microscopy is a relatively insensitive test, with a limit of detection (LOD) of 5000–10000 bacilli per milliliter of sputum.
- It cannot distinguish drug-susceptible strains from drug-resistant strains.

**B. TB Culture:** The current gold standard method for the bacteriological confirmation of TB is culture using commercially available liquid media.

There are two types of TB culture techniques:

- Solid culture: Lowenstein-Jensen (LJ) media
  - Is culture media which with ease of preparation, low cost, and low contamination rate.
  - Solid culture may take several weeks, 21-42 days, to detect growth and produce results.
  - It is the gold standard for diagnosis of MTB.
- Liquid culture:
  - Mycobacterial Growth Indicator Tube (MGIT) is highly enriched media for growing mycobacteria
  - with added 10 % more sensitivity than LJ media,
  - Can produce positive results rapidly.
  - However, the method is prone to higher contamination rate and expensive.

**C. Drug susceptibility testing (DST):** is a technique that is used to screen for susceptibility of the TB bacilli for various Anti-TB drugs using either phenotypic or genotypic means.

## 2. WHO-APPROVED NATIONALLY RECOMMENDED RAPID TESTS FOR DIAGNOSIS OF TB AND DR-TB

- The following rapid tests are currently recommended for use in Ethiopia.
  1. Xpert® MTB/ RIF and Xpert MTB/RIF Ultra assays
  2. Truenat™ MTB, MTB Plus and MTB Rif Dx tests
  3. Line-probe assays (LPAs): GenoType® MTBDRplus and GenoType® MTBDRsl)
  4. Loop-mediated isothermal amplification (TB-LAMP);
  5. Lateral flow lipoarabinomannan assay (LF-LAM) test to assist in diagnosing TB in selected groups of HIV-infected presumed TB patients.

## ADDITIONAL SUPPORTIVE METHODS

### A. Histo-Pathological Examination

- Samples for pathologic examination can be collected using:-
  - Fine needle aspiration from accessible mass like peripheral enlarged lymph nodes
  - Aspiration of effusions from serous membranes; serous fluid analysis however, is much less useful for diagnosis than histology and culture of a serous membrane biopsy specimen.
  - Tissue biopsy from any body tissues such as serous membranes, skin, endometrium as well as bronchial, pleural, peritoneal, colonic, gastric or liver tissue.

### B. Radiological Examination

- Chest radiography, or chest X-ray (CXR), is an important tool for triaging and screening for pulmonary TB.
- It is also useful to aid diagnosis when pulmonary TB cannot be confirmed bacteriologically.
- Radiological examination:

Typical pattern	Atypical
Upper lobe infiltrate	Lower lobe infiltrate
Bilateral infiltrate	Intrathoracic LAP
Cavitation	No cavitation
Pulmonary fibrosis and shrinkage	No parenchymal change

### C) Ultrasonography:

- Is useful in the diagnosis of TB pleural effusion, pericardial TB and peritoneal TB.
- Ultrasonography of the chest may be helpful in demonstrating fibrin bands, septations, pleural thickening, and multi-loculated pleural effusions.

## DEFINITION OF TERMS AND PATIENT REGISTRATION

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### Registration group for DS/DR TB patient

- **New TB:** patients that have never been treated for TB or have taken anti-TB drugs for less than one month.
- **Relapse:** patients who were declared cured or treatment completed at the end of their most recent treatment course, and is now diagnosed with a recurrent episode of TB.
- **Treatment after failure:** refers to patients who were declared treatment failure in their most recent course of treatment as per national protocol.
- **Treatment after loss to follow-up:** refers to patients who were declared lost to follow-up at the end of their most recent course of TB treatment and is now decided to be treated with full course of TB treatment.
- **Others:** refers to patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented, or patients that do not fit into any of the categories listed above.
- **Transfer in:** A patient who is transferred to continue treatment at a given reporting unit after starting treatment in another reporting unit.

## TREATMENT OF DRUG SUSCEPTIBLE TB (DS-TB)

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### Objectives of TB treatment-

- To cure the patient from TB
- To prevent death from TB disease and its late effects
- To prevent relapse of TB
- To prevent the development of acquired drug resistance, and
- To decrease TB transmission

### Essential properties of Tuberculosis treatment

- In order to achieve the designed aim of treatment, an anti-TB treatment regimen should not only be designed considering effectiveness and safety of the drugs but also the treatment needs to be administered:
  - In appropriate combination of drugs

- In the correct dosage
- Regularly taken by the patient, and
- For a sufficient period of time.

### Principles of managements of TB

- Anti TB
- Pyridoxine 50mg for all patients
- Nutritional support
- Family screening and provision of prophylaxis for those less than or equal to 15 years after r/o active TB

### TB PREVENTIVE TREATMENT REGIMENS IN ETHIOPIA

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- Currently recommended TPT regimens include: **3HP, 3RH and 6H**;
- Three months of weekly isoniazid plus rifapentine (3HP) is the preferred regimen for TPT in all PLHIV > two years age who are not receiving protease inhibitor or NVP based regimen, and who do not have any other contraindication for 3HP.
- Six months of isoniazid preventive therapy (IPT) is the recommended regimen for children, adolescents and adults living with HIV who are receiving ART regimen with protease inhibitor or existence of other contraindication for 3HP.
- Three months of weekly isoniazid plus rifapentine (3HP) is also the preferred regimen for TPT in eligible HIV-negative children and adolescents (2- 14 years of age).
- Three months of daily isoniazid plus rifampicin (3HR) is the preferred regimen for eligible HIV-negative children < 2 years of age.
- Six months of isoniazid preventive therapy (IPT) should be offered to HIV-exposed infants taking nevirapine-based prophylaxis who are also exposed to pulmonary TB case
- IPT may be used for all eligible individuals if 3HP or 3HR are not available or contraindicated

## DOSING OF ANTI-TUBERCULOSIS DRUGS

**Table: The Essential Anti-TB Drugs and Their Recommended Dosages**

TB Drug	Recommended Adult dosage		Recommended pediatric dosage	
	Daily dose range(mg/kg BW)	Maximum(mg)	Daily dose range(mg/kg BW)	Maximum(mg)
Isoniazid	5(4-6)	300	10(7-15)	300
Rifampicin	10(8-12)	600	15(10-20)	600
Pyrazinamide	25(20-30)	-	35(30-40)	-
Ethambutol	15(15-20)	-	20(15-25)	-

## STANDARDIZED TB TREATMENT

- Standardized TB treatment means that patients with diagnosis of TB in a defined group receive the same treatment regimen.

**Table: Standard First Line Ant-TB Regimen for Patients Presumed or Known to DS-TB:**

Intensive phase treatment	Continuation phase treatment
Two months of <b>HRZE/2HRZE</b>	Four months of <b>HR/4HR</b>

## PHASES OF CHEMOTHERAPY AND DAILY DOSING FREQUENCY

- DS-TB treatment is administered in two phases:
  - Intensive (initial) phase:** aims to render the patient non-infectious by rapidly reducing the bacillary load in the sputum and brings clinical improvement in most patients receiving effective treatment.
  - Continuation phase:** aims to sterilize the remaining semi-dormant bacilli and is important to ensure cure/ completion of treatment and prevent relapse after completion of treatment.
  - Dosing frequency:** daily administration of all doses of the six month TB treatment should be implemented under DOT in Ethiopia. Intermittent dosing frequency is not recommended.

## TREATMENT OF EXTRA-PULMONARY TB (EPTB)

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- Extra-pulmonary tuberculosis (EPTB) is generally treated with the same regimen as pulmonary tuberculosis.
- The guiding principles for patient registration, regimen designing, monitoring of treatment and outcome definitions are similar to patients with pulmonary TB.

## ADDITIONAL CONSIDERATIONS IN EPTB TREATMENT:

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- Treat patient with extra-pulmonary TB involving any site for six-month with standardized first-line regimen with the exception of CNS TB (meningitis, tuberculoma) and Osteoarticular TB (including vertebral bones, joint and osteomyelitis)
- CNS TB and Osteoarticular TB treatment require prolongation of the continuation phase for 10 months: 2RHZE/10RH.
- An initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8weeks should be used for patients with Tuberculosis meningitis and/or pericarditis to improve outcome and reduce complications.

## PRE-TREATMENT EVALUATION AND PREPARATION FOR TREATMENT

- Before starting TB treatment, it is important to conduct baseline evaluation of the patient. The baseline evaluation shall focus on the following:
  - Checking how diagnosis of TB has been made and for confirmatory bacteriologic information.
  - Determining the site of TB Disease (Pulmonary or Extra pulmonary, multi-system involvement).
  - HIV Status including offering HIV tests
  - Assessment for risk of drug resistance including testing for at least Rifampicin Resistance.
  - Assessment for co-morbid conditions like pregnancy, renal or liver disease.
  - Classification of the TB type and assignment of patient the registration group.
  - Identification of appropriate treatment supporter.
  - Initiation of contact screening and provide adherence counseling for the patient and supporter.

## TB DRUGS AND THEIR COMMON SIDE EFFECT

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- **Isoniazide**
  - Peripheral neuropathy
  - Hepatitis in elderly
- **Rifampin**
  - GI irritation
  - Hepatitis
  - AKI
- **Pyrazinamide**
  - Hepatitis
  - Joint pain
- **Ethambutol**
  - **There are no sources in the current document.**
  - Optic neuritis
- **Streptomycin**
  - Deafness
  - Renal damage

### NOTE

pyrazinamide and streptomycin are the most hepatotoxic and nephrotoxic anti TB drugs respectively.

### Control of tuberculosis infection heavily relies on patient awareness about

- Control of transmission: risk areas include congregated areas, house hold, and health facilities.
- Early diagnosis and effective treatment- patient drug adherence.

## RETRO VIRAL INFECTION

### APPROACH TO RVI

- HIV disease is a chronic infectious disease caused by the Human Immune Deficiency Virus.
- Which is characterized by spectrum starting from primary infection, with or without the acute syndrome,
- followed by a relatively long period of asymptomatic stage after which in most patient's progress to advanced and life threatening disease (AIDS).

### ETIOLOGY

- HIV [retrovirus]-2 type
- HIV1 [M, N, O] most common worldwide
- HIV2 in West Africa
- **NB-** in Ethiopia the most common is HIV 1, M type, subtype C.

### MODE OF TRANSMISSION

#### 1. Sexual Transmission: Vary with mode

- Receptive anal intercourse- b/n 1:100 and 1:30
  - Insertive anal intercourse-1:1000
  - Receptive vaginal intercourse-1:1000
  - Insertive vaginal intercourse-1:10,000
- The risk increases with the presence of ulcerative or inflammatory STDs, trauma, menses, and lack male circumcision.

#### 2. Blood and blood product

#### 3. Mother to child transmission

- by far the largest source of HIV infection in children under 15

## CLINICAL MANIFESTATION OF HIV

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- The clinical consequences of HIV infection encompass a spectrum
  - **Primary HIV Infection:** Acute HIV syndrome and Sero-conversion
  - **Asymptomatic stage** – Clinical latency
  - **Early Symptomatic Diseases** – mild immunodeficiency
  - **AIDS defining illnesses:** Advanced immunodeficiency
- Time taken for a person to develop AIDS after primary HIV infection varies. There are three pattern of HIV disease progression
  1. Typical progressors [85-90 %] develop AIDS after 7-10 years
  2. Rapid progressors [<5%] develop AIDS in <3 years
  3. Long term non progressors [5-10%] may not develop AIDS even after living for more than 15-20 years without receiving any treatment or prophylactic therapy.
- What affects disease progression in HIV Infected individuals?
  - Viral set point.
    - The level of steady-state viremia (set-point) at six months to one year after infection.
  - Immune response.
    - High CD8 slow progression.
    - Low CD8 rapid decline
  - Viral type; HIV 2 slow course
  - Concomitant conditions:
    - Malnutrition hastens the progression of HIV
    - Chronic infectious conditions e.g. TB

## WHO CLINICAL STAGING SYSTEM

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- **CLINICAL STAGE 1**
  - Asymptomatic infection
  - Persistent generalized lymphadenopathy (PGL) defined as;
    - swollen or enlarged lymph nodes > 1cm,
    - in 2 or more non-contiguous extra-inguinal sites,
    - in absence of known cause;
    - lasting more than 3 months
- **CLINICAL STAGE 2**
  - Unexplained Weight loss <10% of presumed body weight
  - Minor mucocutaneous manifestations:
    - Papular pruritic eruptions
    - Seborrhoeic dermatitis
    - Angular chelitis
    - Fungal nail infections of fingers
    - Recurrent oral ulcerations ( $\geq 2$  x/6months)
    - Herpes zoster (current or in last 2 years)
  - Recurrent upper respiratory tract infections (sinusitis, otitis media, pharyngitis)
- **Clinical Stage 3**
  - Oral candidiasis
  - Unexplained Weight loss >10%
  - Recurrent vaginal candidiasis
  - Oral hairy leukoplakia
  - Pulmonary tuberculosis (Current)
  - Unexplained chronic diarrhea > 1 month

- Unexplained prolonged fever (intermittent or constant for >1 month).
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia).
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis.
- Unexplained:
  - Anemia (<8g/dl) or
  - Neutropenia (<500/mm<sup>3</sup>) or For > 1 month
  - Thrombocytopenia (<50 000/mm<sup>3</sup>)
- **CLINICAL STAGE 4**
  - Recurrent severe bacterial pneumonia
  - Chronic herpes simplex infection orolabial, genital, or anorectal of > 1 month duration
  - Cytomegalovirus infection (other than liver, spleen, LN)
  - CNS toxoplasmosis
  - HIV wasting syndrome [Weight loss > 10% plus Unexplained chronic diarrhea > 1 month or Unexplained prolonged fever > 1 month]
  - Pneumocystis pneumonia
  - Candidiasis of the esophagus
  - Extra pulmonary tuberculosis
  - Kaposi's sarcoma
  - Cryptococcal meningitis (or other extra pulmonary crypto)
  - Invasive cervical carcinoma
  - Cryptosporidiosis, Isosporiasis
  - HIV encephalopathy
  - Progressive multifocal leukoencephalopathy (PML)
  - Candidiasis of trachea, bronchi, or lungs

- Any disseminated endemic mycosis Histoplasmosis, Coccidiomycosis, Penicilliosis
- Disseminated Mycobacterial diseases other than tuberculosis
- Recurrent non-typhoidal salmonella septicemia (2 or >episodes in one year)
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Leishmaniasis, visceral
- Visceral Herpes simplex
- HIVN
- Enteropathy

## T-STAGING

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- Refers to clinical staging while on antiretroviral treatment for at least 6 months.
- Used as an indicator for treatment outcome.
- Clinical events before the first six months of therapy are excluded from this definition  
Because it Often represent IRIS related to pre-existing conditions.

**Table : T staging of HIV/AIDS**

New or recurrent event on ART	T- staging
Asymptomatic	T1
Stage 2 event	T2
Stage 3 event	T3
Stage 4 event	T4

## DIAGNOSIS AND LABORATORY MONITORING OF HIV

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### 1. SEROLOGIC TESTS:

- A HIV antibody tests: - detect antibodies formed by the immune system against HIV
  - **ELISA:** used to be standard screening test for HIV
    - Tests for a number of antibody proteins in combination
    - A very sensitive test (99.5 %), but not very specific

- A positive result needs to be confirmed by Western blot for confirmation
- The test need skilled personnel, takes several hours
- **Western blot:** is an excellent confirmatory test.
  - It has high specificity but relatively poor sensitivity
  - It should not be used for screening purpose
- **Rapid HIV antibody testes**
  - Advantages:
    - Rapid tests have reasonably good sensitivity and specificity ( >99 % )
    - Easy logically, does not need continuous water or electric supply
    - Can be done by less skilled personnel and the interpretation of results is easy
    - Test result can be made available in < 30 minutes
  - Because of these advantages of rapid tests WHO has recommend a serious of Rapid HIV antibody testes to be done to diagnose HIV infection.

## 2. DNA – PCR: Viral replication

- It is highly sensitive and the chance of false positivity is high.
- Hence it should not be used for making initial diagnosis of HIV infection
- Used To make early diagnosis of HIV in HIV exposed infants as serology tests are unable to diagnose HIV till the infant is 18 months old

## 3. CD4 T cell count

- Tells you the level of immune damage inflicted by HIV
- It should never be used to make diagnosis of HIV

## 4. Additional tests that should be done is patients with HIV infection include;

- HBV, HCV
- FBP and ESR
- SGOT/AST and SGPT/ALT
- Serum Creatinine

- Syphilis serology: RPR
- AFB chest X-Ray where possible
- Stool examination for parasites
- Malaria blood slide
- Pregnancy test for women in child bearing age.

## TREATMENT OF PEOPLE LIVING WITH HIV INFECTION

- It is critical for people living with HIV to initiate ART as early as possible.
- ART should be initiated for all individuals (children, adolescents and adults) living with HIV immediately after confirming HIV diagnosis, regardless of WHO clinical stage and CD4 cell count.
- Summary of first-line ART regimens for adults, pregnant & breastfeeding women, and adolescents.

**Table : Anti Retro viral drugs**

Population	Preferred first line regimens	Alternative first-line regimens
Adults (including those With TB/ HIV co-infection.)	TDF + $\beta$ TC + DTG (FDC)* OR TDF + $\beta$ TC + EFV (FDC)**	AZT + $\beta$ TC + EFV AZT + $\beta$ TC + NVP TDF + $\beta$ TC + NVP
Pregnant and breastfeeding women	TDF + $\beta$ TC + EFV (FDC)	AZT + $\beta$ TC + EFV AZT + $\beta$ TC + NVP TDF + $\beta$ TC + NVP
Adolescents (10 to 19 years) weight $\geq 35$ kg (Including those with TB/HIV b-coinfection.)	TDF + $\beta$ TC + DTG (FDC)* OR TDF + $\beta$ TC + EFV (FDC)**	AZT + $\beta$ TC + EFV AZT + $\beta$ TC + NVP TDF + $\beta$ TC + NVP

Abbreviation:  $\beta$ TC- Lamivudine, ABC- Abacavir, AZT/ZDV- Zidovudine, DTG- Dolutegravir,

EFV/EFZ- Efavirenz, FDC- Fixed dose combination, IDV –Indinavir, LPV - Lopinavir, NFV- Nelfinavir, NVP- Nevirapine, RTV/r- Ritonavir, RAL- Raltegravir, TDF- Tenofovir

## TREATMENT SUCCESS

- Plasma viral load
  - At 6/12 of treatment LDL (level below detection)
- CD4+ cell count
  - CD4+ cell rise is 50-100 cells within the first year.
  - The CD4+ cell response may lag behind the —virologic response|| in timing and at times the two responses could be (discordant)
- Clinical Parameters
  - An increase in body weight and general wellbeing.
  - Decrease total absence in frequency and severity of Ois
  - No HIV associated malignancies or non-infection conditions.

**Table: Definitions of virological, immunological and clinical failure for the decision to switch ART regimens**

Failure	Definition	Remark
<b>Virologic failure</b>	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months apart, with adherence support following the first viral load test	This is the <b>earliest</b> sign of failure before manifesting any of the clinical or immunological failure.  An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed. VL testing should not be done when there is an acute infection/fever as there can be blips of VL.
Immunologic failure	<b>Adults and adolescents</b>  CD4 count at or below 250 cells/mm <sup>3</sup> following clinical failure Or  <b>Children &lt;5 yrs:</b> Persistent CD4 levels below 200 cells/mm <sup>3</sup> or <10%	Without concomitant or recent infection to cause a transient decline in the CD4 cell count. Persistent is to mean at least 2CD4 measurements below the threshold.  Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virologic failure.
Clinical failure	<b>Adults and adolescents</b>	It is the <b>last</b> presentation that comes after immunological & virological

	<p>New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after 6 months of effective treatment</p> <p><b>Children</b></p> <p>New or recurrent clinical event indicating advanced or severe immune-defiance (WHO clinical stage 3 and 4 clinical conditions with exception of TB) after 6months of effective treatment.</p>	<p>failures.</p> <p>The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART.</p>
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## POST EXPOSURE ASSESSMENT AND POST EXPOSURE PROPHYLAXIS (PEP)

- **Assessment of exposure risk:**
  - **Low-risk exposure:**
    - Exposure to small volume of blood or blood contaminated fluids
    - Following injury with a solid needle
    - Asymptomatic source patient
  - **High-risk exposure:**
    - Exposure to a large volume of blood or potentially infectious fluids.
    - Exposure to blood or potentially infectious fluids from a patient with clinical AIDS or acute HIV infection.
    - Injury with a hollow needle.
    - Needle used in source patient ‘s artery or vein.
    - Visible blood on device.
    - Deep and extensive injury.
  - **Timing of initiation of prophylaxis:**
    - To be effective, PEP should commence as soon as possible (within 1-2 hours).

- The maximum delay for initiation of treatment which would prevent infection is not known in humans. Do not consider PEP beyond 72 hours post exposure.

- Prophylaxis is to be given for 28 days.

- **Recommended regimen**

- AZT or TDF+3TC+EFV for 28 days.

- Alternatively, boosted Lopinavir OR boosted Atazanavir can substitute EFV.

- **PEP is not recommended**

- a) If victim presents more than 72 hours after exposure.

- b) Following condom leak or tear.

## SYSTEMIC MANIFESTATION OF RVI

### RESPIRATORY SYSTEM MANIFESTATION

#### GENERAL CONSIDERATION

- Pulmonary involvement is among the most common complaints in patients with HIV/AIDS
- URTI occur relatively early before advanced immune deficiency
- Bacterial pneumonia and tuberculosis can occur any time during HIV infection [even when the CD4 count is >500]
- Pneumocystis jirovecii pneumonia [PCP] almost always occurs when CD4 <200
- Toxoplasmosis, CMV, and mycobacterium avium complex[MAC] usually occur at CD4 count is <100
- In the advanced stage of disease, more than one pathogen can be found

#### URTIs

- Pharyngitis
- sinusitis
- otitis media

#### LRTIs

- Pneumonia
- Tuberculosis
- PCP

#### OTHERS

- Kaposi sarcoma
- Lymphoma
- LIP

## SINUSITIS

- Presents as: -
  - fever,
  - nasal congestion,
  - Headache
- Etiology: - Encapsulated organisms such as: H. influenza and Streptococcus pneumoniae.
- DX is made by **CT or MRI**

## PNEUMONIA

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- The two most common causes of pneumonia are: -
  - Bacterial infections and
  - The unicellular fungus P. jirovecii infection.

### BACTERIAL PNEUMONIA

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- Common causes are encapsulated organisms such as
  - S. pneumoniae and
  - H. influenza
- This may be a consequence of altered B cell function and/or defects in neutrophil function that may be secondary to HIV disease.
- Clinical presentation Abrupt onset of;
  - Fever
  - Cough of productive purulent sputum
  - dyspnea
  - pleuritic chest pain

### DIAGNOSIS

- In practice, the diagnosis of bacterial pneumonia will often be made based on clinical presentation and may be chest x-ray (it may show consolidation, infiltrate, pleural infusion)

## OTHER INVESTIGATION

- CBC –leukocytosis, Blood culture- may be positive

### N.B.

Do AFB stain [3x] for all patient with a cough for more than 2- 3 weeks, even if the presentation mimics bacterial pneumonia.

## TREATMENT

- **Adults:** For non-severe pneumonia Amoxicillin 1000mg TID or erythromycin 500mgQID or doxycycline 100 mg BID for seven days.
- Avoid doxycycline in pregnancy.
- Alternative, Azithromycin 500 mg PO per day for three days, Clarithromycin 500 mg twice daily for seven days.
- If not improving after three days and if patient is adherent to the antibiotic, review and consider switching to IV regimen, Ceftriaxone 1-2gm IV once per day plus erythromycin 500 mg oral or IV four times a day.

## PNEUMOCYSTIS PNEUMONIA (PCP)

### ETIOLOGY

- *Pneumocystis jirovecii* (unicellular fungus)
- One of hallmark of AIDS
- Overall, 79% of patients with PCP have CD4+ T cell counts<100/micro. L and 95% of patients have CD4+ T cell counts <200/micro.lt.
- The risk is higher in individuals:
  - Who have previous bout of PCP [50%]
  - Whose CD4 count is <200
- Can be transmitted human to human or from environmental reservoir to human

### CLINICAL PRESENTATION

- Indolent course of characterized by weeks of vague symptom (compare with bacterial pneumonia which has abrupt onset).
- Dyspnea and fever are cardinal symptom
- Cough with no or scanty white sputum production (but in bacterial pneumonia productive purulent sputum)
- Sharp or burning retrosternal pain worsen with inspiration

- On P/E, rhonchi and wheeze may be heard (especially in patient with underlying pulmonary disease)
- It has also extra pulmonary manifestation such as ophthalmic lesions of the choroid a necrotizing vasculitis that resembles Burger's disease bone marrow hypoplasia, and Intestinal obstruction.

## INVESTIGATION

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### Chest x-ray

- Most common finding is normal film (if the disease is suspected early) or a faint bilateral interstitial infiltrate.
- The classic finding of a dense perihilar infiltrate is unusual in patients with AIDS
- Cysts and pneumothoraces are common chest radiographic findings,
- Asymmetric patterns, upper-lobe infiltrates, mediastinal adenopathy, nodules, cavities, and effusions.

### Chest CT

- shows diffuse ground-glass opacities in virtually all patients with PCP
- A normal chest CT essentially rules out the diagnosis of PCP.

WBC –mild leukocytosis

Arterial blood gases may indicate hypoxemia with a decline in Pao<sub>2</sub>

**REMEMBER**-A definitive diagnosis of PCP requires demonstration of the organism in samples obtained from;

- induced sputum,
- Broncho alveolar lavage,
- Trans bronchial biopsy, or
- Open lung biopsy

## TREATMENT

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- Trimethoprim 15-25 mg/Kg and sulfamethoxazole 75-125mg/kg, three or four times daily for 21 days.
- If patient grows sicker, administration of oxygen is useful.
- In severely ill adults with marked respiratory distress prednisolone has to be given simultaneously;
  - 40mg BID for the first five days then,

- 40 mg daily for the next 6 days and
- 20 mg daily until completion of intensive co-trimoxazole therapy.
- Secondary prophylaxis immediately after completion of the course of treatment with co-trimoxazole should be started.
  - Alternative regimens for mild to moderate cases of PCP include:
    1. Clindamycin 600 mg QID plus primaquine 15 mg bid or
    2. Clindamycin 600 mg QID plus dapsone 100 mg daily.

## HIV and TB

### THE IMPACT OF HIV/AIDS ON TB

- HIV increases
  - Susceptibility to infection with M. tuberculosis
  - The risk of progression to TB disease
  - TB incidence.
- It also increases the likelihood of re-infections and relapses of TB.
- Clinical presentation of TB in HIV infected patients is depend on CD4 count.
  - In patients with relatively high CD4+ T cell counts; the typical pattern of pulmonary reactivation occurs in which patients present with
    - Fever,
    - Cough,
    - Dyspnea on exertion,
    - Weight loss
    - Night sweats, and
    - Chest x-ray revealing cavitary apical disease of the upper lobes.
  - In patients with lower CD4+ T cell counts, disseminated disease is more common.
    - Chest x-ray-may show
      - Diffuse or lower lobe bilateral reticulonodular infiltrates consistent with miliary spread,
      - Pleural effusions, and
      - Hilar and/or mediastinal adenopathy.

## IMPACT OF TB ON HIV

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- TB increases HIV replication [which leads to increased viral load]. This results in more rapid progression of HIV disease, including development of AIDS defining illnesses.
- TB increases occurrence of other Opportunistic Infections.
- The management of TB and HIV co-infected individual is challenging because of
  - High pill burden,
  - Increased adverse effects,
  - Drug-drug interactions and
  - Immune reconstitution inflammatory Syndrome (IRIS)

## DIAGNOSIS

- Culture of the organism from an involved site provides a definitive diagnosis.
  - **Ziehl Nielsen (ZN) stain**
    - Usually on sputum and/or aspirate
    - Other body fluids can be stained (e.g., stool)
  - **Aspiration of pleural and pericardial fluid**
    - Usually not necessary for diagnosis
    - Only if indicated for clinical reasons
    - Pleural and pericardial effusion in HIV is due to TB in 90% of cases
- **Bronchoscopy:** improves yields

## TREATMENT

- Therapy for TB is generally the same in the HIV-infected patient as in the HIV-negative patient

## FUNGAL LUNG INFECTION

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- Mainly cryptococcosis
- Present with; fever, cough, dyspnea, and in some cases, hemoptysis
- **Diagnosis**-blood and sputum culture
- LP needed to exclude associated meningitis

Rx-fluconazole 200-400 mg po daily

### CMV PNEUMONITIS:

- Present with
  - Fever
  - Cough
  - Dyspnea and
  - Interstitial infiltrate
  - Think of it when you have other sign/symptoms associated with CMV [visual problem, gastrointestinal ulcer].

### DIAGNOSIS

- Biopsy show characteristic intracellular lesion in lung tissue.

### LYMPHOID INTERSTITIAL PNEUMONITIS [LIP]

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- Patient with exertion dyspnea + characteristic fine bibasilar interstitial marking + exclude bacterial pneumonia, PCP and TB.

### KAPOSI SARCOMA

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- In most case associated with Kaposi skin lesion
- Bloody pleural effusion
- Chest x-ray- commonly nodular infiltrate and sign of pleural effusion

Rx- chemotherapy + HAART needed

### GASTROINTESTINAL MANIFESTATION

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#### ORAL LESIONS

- Commonly occurs in patients with CD4 count <300/micro L

#### ORAL CANDIDIASIS

- White painless plaques on the buccal or pharyngeal mucosa or tongue surface that can easily be scraped off.
- Most commonly seen on soft palate

Etiology- candida albicans [endogenous yeast]

### Clinical presentation

- Thrush:
  - Pseudomembranous (classical) > 80%,
  - Atrophic,
  - Erythematous
- Angular cheilitis (perleche)
  - Median rhomboid glossitis
- Rx – antifungal [Nystatin, Miconazole]

### ORAL HAIRY LEUKOPLAKIA

- Presents as white, frond like lesions along the lateral borders of the tongue[commonly], sometimes on the adjacent buccal mucosa
- Non-removable
- Not painful
- No treatment
- Caused by EBV replication in the epithelium of the surface of the tongue

### APHTHOUS ULCERS

- are of unknown etiology
- quite painful and interfere with swallowing
- Topical anesthetics provide immediate symptomatic relief of short duration.

### ESOPHAGITIS

- may present with odynophagia and retrosternal pain
- may be due to Candida, CMV, or HSV
- Upper endoscopy is generally required to make an accurate diagnosis
- Remember-CMV associated with a single large ulcer while HSV associated with multiple small ulcers

### Treatment

- For esophageal candidiasis fluconazole 200 mg (6mg/kg/day in children) PO daily for 14-21 days alternatively, ketoconazole 200 mg (3-6mg/kg/day daily in children) twice daily for 4 weeks.
- If diagnosis suggests HSV esophagitis use acyclovir 400mg po five times for 14 to 21 days.

## STOMACH

- Achlorhydria (absence of hydrochloric acid) is a common gastric problem in patients with HIV infection

## INFECTION OF SMALL AND LARGE INTESTINE

- Presentation
  - diarrhea
  - abdominal pain
  - occasionally fever

### Etiology

- Bacteria [commonly, *Salmonella*, *Shigella*, and *Campylobacter*]
- Protozoa [*Cryptosporidium*, *Microsporidia*, and *Isospora Belli*]
- Virus; CMV colitis, presents with non-bloody diarrhea, abdominal pain, anorexia and weight loss.

### Diagnosis achieved by

- Endoscopy- show multiple ulceration.
- Biopsy reveal- characteristic intranuclear inclusion bodies.

**Table: Diarrheal disease summary**

Agent	CD4	Symptom	Diagnosis	Treatment
<i>E. histolytica</i>	Any	bloody stool, colitis	Stool microscopy	Metronidazole
Giardia	Any	Watery diarrhea	Stool microscopy	Metronidazole
Strongloides stercoralis	Any	Watery diarrhea	Stool microscopy	Ivermectin or Albendazole
<i>Cryptosporidium</i>	<150	Watery diarrhea	Modified AFB	ART
<i>Isospora belli</i>	<100	Watery diarrhea	Modified AFB	TMP-SMX
<i>Microsporidium</i>	< 50	Watery diarrhea	Giemsa stain	Albendazole
CMV	<50	Watery/bloody diarrhea, colitis	Tissue biopsy	Ganciclovir

## CHRONIC DIARRHEAL SYNDROME

- Also known as AIDS enteropathy or HIV enteropathy Chronic diarrhea for which no etiologic agent other than HIV can be identified [no secondary infection].
- Most likely a direct result of HIV infection in the gastrointestinal tract.

## NEUROLOGIC MANIFESTATION

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### DIRECT HIV-1 INFECTION

- Aseptic Meningitis
- AIDS Dementia complex (HIV encephalopathy)
- Peripheral Neuropathy
- Acute polyneuropathy
- Myopathy
- Vacuolar Myelopathy

### OPPORTUNISTIC INFECTIONS

- Cryptococcal meningitis
- Cerebral toxoplasmosis
- Tuberculous meningitis
- Cytomegalovirus encephalitis
- Neurosyphilis
- Herpes Simplex Virus
- Varicella Zoster Virus
- Progressive Multi-Focal Leukoencephalopathy (PML) ☐

### OPPORTUNISTIC NEOPLASMS

- Primary CNS lymphoma
- Metastatic lymphoma
- Kaposi Sarcoma

### DRUG SIDE EFFECTS (EFV, D4T, DDI, and AZT etc.)

### AIDS DEMENTIA COMPLEX

- Characterized by the classic triads: -
  - Sub-cortical dementia (Memory and psychomotor)
  - Depressive symptoms (apathy, social withdrawal)
  - Movement disorders (impaired rapidly alternating movements, ocular motility, weakness,)

- **Diagnosis-** diagnosis of exclusion

### CEREBRAL TOXOPLASMOSIS

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- Is usually reactivation of latent infection
- Mainly in patients with CD4 < 100 cells/mm<sup>3</sup>

### CLINICAL PRESENTATION

- Most common- fever, headache, and focal neurologic deficits.
- Other -seizure, Confusion, cognitive disorders (encephalitis)
- Remember-No neck stiffness in the majority of cases

### DIAGNOSIS

- Suspected on the basis of MRI/CT findings of multiple lesions in multiple locations (ring enhanced lesion on contrast MRI/CT).
- In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the HIV-infected patient includes;
  - Primary CNS lymphoma
  - TB [tuberculoma]
  - Fungal [cryptoccocoma]
  - Bacterial abscesses.
- The definitive diagnostic procedure is brain biopsy [invasive procedure].

### TREATMENT

- **First line treatment** regimen for toxoplasma encephalitis in the Ethiopian context is
  - For Adults: **Trimethoprim/sulfamethoxazole 80/400**, oral, **4 tablets 12 hourly for 28 days**, followed by 2 tablets 12 hourly for 3 months in adults.
- **Secondary prophylaxis:** use co-trimoxazole 960mg daily for adults **Alternative regimen**

- I. **Sulfadiazine**, 1-2 gm po. Q 6h for six weeks or 3 weeks after resolution of lesion
  - S/E: crystal urea, rash
  - C/I: severe liver, renal and hematological disorders; known hypersensitivity to Sulfonamides
  - Dosage/form: 500 mg tablets,

**PLUS Pyrimethamine**, loading dose of 200 mg once, followed by:

- Pyrimethamine 50-75 mg/day S/E: rash, fever and bone marrow depression (neutropenia and thrombocytopenia)

- C/I: folate deficiency
- Dosage/form: 25 mg tablets PLUS
- Folinic acid (Leucovorin): 10-20 mg/d OR

**II. Pyrimethamine and Folinic Acid (Leucovorin): (standard dose) PLUS Clindamycin: 600 mg q 6 hrs.**

- S/E: toxicities include fever, rash, and nausea, diarrhea (including pseudo-membranous colitis or diarrhea related to Clostridium difficile toxin)
- **Adjunctive corticosteroids** should be used for patients with
  - radiographic evidence of midline shift,
  - signs of critically elevated intracranial pressure
  - Clinical deterioration within the first 48 hours of therapy.
  - Dexamethasone (4 mg every six hours (0.15mg/kg/dose every 6 hours for children)) is usually chosen and is generally tapered over several days and discontinued as soon as possible.
- **Anticonvulsants** should be administered to patients with a history of seizures, but should not be given routinely for prophylaxis to all patients with the presumed diagnosis of TE.
- Careful attention needs to be paid to any potential drug interactions.

## CRYPTOCOCCAL MENINGITIS

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- Caused by an invasive fungal infection Cryptococcal neoformans.
- Occurs in patients with CD4+ T cell counts <100/micro. L.

### PRESENTATION

- Most patients present with a picture of sub-acute meningoencephalitis [median time before diagnosis is 30 days]
- Severe Headache
- Fever, nausea, vomiting, photophobia
- Alteration in consciousness and cognition
- Cranial nerve palsies: blindness and deafness (due to invasion by yeast)
- poor prognosis
- Seizures (10%)
- Stiff neck is absent in up to 70% of cases
- The CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose.

### DIAGNOSIS

- **Clinical:** Consider Cryptococcal Meningitis in known HIV infected patients with severe headache
- **LP /CSF -** Opening pressure is high,
  - Protein 30-150mg/dl,
  - WBC 0-100/mm<sup>3</sup> (monocyte).
  - **Indian Ink** is Positive [60-80%]
  - **CSF Cryptococcal Ag** is positive [90-95%]
  - Gold standard is **cryptococcal culture**
- **NB -** LP should be done unless there is lateralizing sign
- Antigen test from serum and CSF will be positive

## MANAGEMENT

- Management of Cryptococcal requires hospitalization and evaluation by physician.
- The management of **Cryptococcal meningitis** is **phased**:

### Option A

- The preferred regimen in Ethiopian, and it has 3 phases: induction, consolidation and maintenance.
  - **Induction phase (2 weeks):** High dose fluconazole:
    - Fluconazole 600 mg twice daily alone (children: 12mg/kg/day in 2 divided doses)
  - **Consolidation phase (8 weeks):** Fluconazole 800 mg/day (in children 12mg/kg/day)
  - **Maintenance treatment** (Secondary prophylaxis): Fluconazole 200 mg daily (in children, 6mg/kg/day)

### Option B. (Alternative in Ethiopian situation)

- **Induction phase (2 weeks):** Amphotericin B + Fluconazole:
  - Amphotericin 0.7-1 mg/kg/day + Fluconazole 800 mg/day
- **Consolidation phase (8 weeks):** Fluconazole 400-800 mg/day
- **Maintenance treatment** (Secondary prophylaxis): Fluconazole 200mg daily (in children, Fluconazole 6mg/kg/day).

### **ADDITIONAL POINTS ABOUT CRYPTOCOCCAL MENINGITIS MANAGEMENT:**

#### **1. Management of elevated Intracranial pressure (ICP):**

- Management of increased ICP is critical as >90% of deaths in the first two weeks and 40% of deaths in weeks 3-10 are due to increased ICP.
- Failure to manage elevated ICP is the most common and most dangerous mistake in management (Since the ICP is non-communicating hydrocephalus there is no risk of CSF tapping within the recommended volume).
- Daily serial LP should be done to control increased ICP by drawing 20-30 ml of CSF based on patient's clinical response.
- Signs of ICP include headache, altered mental status, meningismus and changing in hearing or vision should be closely monitored, if possible opening pressure should be measured.
- There is no role for acetazolamide, mannitol, or corticosteroids to reduce intracranial pressure.

#### **2. Discontinuation of maintenance treatment (secondary prophylaxis)**

- When patients are stable and adherent to ART and anti-fungal maintenance treatment for at least one year and
- Have a CD4 cell count of greater than or equal to 200 cells/mm<sup>3</sup> (two measurements six months apart).

#### **3. Timing of ART initiation for patient with Cryptococcal meningitis**

- Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening.
- ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy, and
- After 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with fluconazole, or
- After 4-6 weeks of induction and consolidation treatment with high-dose oral fluconazole regimen

### **POOR PROGNOSTIC SIGNS OF CRYPTOCOCCAL MENINGITIS:**

- Extra CNS manifestation (especially pulmonary)
- Altered mental status
- Low CSF WBC cell count less than 20 cells/ $\mu$ L

## ASEPTIC MENINGITIS

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- Commonly seen during acute HIV infection
- Presented with headache, photophobia, and meningismus
- Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII.
- usually resolves spontaneously within 2–4 week
- Diagnosis –CSF analysis
- Lymphocytic pleocytosis, elevated protein level, and normal glucose level.

## HIV ENCEPHALOPATHY [HIV-ASSOCIATED DEMENTIA OR AIDS DEMENTIA COMPLEX]

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- Is the initial AIDS-defining illness in ~3% of patients with HIV infection
- Characterized by triad:
  1. Dementia-a decline in cognitive ability from a previous level.
  2. Depressive symptom [apathy, social withdrawal]
  3. Movement disorder [impaired rapid alternating movement, ocular motility, weakness, incontinence]
- It is diagnosis of exclusion

## PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

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- Caused by JC virus
- It is a late manifestation of AIDS and is seen in ~4% of patients with AIDS.
- **Presentation**
  - The patient is afebrile, has no headache
  - Multifocal neurological deficit
- **Classic triad-**
  1. Dementia
  2. Hemiparesis &
  3. Hemianopia
- **Diagnosis:**
  - CSF is normal [not diagnostic]
  - JC virus PCR or brain biopsy may help to make diagnosis

## PRIMARY CNS LYMPHOMA

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- Accounts for ~20% of the cases of lymphoma in patients with HIV infection.
- The median CD4+ T cell count at the time of diagnosis is ~50/micro. L
- Presentation
  - B-type symptoms of fever, night sweats, or weight loss.
  - focal neurologic deficits, including cranial nerve findings,
  - headaches, and/or seizures
- Diagnosis
  - CT/MRI - multiple or single ring enhancing lesion
  - CSF- EBV DNA PCR
  - Histology- is ~ 100% effective diagnosis

## TB MENINGITIS

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- Occur on 10% of AIDS patient
- Clinically, cases are classified into three stages:
  - **STAGE 1**
    - The patient is fully conscious and presents with nonspecific symptoms such as;
      - General malaise, low-grade fever,
      - Apathy, irritability, personality changes, depression
      - Intermittent headache
    - No focal signs and little or no evidence of meningitis.
    - **N.B:** Symptoms may be limited or even absent in immunosuppressed patients, including those who are HIV-positive
  - **STAGE 2**
    - The patient is mentally confused and/or has focal neurological signs such as cranial nerve palsies.
    - Other symptoms include; More severe and persistent headache, Vomiting and some degree of photophobia.
  - **STAGE 3**

- The patient is deeply stuporose or comatose and/or has complete hemiplegia, paraplegia or quadriplegia
- **DIAGNOSIS**
  - LP/CSF - Lymphocytosis (< 500cells/mm<sup>3</sup>)
  - Low glucose
  - High protein (100-500 mg/dl)
  - AFB is positive (10-40%)

## HIV AND SEIZURE

- Consequence of opportunistic infections, neoplasms, or HIV encephalopathy
- The seizure threshold is often lower than normal in patients with advanced HIV infection due to the frequent presence of electrolyte abnormalities.
- Seizures are seen in
  - 15–40% of patients with cerebral toxoplasmosis,
  - 15–35% of patients with primary CNS lymphoma,
  - 8% of patients with cryptococcal meningitis, and
  - 7–50% of patients with HIV encephalopathy.

## HEMATOLOGIC MANIFESTATION OF RVI

- General consideration
  - Hematological complications are among the commonest manifestations in advanced HIV disease
  - The frequency and severity of the complications increase with advance in immunodeficiency.
  - The complications contribute to morbidity and mortality of HIV infected patients
  - Therefore, they should always be assessed and appropriately managed
  - They are also used for WHO staging
  - The commonest are;
    - Anemia
    - Leukopenia

- Thrombocytopenia

## **ANEMIA**

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<b>Table: Pathogenesis of the Anemia</b>	
<b>Decreased Production</b>	<b>Increased Destruction</b>
Anemia of chronic disease	Hypersplenism
Marrow infiltration	Thrombocytopenic Purpura (TTP)
Parvovirus B19 infection	Auto immune Hemolytic Anemia (AIHA)
Megaloblastic anemia	GI bleeding
	Others: Blood loss (direct blood loss or parasites like hookworm)

- Drugs Associated with Anemia
  - Zidovudine
  - Trimethoprim-sulfamethoxazole
  - Amphotericin B
  - Ganciclovir
  - Dapsone
  - Primaquine
- Marrow Infiltration
  - Mycobacterium avium complex (MAC)
  - Tuberculosis
  - Histoplasmosis
  - Extra pulmonary Pneumocystis carinii
  - Non-Hodgkin lymphoma

## **DIAGNOSIS**

- Clinical diagnosis of the underlying cause

- CBC (Hgb, HCT, derived values)
- Peripheral Morphology
- Bone marrow aspiration
- Bone marrow Biopsy
- Antibody Tests: (parvo virus and auto immune)

### **TREATMENT**

- Treatment of underlying condition
- Erythropoietin
- Blood transfusion

### **LEUKOPENIA**

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- Cause:
  - Decreased Production
    - HIV infection
    - Adverse drug reaction
    - Marrow infiltration
  - Increased Destruction
    - Autoimmune neutropenia
    - Hypersplenism
  - Drug associated with Leukopenia
    - Ganciclovir
    - Zidovudine
    - Trimethoprim-sulfamethoxazole
    - Pentamidine
    - Rifabutin
    - Antineoplastic chemotherapy

- Dapsone
- **Diagnosis of Neutropenia**
  - WBC count < 500 cells/mm<sup>3</sup>
  - Clinical diagnosis of the underlying cause
  - CBC (WBC differential count)
  - Peripheral Morphology
  - Bone marrow aspiration
  - Bone marrow Biopsy
  - Antibody Tests: (parvo virus and auto immune)
- **Treatment of Neutropenia**
  - Diagnose and treat the underlying cause
  - Antibiotic therapy if indicated for ongoing infection from low immunity
  - Antiretroviral therapy
  - Drug withdrawal
  - Granulocyte Colony Stimulating Factor
  - Granulocyte and Monocyte Colony Stimulating Factor

## THROMBOCYTOPENIA

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- Decreased Production
  - HIV infection
  - Adverse drug reaction
  - Marrow infiltration
  - Myelodysplasia
  - Acute retroviral infection
    - Immune Thrombocytopenic Purpura
    - Unexplained Platelet count <100,000 due to HIV infection of precursor in Bone

marrow

## **PATHOGENESIS**

- In usual ITP, IgG reacts against normal platelets as well Rheumatoid factor sequesters IgG antiplatelet antibodies

## **DIAGNOSIS**

- Clinical diagnosis of the underlying cause
- CBC (Platelet count)
- Peripheral Morphology
- Bleeding time and coagulation Time
- Bone marrow aspiration and Biopsy
- Anti-body test (Autoimmune thrombocytopenia)

## **TREATMENT**

- Treat the underlying cause
- Platelet or fresh blood transfusion

## **THROMBOTIC THROMBOCYTOPENIC PURPURA**

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- This clinical syndrome, consisting of
  - Fever,
  - Thrombocytopenia,
  - Hemolytic Anemia, and
  - Neurologic and
  - Renal dysfunction,
- A rare complication of early HIV infection.
  - Venous thrombosis
    - Approximately 4% of patients with HIV infection experience venous thrombotic events such as:
      - Deep Vein Thrombosis or
      - Pulmonary Embolism.
  - Among the factors associated with clinical thrombosis are
    - Age over 45,

- History of an opportunistic infection, and
- Estrogen

## **SKIN MANIFESTATIONS OF RVI**

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- Herpes zoster
- Mucocutaneus Herpes simplex
- Warts (Condyloma accumunata & Labial)
- Molluscum Contagiosum
- HIV associated exantum
- Impetigo
- Eosinophilic folliculaites
- Tinea
- Balanitis
- Cryptococcus skin lesion
- Cutaneous leishmaniasis
- Scabies
- Seborric Dermatitis
- Kaposi sarcoma
- Papule pruritic eruption
- Psoriasis

## **GENITOURINARY MANIFESTATIONS OF RVI**

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### **CAUSES**

- A direct consequence of HIV infection
- HIV-associated nephropathy [HIVAN]
- Opportunistic infection
- Genitourinary tract infections
- Opportunistic neoplasm

- Drug toxicity

## **ENDOCRINE AND METABOLIC DISORDERS**

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- Thyroid dysfunction (Both hypo- and hyperthyroidism may be seen).
- Hypogonadism [~50% of men.] is generally a complication of underlying illness, testicular dysfunction may also be a side effect of ganciclovir therapy.
- Hyponatremia, may be due to:
  - Syndrome of inappropriate antidiuretic hormone (vasopressin) secretion (SIADH)
  - Adrenal insufficiency

## ACUTE RHEUMATIC FEVER

### INTRODUCTION

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- Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A Streptococcus.
- Although many parts of the body may be affected, almost all of the manifestations resolve completely.
- The major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared.

### GLOBAL CONSIDERATIONS

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- ARF and RHD are diseases of poverty.
- They were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations.
  - This decline was largely attributable to improved living conditions (particularly less crowded housing and better hygiene) which resulted in reduced transmission of group A streptococci.
  - The introduction of antibiotics and improved systems of medical care had a supplemental effect.
- The virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the first half of the twentieth century unfortunately was not replicated in developing countries, where these diseases continue unabated.
- RHD is the most common cause of acquired heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well.
- It has been estimated that between 29.7 and 43.1 million people worldwide are affected by RHD, with >300,000 deaths occurring each year.
- Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high rates in sub-Saharan Africa, Pacific nations, Australasia, and South and Central Asia.
- The pathogenetic pathway from exposure to group A Streptococcus followed by pharyngeal or superficial skin infection and subsequent development of ARF, ARF recurrences, and development of RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point.
- In affluent countries, many of these risk factors are well controlled, and where needed, interventions are in place.
- Unfortunately, the greatest burden of disease is found in developing countries, most of

which do not have the resources, capacity, and/or interest to tackle this multifaceted disease.

- In particular, few developing countries have a coordinated, register-based RHD control program, which is proven to be cost-effective in reducing the burden of RHD.
- Enhancing awareness of RHD and mobilizing resources for its control in developing countries are issues requiring international attention.

## EPIDEMIOLOGY

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- ARF is mainly a disease of children age 5–14 years.
- Initial episodes become less common in older adolescents and young adults and are rare in persons aged >30 years.
- By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults.
- This pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years.
- There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

## PATHOGENESIS

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### ORGANISM FACTORS

- Conventional teaching has it that ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci.
- Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, recent evidence demonstrates that many more M-serotypes are rheumatogenic and that so-called “rheumatogenic motifs” are found in only a minority of serotypes associated with rheumatic fever.
- This epidemiologic evidence also points to a clear role of skin infection in the pathogenesis of ARF.
- The potential role of groups C and G streptococci is unclear at this time.

### HOST FACTORS

- Based on epidemiologic evidence, ~3–6% of any population may be susceptible to ARF, and this proportion does not vary dramatically between populations.
- Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic, with 44% concordance in monozygotic twins compared to 12% in dizygotic twins and heritability more recently estimated at 60%.
- Most evidence for host factors focuses on immunologic determinants.

- Some human leukocyte antigen (HLA) class II alleles, particularly HLA-DR7 and HLA-DR4, appear to be associated with susceptibility, whereas other class II alleles have been associated with protection (HLA-DR5, HLA-DR6, HLA-DR51, HLA-DR52, and HLA-DQ).
- Associations have also been described with polymorphisms at the tumor necrosis factor  $\alpha$  locus (TNF- $\alpha$ -308 and TNF- $\alpha$ -238), high levels of circulating mannose-binding lectin, and Toll-like receptors.
- Recent genome-wide association studies in different populations have identified connections at the HLA region, particularly HLA-DQA1 to HLA-DQB1, and the immunoglobulin heavy chain locus.

### **THE IMMUNE RESPONSE**

- The most widely accepted theory of rheumatic fever pathogenesis is based on the concept of molecular mimicry, whereby an immune response targeted at streptococcal antigens (mainly thought to be on the M protein and the N-acetylglucosamine of group A streptococcal carbohydrate) also recognizes human tissues.
- In this model, cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule VCAM-1, with resulting recruitment of activated lymphocytes and lysis of endothelial cells in the presence of complement.
- The latter leads to release of peptides including laminin, keratin, and tropomyosin, which, in turn, activates cross-reactive T cells that invade the heart, amplifying the damage and causing epitope spreading.
- An alternative hypothesis proposes that the initial damage is due to streptococcal invasion of epithelial surfaces, with binding of M protein to type IV collagen allowing it to become immunogenic, but not through the mechanism of molecular mimicry.

### **CLINICAL FEATURES**

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- There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF.
- The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months.
- Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing.
- The most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–75%).
- The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%.
- Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of

cases.

## HEART INVOLVEMENT

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- Up to 75% of patients with ARF progress to RHD.
- The endocardium, pericardium, or myocardium may be affected.
- Valvular damage is the hallmark of rheumatic carditis.
- The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare.
- Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease.
- Early valvular damage leads to regurgitation.
- Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop
- Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation.
- Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree atrioventricular block or rarely higher-level block) and softening of the first heart sound.
- People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure.
- Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it.
- These cases can be diagnosed using echocardiography; auscultation is poorly sensitive and specific for RHD diagnosis in asymptomatic patients.
- Echocardiographic screening of school-aged children in populations with high rates of RHD is becoming more widespread and has been facilitated by improving technologies in portable echocardiography and the availability of consensus guidelines for the diagnosis of RHD on echocardiography.
- Although a diagnosis of definite RHD on screening echocardiography should lead to commencement of secondary prophylaxis, the clinical significance of borderline RHD has yet to be determined.

**Table: World Heart Federation Criteria for Echocardiographic Diagnosis of Rheumatic Heart Disease (RHD) in Individuals <20 Years of Age**

Definite RHD (either A, B, C, or D)
4) Pathologic MR and at least two morphologic features of RHD of the mitral valve 5) MS mean gradient $\geq 4$ mmHg (note: congenital MV anomalies must be excluded) 6) Pathologic AR and at least two morphologic features of RHD of the AV (note: bicuspid AV and dilated aortic root must be excluded) 7) Borderline disease of both the MV and AV
Borderline RHD (either A, B, or C)
A. At least two morphologic features of RHD of the MV without pathologic MR or MS B. Pathologic MR C. Pathologic AR
Normal Echocardiographic Findings (all of A, B, C, and D)
A. MR that does not meet all four Doppler criteria (physiologic MR) B. AR that does not meet all four Doppler criteria (physiologic AR) C. An isolated morphologic feature of RHD of the MV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation D. Morphologic feature of RHD of the AV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
Definitions of Pathologic Regurgitation and Morphologic Features of RHD
<ul style="list-style-type: none"> <li>- <i>Pathologic MR:</i> All of the following: seen in two views; in at least one view, jet length <math>\geq 2</math> cm; peak velocity <math>\geq 3</math> m/s; pansystolic jet in at least one envelope</li> <li>- <i>Pathologic AR:</i> All of the following: seen in two views; in at least one view, jet length <math>\geq 1</math> cm; peak velocity <math>\geq 3</math> m/s; pandiastolic jet in at least one envelope</li> <li>- <i>Morphologic features of RHD in MV:</i> anterior MV leaflet thickening <math>\geq 3</math> mm (age specific); chordal thickening; restricted leaflet motion; excessive leaflet tip motion during systole</li> <li>- <i>Morphologic features of RHD in AV:</i> irregular or focal thickening; coaptation defect; restricted leaflet motion; prolapse</li> </ul>

Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.

## JOINT INVOLVEMENT

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- The most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., polyarthritis).
- Polyarthritis is typically migratory, moving from one joint to another over a period of hours.
- ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric.
- The pain is severe and usually disabling until anti-inflammatory medication is commenced.
- Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria.
- Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis.
- In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established.
- The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

## CHOREA

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- Sydenham's chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females.
- The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs.
- They may be generalized or restricted to one side of the body (hemi-chorea).
- In mild cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living.
- There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the choreiform movements (which usually resolve within 6 weeks but sometimes may take up to 6 months).
- More than 50% of patients presenting with chorea will have carditis, for which reason echocardiography should be part of the workup.

## SKIN MANIFESTATIONS

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- The classic rash of ARF is erythema marginatum, which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge.
- The rash is evanescent, appearing and disappearing before the examiner's eyes.
- It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.
- Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae.
- They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

## OTHER FEATURES

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- Fever occurs in most cases of ARF, although rarely in cases of pure chorea.
- Although high-grade fever ( $\geq 39^{\circ}\text{C}$ ) is the rule, lower grade temperature elevations are not uncommon.
- Elevated acute-phase reactants are also present in most cases.

## EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

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- With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis of ARF.
- Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed.
- The most common serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers.
- Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

## CONFIRMING THE DIAGNOSIS

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- Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses.
- This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the Jones criteria) to aid in the diagnosis.
- The most recent revision of the Jones criteria requires the clinician to determine if the patient is from a setting or population known to experience low rates of ARF.
- For this group, there is a set of "low-risk" criteria; for all others, there is a set of more

sensitive criteria.

**Table: Jones Criteria**

<b>A. For All Patient Populations with Evidence of Preceding Group A Streptococcal Infection</b>	
Diagnosis: initial ARF	2 major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 major or 1 major and 2 minor or 3 minor
<b>B. Major Criteria</b>	
Low-risk populations <sup>a</sup>	Moderate- and high-risk populations
Carditis <sup>b</sup> – Clinical and/or subclinical	Carditis – Clinical and/or subclinical
Arthritis – Polyarthritis only	Arthritis – Monoarthritis or Polyarthritis – Polyarthralgia <sup>c</sup>
Chorea	Chorea
Erythema marginatum	Erythema marginatum
SC nodules	SC nodules
<b>C. Minor Criteria</b>	
Low-risk populations <sup>a</sup>	Moderate- and high-risk populations
Polyarthralgia	Monoarthralgia
Fever ( $\geq 38.5^{\circ}\text{C}$ )	Fever ( $\geq 38^{\circ}\text{C}$ )
ESR $\geq 60$ mm in the first hour and/or CRP $\geq 3.0$ mg/dL <sup>d</sup>	ESR $\geq 30$ mm/h and/or CRP $\geq 3.0$ mg/dL <sup>d</sup>
Prolonged PR interval <sup>e</sup> , after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval <sup>e</sup> , after accounting for age variability (unless carditis is a major criterion)

<sup>a</sup>Low-risk populations are those with ARF incidence  $\leq 2$  per 100,000 school-age children or all-age rheumatic heart disease prevalence of  $\leq 1$  per 1000 population per year.

<sup>b</sup>Subclinical carditis indicates echocardiographic valvulitis.

<sup>c</sup>Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely “standalone” major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.

<sup>d</sup>CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

<sup>e</sup>Prolonged PR interval can only be considered in the absence of carditis as a major criterion.

## TREATMENT

- Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment of heart failure and other symptoms is undertaken, and preventive measures including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced.
- Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis.
- Other tests that should be performed are listed in the table below.
- There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of, RHD.
- With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

**Table: Testing and Monitoring of ARF in the Acute Setting**

Investigations
<b>Always request:</b>
<ul style="list-style-type: none"> <li>• Electrocardiogram (ECG)</li> <li>• Echocardiogram</li> <li>• Complete blood count (CBC)</li> <li>• C-reactive protein (CRP)</li> <li>• Streptococcal serology (antistreptolysin and anti-DNase B)</li> </ul>
<b>In relevant situations:</b>
<ul style="list-style-type: none"> <li>• Throat swab</li> <li>• Skin sore swab</li> <li>• Blood cultures</li> <li>• Synovial fluid aspirate <ul style="list-style-type: none"> <li>– Ensure sample does not clot by using correct tubes that have been well mixed and transported promptly to the laboratory</li> <li>– Include request for cell count, microscopy, culture, and gonococcal polymerase chain reaction (PCR)</li> </ul> </li> <li>• Pregnancy test</li> <li>• Creatinine test (UEC [urea, electrolytes, creatinine]) since nonsteroidal anti-inflammatory drugs can affect renal function</li> </ul>
<b>Tests to exclude alternative diagnoses, depending on clinical presentation and locally endemic infections:</b>
<ul style="list-style-type: none"> <li>• Autoantibodies, double-stranded DNA, anti-cyclic citrullinated peptide (anti-CCP) antibodies</li> <li>• Urine for Neisseria gonorrhoeae molecular test</li> <li>• Urine for Chlamydia trachomatis molecular test</li> <li>• Serologic or other testing for viral hepatitis, Yersinia spp., cytomegalovirus (CMV), parvovirus B19, respiratory viruses, Ross River virus, Barmah Forest virus</li> </ul>

## ANTIBIOTICS

- All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.
- Penicillin is the drug of choice and can be given orally (as phenoxymethyl penicillin, 500 mg [250 mg for children  $\leq$  27 kg] PO twice daily, or amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days) or as a single dose of 1.2 million units (600,000 units for children  $\leq$  27 kg) IM benzathine penicillin G.

## SALICYLATES AND NSAIDS

- These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed.
- They are of no proven value in the treatment of carditis or chorea.
- Aspirin is a common first-line choice, delivered at a dose of 50–60 mg/kg per day, up to a maximum of 80–100 mg/kg per day (4–8 g/d in adults) in 4–5 divided doses.
- At higher doses, the patient should be monitored for symptoms of salicylate toxicity such as nausea, vomiting, or tinnitus; if symptoms appear, lower doses should be used.
- When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses can have the dose reduced to 50–60 mg/kg per day for a further 2–4 weeks.
- Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued.
- This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period.
- Many clinicians prefer to use naproxen at a dose of 10–20 mg/kg per day, because it may be safer than aspirin and has the advantage of twice-daily dosing.

## CONGESTIVE HEART FAILURE

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### Glucocorticoids

- The use of glucocorticoids in ARF remains controversial.
- Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer-term outcome of carditis.
- However, the studies included in these meta-analyses all took place  $>$  40 years ago and did not use medications in common usage today.
- Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure.

- However, the potential benefits of this treatment should be balanced against the possible adverse effects.
- If used, prednisone or prednisolone is recommended at a dose of 1–2 mg/kg per day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks.

## MANAGEMENT OF HEART FAILURE

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See under Chapter 3

### BED REST

- Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced.
- Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure.
- Once symptoms are well controlled, gradual mobilization can commence as tolerated.

### CHOREA

- Medications to control the abnormal movements do not alter the duration or outcome of chorea.
- Milder cases can usually be managed by providing a calm environment.
- In patients with severe chorea, carbamazepine or sodium valproate is preferred to haloperidol.
- A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside.
- There is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea.
- They should be considered in severe or refractory cases.
- Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen.

### INTRAVENOUS IMMUNOGLOBULIN (IVIG)

- Small studies have suggested that IVIg may lead to more rapid resolution of chorea but have shown no benefit on the short- or long-term outcome of carditis in ARF without chorea.
- In the absence of better data, IVIg is not recommended except in cases of severe chorea refractory to other treatments.

## PROGNOSIS

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- Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks.
- Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis.
- Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.
- Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis.
- Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary prophylaxis before the patient is discharged.
- Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis.

## PREVENTION

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### PRIMARY PREVENTION

- Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing.
- This is difficult to achieve in most places where ARF is common.
- Concerted international efforts are underway to develop a vaccine against group A Streptococcus that would prevent infection of the throat or skin and consequently prevent ARF in the absence of a suitable vaccine; however, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics).
- If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed.
- In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries, primary care guidelines often recommend that all patients with sore throat be treated with penicillin or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis.

- Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A Streptococcus.
- Although there is no proof that antibiotic treatment of group A streptococcal skin infections can prevent ARF, the increasing evidence that impetigo is strongly associated with ARF in some populations argues for a focus on treatment and prevention of group A streptococcal skin infections as part of a comprehensive ARF control strategy in regions with endemic impetigo.

### **SECONDARY PREVENTION**

- The mainstay of controlling ARF and RHD is secondary prevention.
- Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences.
- The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if  $\leq 27$  kg) delivered every 4 weeks.
- It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with an every-4-week dosing schedule can be achieved, more frequent dosing is rarely needed.
- Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G.
- Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.
- The duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences)
- Secondary prophylaxis is best delivered as part of a coordinated RHD control program, based around a registry of patients.
- Registries improve the ability to follow patients and identify those who default from prophylaxis and to institute strategies to improve adherence.

**Table: American Heart Association Recommendations for Duration of Secondary Prophylaxis<sup>a</sup>**

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

<sup>a</sup>These are only recommendations and must be modified by individual circumstances as warranted. Note that some organizations recommend a minimum of 10 years of prophylaxis after the most recent episode, or until 21 years of age (whichever is longer), regardless of the presence of carditis with the initial episode.

## INFECTIVE ENDOCARDITIS

### INTRODUCTION

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- Infective endocarditis (IE) refers to infection of the endocardial surface of the heart; it usually refers to infection of one or more heart valves or infection of an intracardiac device.
- Infection most commonly involves heart valves but may also occur on
  - The low-pressure side of a ventricular septal defect,
  - Mural endocardium damaged by aberrant jets of blood or foreign bodies, or
  - Intracardiac devices.

### ETIOLOGY

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- Although many species of bacteria and fungi cause sporadic episodes of endocarditis, a few bacterial species (*Staphylococci* and *streptococci*) cause the majority of cases.
- Recent large studies from developed areas identify *Staphylococcus aureus* as the most common bacterial species causing IE.
- The pathogens involved vary somewhat with the clinical types of endocarditis (different portals of entry).
- Prosthetic valve endocarditis (PVE) arising within 2 months of valve surgery (early PVE) is generally nosocomial and is the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication.
- Causes: *S. aureus*, CoNS, facultative gram-negative bacilli, diphtheroids, and fungi.
- The portals of entry and organisms causing cases beginning >12 months after surgery—i.e., late PVE—are similar to those in community acquired NVE.
- PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection.
- Regardless of the time of onset after surgery, at least 68–85% of CoNS strains that cause PVE are resistant to methicillin.
- Health care-associated NVE has a nosocomial onset (55%) or a community onset (45%) in patients who have had extensive contact with the health care system over the preceding 90 days.
- Health care-associated NVE most commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci,
- Endocarditis complicates 6–25% of episodes of catheter-associated *S. aureus* bacteraemia; the higher rates are detected in high-risk patients studied by transesophageal echocardiography (TEE)

- Injection drug use-associated endocarditis
  - especially that involving the tricuspid valve, is commonly caused by *S. aureus*, which in many cases is resistant to methicillin.
  - Left-sided valve infections in addicts have a more varied etiology.
  - In addition to the usual causes of endocarditis, these cases can be due to *Pseudomonas aeruginosa* and *Candida* species, and sporadic cases can be caused by unusual organisms such as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species.
  - Polymicrobial endocarditis occurs among injection drug users.
  - HIV infection in drug users **does not** significantly influence the causes of endocarditis.
- Culture negative endocarditis
  - 5-15% of patients with endocarditis
  - Causes: -
    - Prior antibiotic exposure (one third to half of cases)
    - Fastidious organisms (*streptococci* (nutritionally variant bacteria now designated *Granulicatella* and *Abiotrophia* species), HACEK organisms, *Coxiella burnetii*, and *Bartonella* species.)

**Table: Portals of entry of causes of IE**

Portals of entry	Etiology	Remarks
Oral cavity, URT, skin	Viridans streptococci, staphylococci, and HACEK organisms	
GIT	<i>Streptococcus gallolyticus</i> (formerly <i>S. bovis</i> )	Associated with polyps and colonic tumors
GUT	Enterococci	

## RISK FACTORS

- Risk factors for infective endocarditis (IE) include
  - Cardiac factors
    - history of prior IE,
    - presence of a prosthetic valve or cardiac device, or
    - history of valvular or congenital heart disease
  - Noncardiac factors
    - intravenous drug use
    - indwelling intravenous catheter

- immunosuppression, or
- a recent dental or surgical procedure.

## CLINICAL MANIFESTATIONS

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- “Incubation period” usually < 2 weeks (quite short)
- Time of onset of Symptoms until Diagnosis is 4-5 weeks (quite long)
- Essentially any organ system may be involved
- Four processes contribute to the clinical picture:
  - infectious process on the valve
  - embolization to virtually any organ
  - constant bacteremia, often with metastatic foci of infection
  - circulating immune complexes and other immunopathologic factors
- As a result, clinical manifestations of infective endocarditis (IE) are highly variable; IE may present as
  - an acute, rapidly progressive infection or
  - as a subacute or
  - chronic disease with low-grade fever and nonspecific symptoms
- In general, patients in developed settings typically present acutely at an early stage of disease, while patients in developing settings may have a delayed presentation with manifestations of subacute IE.

## SYMPTOMS AND SIGNS

- Fever is the most common symptom of IE (up to 90 percent of patients); it is often associated with chills, anorexia, and weight loss.
- Other common symptoms of IE include malaise, headache, myalgias, arthralgias, night sweats, abdominal pain, dyspnea, cough, and pleuritic pain.
- Patients with IE associated with dental infection may report tooth pain or related symptoms.
- Cardiac murmurs are observed in approximately 85 percent of patients.
- Supportive signs include splenomegaly and cutaneous manifestations such as petechiae or splinter hemorrhages.
  - *Petechiae* are observed in 10 to 40 percent of patients; they may be present on the skin (usually on the extremities) or on mucous membranes such as the palate or conjunctivae.
  - *Splinter hemorrhages* consist of nonblanching linear reddish-brown lesions under the nail bed.
- Clinical manifestations reflecting complications of IE may be present at the time of initial presentation and/or may develop subsequently

- When present, such findings warrant independent diagnostic evaluation, concurrent with evaluation for IE.
- Relatively uncommon clinical manifestations that are highly suggestive of IE include:
  - **Janeway lesions** – Nontender erythematous macules on the palms and soles
  - **Osler nodes** – Tender subcutaneous violaceous nodules mostly on the pads of the fingers and toes, which may also occur on the thenar and hypothenar eminences
  - **Roth spots** – Exudative, edematous hemorrhagic lesions of the retina with pale centers
- Janeway lesions are more common in acute than subacute IE; histologically, they reflect microabscesses with neutrophil infiltration of capillaries.
- Osler nodes and Roth spots occur most frequently in the setting of protracted bacteremia; they probably represent the sequelae of vascular occlusion by microthrombi leading to localized immune-mediated vasculitis.
- Roth spots (also described as Litten spots) occur in 2 percent of patients with IE.
- Osler nodes were commonly observed among patients with IE in the preantibiotic era though are now uncommon since IE is frequently diagnosed and treated before their development.

### COMPLICATIONS AS PRESENTING SYMPTOMS

- IE is associated with a broad array of systemic complications due to septic embolization, which may be associated with localized thrombosis, bleeding, infection, and/or development of immune reactions.
- Clinical manifestations reflecting these complications may be present at the time of initial presentation and/or may develop subsequently:
  - *Cardiac complications* (up to 50 percent of patients) – Valvular insufficiency, heart failure, and others
  - *Neurologic complications* (up to 40 percent of patients) – Embolic stroke, intracerebral hemorrhage, brain abscess, and others
  - *Septic emboli* (up to 25 percent of patients) – Infarction of kidneys, spleen, and other organs. In right-sided endocarditis (common among intravenous drug users), septic pulmonary emboli may be seen.
  - *Metastatic infection* (such as vertebral osteomyelitis, septic arthritis, psoas abscess)
  - *Systemic immune reaction* (eg, glomerulonephritis)
- Clinical manifestations of a complication of IE warrant independent diagnostic evaluation, concurrent with evaluation for IE.

- As examples, patients with IE may present with clinical manifestations of congestive heart failure due to valvular regurgitation, focal neurologic complaints due to an embolic stroke, or back pain due to vertebral osteomyelitis.
- A thorough investigation of extracardiac manifestations is particularly important in the setting of *Staphylococcus aureus* bacteremia given the virulence of this organism.

### LABORATORY FINDINGS

- Routine laboratory findings in the setting of IE are relatively nonspecific; they may include
  - elevated inflammatory markers (erythrocyte sedimentation rate and/or elevated C-reactive protein),
  - normochromic-normocytic anemia, and
  - positive rheumatoid factor.
- Hyperglobulinemia, cryoglobulinemia, circulating immune complexes, hypocomplementemia, and false-positive serologic tests for syphilis occur in some patients.
- Urinalysis may demonstrate microscopic hematuria, proteinuria, and/or pyuria.
- The presence of red blood cell casts on urinalysis is generally indicative of glomerulonephritis, which is a minor diagnostic criterion for IE.
- Electrocardiography may demonstrate new or evolving conduction disease (first-degree atrioventricular block, bundle branch block, or complete heart block), reflecting paravalvular or myocardial extension of infection.

**Table: Clinical and Laboratory Features of Infective Endocarditis**

FEATURE	FREQUENCY, %
Fever	80 - 90
Chills and sweats	40 - 75
Anorexia, weight loss, malaise	25 - 50
Myalgias, arthralgias	15 - 30
Back pain	7 - 15
Heart murmur	80 - 85
New/worsened regurgitant murmur	20 - 50
Arterial emboli	20 - 50
Splenomegaly	15 - 50
Clubbing	10 - 20
Neurologic manifestations	20 - 40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2 - 15

Petechiae	10 - 40
<b>Laboratory manifestations</b>	
• Anemia	70 - 90
• Leukocytosis	20 - 30
• Microscopic hematuria	30 - 50
• Elevated erythrocyte sedimentation rate	60 - 90
• Elevated C-reactive protein level	>90
• Rheumatoid factor	50
• Circulating immune complexes	65 - 100
• Decreased serum complement	5 - 40

## DIAGNOSIS

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- Overview of diagnostic approach — The diagnosis of infective endocarditis (IE) should be suspected in patients with fever (with or without bacteremia) and/or relevant risk factors.
- The diagnosis is established based on clinical manifestations, blood cultures (or other microbiologic data), and echocardiography.
- The accepted criteria for diagnosis of IE are the **Modified Duke criteria**.
- Additional evaluation for patients with suspected IE includes electrocardiography, chest radiography, other radiographic imaging tailored to clinical manifestations, and dental evaluation.
- At least three sets of blood cultures should be obtained from separate venipuncture sites prior to initiation of antibiotic therapy.
- For patients who are clinically stable, antimicrobial therapy may be deferred while awaiting the results of blood cultures and other diagnostic tests.
- For patients with signs of clinical instability, initiation of empiric antimicrobial therapy (after blood cultures have been obtained) is appropriate.
- Follow-up blood cultures should be obtained 48 to 72 hours after antimicrobial therapy is begun and repeated every 48 to 72 hours until clearance of bacteremia is documented.
- **Echocardiography** should be performed in all patients with suspected IE.
  - In general, transthoracic echocardiography (TTE) is the first diagnostic test for patients with suspected IE.
  - Transesophageal echocardiography (TEE) has higher sensitivity than TTE and is better for detection of cardiac complications such as abscess, leaflet perforation, and pseudoaneurysm.
  - In some circumstances, it is reasonable to forgo TTE and proceed to TEE.

- Additional diagnostic evaluation for patients with suspected or known IE includes:
  - **Electrocardiography (ECG)**
    - Baseline ECG should be performed as part of the initial evaluation for all patients with suspected IE, with subsequent telemetry monitoring or serial electrocardiograms.
    - The presence of heart block or conduction delay (which may manifest initially as a prolonged PR interval) may provide an important clue to paravalvular extension of infection to the valve annulus and adjacent septum.
    - In addition, the presence of findings consistent with ischemia or infarction may suggest the presence of emboli to the coronary circulation. (See Chest radiography – Chest radiography is warranted to evaluate for presence of septic pulmonary emboli, infiltrate (with or without cavitation), congestive heart failure, and potential alternative causes of fever and systemic symptoms.
  - **Computed tomography**
    - CT of the torso is useful to evaluate for subclinical sites of metastatic infection (such as splenic infarct, renal infarcts, psoas abscess, or other sites of infection) that may warrant localized drainage.
    - Routine brain imaging with CT or magnetic resonance imaging (MRI) is not necessary, though further study is warranted; in one study including 53 patients, early use of cerebral MRI led to upgraded classification of IE to definite or possible in one-third of cases.
  - **Additional radiographic imaging** to evaluate for complications of IE should be tailored to findings on history and physical examination. As examples:
    - Patients with back pain should be evaluated for vertebral osteomyelitis with MRI, and
    - Patients with headache, neurologic deficits, or meningeal signs should be evaluated with head MRI for neurologic complications (including intracranial mycotic aneurysm or central nervous system bleeding).
- Lastly, patients with IE should undergo a thorough dental evaluation; the examination should focus on periodontal inflammation, pocketing around teeth, and caries that may result in pulpal infection and subsequent abscess.
- All active sources of oral infection should be eradicated, and patients should be counseled regarding the importance of daily dental hygiene with serial dental evaluation.

- **Modified Duke criteria** — The modified Duke criteria stratify patients into the following categories:
  - **Definite IE** is established in the presence of any of the following :
    - Pathologic criteria:
      - Pathologic lesions – Vegetation or intracardiac abscess demonstrating active endocarditis on histology
      - Microorganisms – Demonstrated by culture or histology of a vegetation or intracardiac abscess
    - Clinical criteria:
      - Two major clinical criteria
      - One major and three minor clinical criteria
      - Five minor clinical criteria
  - **Possible IE** is defined as the presence of one major and one minor clinical criteria or the presence of three minor clinical criteria.
    - The diagnosis of IE may be **rejected** if any of the following are present:
      - A firm alternate diagnosis is made.
      - Resolution of clinical manifestations occurs after  $\leq 4$  days of antibiotic therapy.
      - No pathological evidence of infective endocarditis is found at surgery or autopsy after antibiotic therapy for four days or less.
      - Clinical criteria for possible or definite infective endocarditis is not met.
- The Duke criteria should be used as a diagnostic guide together with clinical judgment and must be interpreted in view of the pretest probability for IE.
- The criteria were developed for evaluation of patients with left-sided native valve IE; their sensitivity is diminished in patients with suspected prosthetic valve IE, right-sided IE, and cardiac device infection.
- Clinical criteria (major and minor) for the diagnosis of IE are summarized in the following table

**Table: The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis**

Major Criteria	Minor Criteria
<p><b>1. Positive blood culture</b>            Typical microorganism for infective endocarditis from two separate blood cultures</p> <ul style="list-style-type: none"> <li>• Viridans streptococci, Streptococcus gallolyticus, HACEK group organisms, Staphylococcus aureus, or</li> <li>• Community-acquired enterococci in the absence of a primary focus,</li> </ul> <p><b>or</b></p> <p>Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:</p> <ul style="list-style-type: none"> <li>▪ Blood cultures drawn &gt;12 h apart; or</li> <li>▪ All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart</li> </ul> <p><b>or</b></p> <p>Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer of &gt;1:800</p> <p><b>2. Evidence of endocardial involvement</b>            Positive echocardiogram<sup>a</sup></p> <ul style="list-style-type: none"> <li>• Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, or</li> <li>• Abscess, or</li> <li>• New partial dehiscence of prosthetic valve,</li> </ul> <p><b>or</b></p> <p>New valvular regurgitation (increase or change in preexisting murmur not sufficient)</p>	<p>1. Predisposition: predisposing heart conditions<sup>b</sup> or injection drug use</p> <p>2. Fever <math>\geq 38.0^{\circ}\text{C}</math> (<math>\geq 100.4^{\circ}\text{F}</math>)</p> <p>3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions</p> <p>4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor</p> <p>5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,<sup>c</sup> or serologic evidence of active infection with an organism consistent with infective endocarditis</p>

<sup>a</sup>Transesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.

<sup>b</sup>Valvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.

<sup>c</sup>Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

## DIAGNOSTIC TOOLS

Diagnostic tools for IE include microbiologic data (usually blood cultures) and echocardiography.

- **Microbiology cultures**

- **Blood cultures** — Positive blood culture is the cornerstone of microbiological diagnosis of IE; three sets of blood cultures detect 96 to 98 percent of bacteremia.
- At least three sets of blood cultures should be obtained from separate venipuncture sites prior to initiation of antibiotic therapy.
- Patients with IE typically have continuous bacteremia; therefore, blood cultures may be collected at any time and need not necessarily be obtained at the time of fever or chills.
- Blood culture results should be interpreted based on the modified Duke criteria, as summarized above.
- The diagnostic yield of more than three sets of blood cultures is minimal in the absence of recent antimicrobial therapy.
- In one series including 206 cases of IE, the initial blood culture in patients with streptococcal endocarditis was positive in 96 percent of cases, and one of the first two blood cultures was positive in 98 percent.
- In patients with IE caused by organisms other than Streptococcus, the first blood culture was positive in 82 percent of cases, and one of the first two cultures was positive in 100 percent of cases.
- Most clinically significant bacteremias are detected within 48 hours; common and fastidious pathogens (such as members of the HACEK group) may be detected within five days of incubation with modern automated blood culture detection systems.
- The volume of blood for each blood culture set in adults is 20 mL (10 mL into each bottle).
- In patients who have received recent antimicrobial therapy, additional blood cultures may be useful (two to three sets over several days).
- Typical microorganisms consistent with IE include: *S. aureus*, *viridans streptococci*, *S. gallolyticus* (formerly *S. bovis*), HACEK organisms, or community-acquired enterococci.
- False-positive culture results occasionally occur.
- Organisms for which it can be difficult to distinguish between pathogenicity and contamination include *Cutibacterium* (formerly *Propionibacterium*) *acnes*, *Corynebacterium* species, *Bacillus* species, and coagulase-negative staphylococci.
- In general, the likelihood of pathogenicity is increased if the organism is observed in

multiple blood cultures obtained by independent venipunctures.

- Recovery of these organisms from a single blood culture or a minority of blood culture bottles likely reflects a false-positive result.
- Culture-negative endocarditis — Culture-negative endocarditis is defined as endocarditis with no definitive microbiologic etiology following inoculation of at least three independently obtained blood samples in a standard blood-culture system, with negative cultures after five days of incubation and subculturing.
- Culture-negative IE should be suspected in patients with negative blood cultures and persistent fever with one or more clinical findings consistent with IE (eg, stroke or other manifestations of emboli).
- Culture-negative IE should also be suspected in patients with vegetation on echocardiogram and no clear microbiologic diagnosis.
- Some causes of culture-negative IE may be identified via serology or polymerase chain reaction (PCR); these include *Coxiella burnetii*, *Bartonella* spp, *Chlamydia* spp, *Legionella* spp, *Mycoplasma*, and *Brucella*.
- Valve culture and histopathology — The diagnosis of IE may be established via pathologic criteria, including presence of microorganisms (demonstrated by culture or histology of a vegetation or intracardiac abscess), or histology (vegetation or intracardiac abscess demonstrating active endocarditis).
- Culture of resected heart valves may be useful for cases in which blood cultures have been negative, but routine valve culture is not warranted in the absence of clinical suspicion for IE because it may be associated with false-positive findings.
- **Echocardiography** - is the mainstay of for diagnosis of IE.
  - It should be performed in all patients with suspected IE as soon as possible after the diagnosis of IE is suspected; false-negative results may be obtained if vegetations are small and/or if vegetations have embolized.
  - It is warranted even for patients with an associated condition that requires a protracted course of antimicrobial therapy (such as vertebral osteomyelitis), since documenting the presence or absence of vegetation is important for determination of subsequent follow-up.
  - It is considered positive for IE in the setting of vegetation, abscess, or new dehiscence of a prosthetic valve.
  - It is also useful for evaluating valvular dysfunction, assessing hemodynamic severity of the valve lesion, assessing underlying ventricular function, and detecting associated abnormalities such as shunts.

- In addition, echocardiography is an important tool for follow-up evaluation of patients with persistent or recurrent bacteremia or other clinical deterioration.
- In general, TTE is the first diagnostic test for patients with suspected IE.
  - The sensitivity is modest (up to 75 percent); the specificity approaches 100 percent.
  - Thus, the absence of vegetation on TTE does not preclude the diagnosis of IE, although the presence of normal valve morphology and function on TTE substantially reduces the likelihood of IE.
- TEE has a sensitivity of >90 percent for detection of valvular vegetation and is superior to TTE for detection of cardiac complications such as abscess, leaflet perforation, and pseudoaneurysm.
- Therefore, TEE is useful in most cases, even if TTE was sufficient to establish the diagnosis of IE.
- Of note, the specificity of TEE is not 100 percent; false-positive findings can occur with cardiac tumors, mural thrombi, or fibrous strands on the aortic valve.
- TEE is warranted in the following circumstances:
  - Negative or technically inadequate TTE with high clinical suspicion for IE (bacteremia due to an organism known to be a common cause of IE, particularly *S. aureus*, and/or multiple minor criteria for endocarditis)
  - Positive TTE with concern for presence of intracardiac complications such as paravalvular abscess (risk factors include new conduction delay on electrocardiogram, aortic valve endocarditis, and persistent bacteremia or fever despite appropriate antimicrobial therapy)
  - Positive TTE and significant valvular regurgitation to determine need for surgery
- It is reasonable to forgo TTE and proceed to TEE in the following circumstances:
  - Presence of prosthetic valve(s), particularly prosthetic aortic or mitral valve, in which shadowing may make visualization via TTE difficult.
  - Presence of cardiac device
  - A prior valvular abnormality (including previous endocarditis)
  - Limited transthoracic windows (eg, due to obesity, chest wall deformity, or mechanical ventilation)
- Patients with a negative TEE for whom the clinical suspicion for IE is high should undergo repeat TEE approximately one week later.
- Repeat TEE is also warranted after an initial positive TEE if clinical features suggest new development of an intracardiac complication.
- In the setting of indeterminate TEE, cardiac CT may be useful (if available).

- Three-dimensional TEE is a newer imaging modality; pending further study, this technique should be regarded as a supplement to standard echocardiography.
- Three-dimensional TEE is useful for detection and delineation of vegetations but may overestimate vegetation size and may be less sensitive than two-dimensional TEE for detection of smaller vegetations.
- **Other imaging tools** — Additional cardiac imaging tools for diagnosis of IE include cardiac computed tomography (also known as multidetector computed tomography [MDCT] or multislice computed tomography [MSCT]) and fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT).
  - Cardiac MRI may be useful for detection of antegrade and retrograde dissemination, paravalvular tissue extension, and subendocardial and vascular endothelial involvement.
  - Cardiac CT may be helpful for cases in which definitive evidence of IE and its complications cannot be demonstrated with TEE.
  - It may be superior to TEE for evaluation of paravalvular extension of infection and has similar accuracy to TEE for detection of abscess and pseudoaneurysm.
  - Cardiac CT is also useful for evaluation of the coronary arteries prior to surgery, which may obviate the need for coronary angiography in some cases.
  - In addition, CT imaging of the brain and/or torso may be obtained at the same time (if clinically warranted) to evaluate for evidence of systemic embolization.
  - The utility of FDG PET/CT for evaluation of native valve IE is limited; it has been used to demonstrate abscess formation and paravalvular extension of infection as well as extracardiac complications of IE, although it has mostly been used to confirm the diagnosis of IE.
  - FDG PET/CT may be more useful for evaluation of prosthetic valve endocarditis.

## TREATMENT

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### ANTIMICROBIAL THERAPY

- To cure IE, all bacteria in the vegetation must be killed.
- This is difficult because local host defenses are deficient and because the bacteria are largely nongrowing and metabolically inactive and thus are less easily killed by antibiotics.
- Consequently, therapy must be bactericidal and prolonged.
- Antibiotics are generally given parenterally to achieve serum concentrations that, through passive diffusion, result in effective concentrations in the depths of the vegetation.
- The decision to initiate treatment empirically must balance the need to establish a

microbiologic diagnosis against the potential disease progression or the need to control infection prior to urgent surgery.

- Infection at other sites (such as the meninges), allergies, end-organ dysfunction, interactions with concomitantly administered medications, and risks of adverse events must be considered in the selection of therapy.
- The regimens recommended for the treatment of PVE (except that caused by staphylococci), although given for several weeks longer, are similar to those used to treat NVE
- Recommended antibiotic dosing and duration of therapy, which is measured from the time blood cultures become negative, should be followed unless alterations are required by end-organ dysfunction or adverse events.

#### ORGANISM-SPECIFIC THERAPIES

Will be summarized in the following table

**Table: Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms<sup>a</sup>**

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
<b>Streptococci</b>		<b>For PVE 6-week regimens are preferred.</b>
Penicillin-susceptible streptococci, <i>S. gallolyticus</i> (MIC $\leq 0.12 \mu\text{g/mL}^b$ )	Penicillin G (2–3 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	Ceftriaxone (2 g daily as a single dose for 4 weeks)	Can use ceftriaxone in patients with non-immediate penicillin allergy.
	Vancomycin <sup>c</sup> (15 mg/kg IV q12h for 4 weeks)	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of $\beta$ -lactam desensitization.
	Penicillin G (2–3 mU IV q4h) or ceftriaxone (2 g IV daily) for 2 weeks <b>plus</b> Gentamicin <sup>d</sup> (3 mg/kg daily IV or IM, as a single dose <sup>e</sup> or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic-valve or complicated endocarditis. Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
Relatively penicillin-resistant streptococci, <i>S. gallolyticus</i> (MIC $>0.12 \mu\text{g/mL}$ and $<0.5 \mu\text{g/mL}^f$ )	Penicillin G (4 mU IV q4h) or ceftriaxone (2 g IV daily) for 4 weeks <b>plus</b> Gentamicin <sup>d</sup> (3 mg/kg daily IV or IM, as a single dose <sup>e</sup> or divided into equal doses q8h for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for PVE caused by streptococci with penicillin MICs of $\leq 0.12 \mu\text{g/mL}$ .
	Vancomycin <sup>c</sup> as noted above for 6	Use vancomycin for patients with immediate

	weeks	(urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of $\beta$ -lactam desensitization. Ceftriaxone alone or with gentamicin can be used in patients with non-immediate $\beta$ -lactam allergy.
Moderately penicillin-resistant streptococci (MIC, $\geq 0.5 \mu\text{g}/\text{mL}$ and $< 8 \mu\text{g}/\text{mL}^g$ ); Granulicatella, Abiotrophia, or Gemella spp.	Penicillin G (4–5 mU IV q4h) or ceftriaxone (2 g IV daily) for 6 weeks <b>plus</b> Gentamicin <sup>d</sup> (3 mg/kg daily IV or IM as a single dose <sup>e</sup> or divided into equal doses q8h for 6 weeks)	Preferred for PVE caused by streptococci with penicillin MICs of $>0.12 \mu\text{g}/\text{mL}$ . Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	Vancomycin <sup>c</sup> as noted above for 6 weeks	Regimen is preferred by some.
<b>Enterococci<sup>h</sup></b>		<b>For PVE 6-week regimens are preferred.</b>
	Penicillin G (4–5 mU IV q4h) plus gentamicin <sup>d</sup> (1 mg/kg IV q8h), both for 4–6 weeks	Can treat NVE for 4 weeks if symptoms last $<3$ months. Treat NVE with $>3$ months of symptoms for 6 weeks. Can abbreviate gentamicin course in some patients.
	Ampicillin (2 g IV q4h) plus gentamicin <sup>d</sup> (1 mg/kg IV q8h), both for 4–6 weeks	Can use IV amoxicillin in lieu of ampicillin (same dose). Can abbreviate gentamicin course in some patients.
	Vancomycin <sup>c</sup> (15 mg/kg IV q12h) plus gentamicin <sup>d</sup> (1 mg/kg IV q8h), both for 6 weeks	Use vancomycin plus gentamicin only for penicillin-allergic patients (preferable to desensitize to penicillin if immediate (urticarial) allergy; consult allergy) and for isolates resistant to penicillin/ampicillin.
	Ampicillin (2 g IV q4h) plus ceftriaxone (2 g IV q12h), both for 6 weeks	Use for <i>E. faecalis</i> isolates with or without high-level resistance to gentamicin or for patients at high risk for aminoglycoside nephrotoxicity (creatinine clearance rate $<50 \text{ mL/min}$ ).
<b>Staphylococci (<i>S. aureus</i> and coagulase-negative)</b>		
MSSA infecting native valves (no foreign devices) including Complicated right-sided and leftsided endocarditis.	Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 6 weeks)	Addition of gentamicin is not recommended. For uncomplicated rightsided endocarditis a 2-week course may be effective.
	Cefazolin (2 g IV q8h for 6 weeks)	Can use cefazolin regimen for patients with non-immediate penicillin allergy; see text regarding cefazolin vs antistaphylococcal penicillin as primary therapy. Addition of gentamicin not recommended.
	Vancomycin <sup>c</sup> (15 mg/kg IV q12h for 6	Only use vancomycin for patients with immediate

	weeks)	(urticarial) or severe penicillin allergy until allergy consultation can be obtained for $\beta$ -lactam desensitization evaluation; addition of gentamicin not recommended.
MRSA infecting native valves (no foreign devices)	Vancomycin <sup>c</sup> (15 mg/kg IV q8–12h) or daptomycin (8–10 mg/kg daily) for 6 weeks	No role for routine use of rifampin.
MSSA infecting prosthetic valves	Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 6–8 weeks) <b>plus</b> Gentamicin <sup>d</sup> (1 mg/kg IM or IV q8h for 2 weeks) <b>plus</b> Rifampin <sup>i</sup> (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin; if patient is highly allergic to penicillin, use regimen for MRSA and obtain allergy consultation; if $\beta$ -lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	Vancomycin <sup>c</sup> (15 mg/kg IV q12h for 6–8 weeks) <b>plus</b> Gentamicin <sup>d</sup> (1 mg/kg IM or IV q8h for 2 weeks) <b>plus</b> Rifampin <sup>i</sup> (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin. Daptomycin (8–10 mg/kg daily) could be considered as an alternative to vancomycin but data are limited.
<b>HACEK Organisms</b>	<b>For PVE 6-week regimens are preferred.</b>	
	Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use another third-generation cephalosporin at comparable dose.
	Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	Use ampicillin only if $\beta$ -lactamase production can be excluded. If the isolate is susceptible, ciprofloxacin (400 mg IV q12h) can be used.
<b>Coxiella burnetii</b>		
	Doxycycline (100 mg PO q12h) plus hydroxychloroquine (200 mg PO q8h), both for at least 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased 4-fold and IgM antiphase II negative) and thereafter for relapse.
<b>Bartonella spp.</b>		
	Doxycycline (100 mg q12h PO) for 6 weeks <b>plus</b> Gentamicin (1 mg/kg IV q8h for 2 weeks)	If doxycycline is not tolerated, use azithromycin (500 mg PO daily). Some experts recommend that doxycycline be continued for 3–6 months unless all infection is resected surgically.

<sup>a</sup>Regimens adapted from the guidelines of the American Heart Association and the European Society of Cardiology (ESC). Doses of gentamicin, vancomycin, and daptomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and daptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet). <sup>b</sup>MIC ≤0.125 µg/mL per ESC. <sup>c</sup>Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 µg/mL for streptococcal and enterococcal infections and 15–20 µg/mL for staphylococcal infections. <sup>d</sup>Aminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 µg/mL and ≤ 1 µg/mL, respectively; <sup>e</sup>Netilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin for streptococcal infection only. <sup>f</sup>MIC >0.125 µg/mL and ≤ 0.1 µg/mL per ESC. <sup>g</sup>MIC >2.0 µg/mL per ESC; treat with regimen for enterococci (BSAC). <sup>h</sup>Antimicrobial susceptibility must be evaluated. <sup>i</sup>Rifampin increases warfarin and dicumarol requirements for anticoagulation.

**Abbreviations:** MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis.

## PREVENTION

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- Prevention of IE has been a goal of clinical practice; however, the evidence establishing benefit from antibiotic prophylaxis for IE is insufficient to recommend it as a widespread standard of care.
- The American Heart Association and the European Society of Cardiology recommend limiting prophylactic antibiotics to only patients at highest risk for severe morbidity or death from IE
- The National Institute for Health and Clinical Excellence in the United Kingdom initially advised discontinuation of all antibiotic prophylaxis for IE but recently became less dogmatic, allowing clinicians to use clinical judgment in the settings outlined.
- In at-risk patients, maintaining good dental hygiene is recommended and antibiotic prophylaxis is recommended only when there is manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including with respiratory tract surgery).
  
- Recent studies suggest that severe adverse events related to amoxicillin prophylaxis are exceedingly rare; however, clindamycin prophylaxis has been associated with low but significant rates of fatal and nonfatal adverse reactions with *Clostridioides difficile*

infection.

- Consequently, the American Heart Association now recommends against the use of clindamycin for prophylaxis.
- Although prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures, genitourinary tract infections (or skin infection) should be treated before or when these sites undergo procedures.
- In patients with aortic or mitral valve regurgitation or a prosthetic valve, treatment of acute Q fever for 12 months with doxycycline plus hydroxychloroquine is highly effective in preventing *C. burnetii* IE.

**Table: Antibiotic Regimens for Prophylaxis of Endocarditis in**

**Adults with High-Risk Cardiac Lesions<sup>a,b</sup>**

- |   |
|---|
| A. Standard oral regimen  |
| Amoxicillin: 2 g PO 1 h before procedure  |
| B. Inability to take oral medication  |
| Ampicillin: 2 g IV or IM within 1 h before procedure                                      |
| C. Penicillin allergy   |
| 1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure                         |
| 2. Cephalexin: 2 g PO 1 h before procedure  |
| 3. Doxycycline: 100 mg PO 1 h before procedure  |
| D. Penicillin allergy, inability to take oral medication                                  |
| Cefazolin <sup>c</sup> or ceftriaxone <sup>c</sup> : 1 g IV or IM 30 min before procedure |

<sup>a</sup>Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. <sup>b</sup>For high-risk lesions, see Table 128-9. Prophylaxis is not advised for other lesions. <sup>c</sup>Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

**Table: High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis is Advised Before Dental Procedures**

- Prosthetic heart valves or material
- Left ventricular assist devices or implantable heart
- Prior endocarditis
- Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
- Completely repaired congenital heart defects during the 6 months after repair
- Repaired congenital heart disease with residual defects adjacent to prosthetic material
- Surgical or transcatheter pulmonary artery valve or conduit placement
- Valvulopathy developing after cardiac transplantation<sup>a</sup>

<sup>a</sup>Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.

## LEISHMANIASIS

- Leishmaniasis is caused by unicellular eukaryotic obligatory intracellular protozoa of the genus *Leishmania*.
- Primarily affects the host's **reticuloendothelial system**.
- Fall into three broad categories:
  - Visceral leishmaniasis (VL),
  - Cutaneous leishmaniasis (CL), and
  - Mucosal leishmaniasis (ML).

## ETIOLOGY AND LIFE CYCLE

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- Leishmaniasis is caused by ~20 species of the genus *Leishmania*.
- The organisms are transmitted by phlebotomine sandflies of the genus *Phlebotomus* in the “Old World” (Asia, Africa, and Europe) and the genus *Lutzomyia* in the “New World” (the Americas).
- *Leishmania* organisms occur in two forms:
  - Extracellular, flagellate **promastigotes** (length, 10–20 µm) in the sand fly vector and
  - Intracellular, nonflagellate **amastigotes** (length, 2–4 µm) in vertebrate hosts, including humans.
- Promastigotes are introduced through the proboscis of the female sand fly into the skin of the vertebrate host.
- The parasites multiply as amastigotes inside macrophages, causing cell rupture with subsequent invasion of other macrophages.
- While feeding on infected hosts, sandflies pick up amastigotes, which transform into the flagellate form in the flies’ posterior midgut and multiply by binary fission;
- The promastigotes then migrate to the anterior midgut and can infect a new host when flies take another blood meal.

## VISCERAL LEISHMANIASIS

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- Also known as **kala-azar**, a Hindi term meaning “black fever”.
- caused by the *Leishmania donovani* complex, which includes
  - *L. donovani* and
  - *Leishmania infantum* (*L.chagasi*).
- India and neighboring Bangladesh, Sudan and neighboring South Sudan, Ethiopia, and Brazil are the four largest foci of VL and account for 90% of the world’s VL burden.
- In Mediterranean Europe, 70% of adult VL cases are associated with HIV co-infection. The combination is deadly because of the combined impact of the two infections on the immune system.

## RISK FACTORS

- IV drug users
- Immune suppression
  - ↳ ~30 and 5% of VL patients are co-infected with HIV in Ethiopia and India, respectively.

## IMMUNOPATHOGENESIS

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- The majority of individuals infected by *L. donovani* or *L. infantum* mount a successful immune response and control the infection, never developing symptomatic disease.
- Organs of the reticuloendothelial system are predominantly affected, with remarkable enlargement of the spleen, liver, and lymph nodes in some regions.
- The tonsils and intestinal submucosa are also heavily infiltrated with parasites.
- Bone marrow dysfunction results in pancytopenia.

## CLINICAL FEATURES

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- The most common presentation of VL is an abrupt onset of moderate- to high-grade fever associated with rigor and chills.
- The spleen may be palpable by the second week of illness and, depending on the duration of illness, may become hugely enlarged.
- Hepatomegaly (usually moderate in degree) soon follows.
- Lymphadenopathy is common in most endemic regions of the world.
- Patients lose weight and feel weak, and the skin gradually develops dark discoloration due to hyperpigmentation that is most easily seen in brown-skinned individuals.
- In advanced illness, hypo-albuminemia may manifest as pedal edema and ascites.
- Anemia appears early and may become severe enough to cause congestive heart failure.
- Epistaxis, retinal hemorrhages, and gastrointestinal bleeding are associated with thrombocytopenia.
- Secondary infections such as measles, pneumonia, tuberculosis, bacillary or amebic dysentery, and gastroenteritis are common.
- Herpes zoster, chickenpox, boils in the skin, and scabies may also occur.
- Leukopenia and anemia occur early and are followed by thrombocytopenia.
- Renal dysfunction is uncommon.

## DIAGNOSIS OF VISCERAL LEISHMANIASIS

- The Diagnosis of VL relies on clinical, serological, parasitological and molecular findings.
- The definitive diagnosis is demonstration of the parasite in a tissue aspirate.

### 1. CLINICAL DIAGNOSIS

- Clinical signs and symptoms associated with VL.
- The clinical diagnosis of VL is therefore based on the standard case definition of visceral Leishmaniasis.

**VL CASE DEFINITION:** A person who presents with fever for more than two weeks and an enlarged spleen (splenomegaly) and/or enlarged lymph nodes (lymphadenopathy), or either loss of weight, anemia or leucopenia while living in a known VL endemic area or having travelled to an endemic area.

### 2. LABORATORY DIAGNOSIS

#### Non-Leishmanial Tests: -

- Hematologic data, such as reduction in the number of red blood cells, white blood cells and platelets (**pancytopenia**),
- Have a higher sensitivity (98%) but a lower specificity (16%) according to a study made in Nepal.

#### Parasite Detection

- Definitive diagnosis of VL is made by **visualization of the amastigote form of the parasite by microscopic examination of aspirates from lymph nodes, bone marrow or spleen aspiration.**
- Demonstration of amastigotes in smears of tissue aspirates is the **gold** standard for the diagnosis of VL.
- The sensitivity of splenic smears is >95%, whereas smears of bone marrow (60–85%) and lymph node aspirates (50%) are less sensitive.
- Culture of tissue aspirates increases sensitivity.

#### Antibody Detection

- An enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescent antibody test (IFAT) are used in sophisticated laboratories.
- In the field, however, a rapid immunochromatographic test based on the detection of antibodies to a recombinant antigen (rK39) consisting of 39 amino acids conserved in the kinesin region of *L. infantum* is used worldwide.
- The sensitivity of the rK39 rapid diagnostic test (RDT) in immunocompetent individuals is ~98% and its specificity is ~90%.

### Antigen Detection Test

- The antigen detection test is an ideal test because it is more specific than the antibody-based immunodiagnostic test.
- It helps to distinguish active from past infections.
- A urine latex agglutination (KATEX) that detects heat-stable, low molecular weight carbohydrate antigen in the urine of VL patients has been developed.
- Has a good specificity but only a low to moderate sensitivity.

### Molecular Techniques

- The polymerase chain reaction (PCR) based assays currently constitute the main molecular diagnostic approach of Leishmaniasis.
- PCR-based technique is its high sensitivity and specificity (up to 100%) irrespective of the species or genus.
- Second, the burden of infection could be assessed by PCR.
- This may be highly relevant in monitoring disease progression and outcome of an anti-Leishmanial therapy.
- Third, the viability of detected parasites could be demonstrated by other forms of nucleic acid-based techniques, reverse transcription real time PCR (which is expensive).

## TREATMENT OF VISCERAL LEISHMANIASIS

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- The best strategy to control anthroponotic VL is through early case detection and adequate treatment.
- VL is invariably fatal if left untreated.
- The treatment options for VL are not safe and often unaffordable.
- The objectives of VL treatment are to:
  - Reduce the parasite burden,
  - Prevent drug resistance,
  - Avoid toxic drug effects, and
  - Improve the clinical condition of patients and
  - To manage complications (anemia, malnutrition and secondary infections).
- Patient monitoring is vital during VL treatment as the currently used antileishmanial drugs are toxic.
- Supportive treatment is important.

- Sterile cure by drugs in VL treatment is not always possible

### FIRST-LINE REGIMENS FOR PRIMARY VL

- The first-line drugs for the management of primary visceral Leishmaniasis in Ethiopia are a combination of antimonial with aminoglycosides and Liposomal Amphotericin B for special situations.
- Although liposomal Amphotericin B is the safest drug, it is also the most expensive one.

#### A) Combination Therapy: Sodium Stibogluconate (SSG) and Paromomycin

- Sodium stibogluconate (20mg/kg body weight/day), and Paromomycin (15mg/kg body weight/day) injections are given intramuscularly for 17 days.
- The efficacy of the combination therapy is similar to that of the pentavalent antimonials monotherapy, with the advantage of a decreased toxicity, shorter treatment duration and cheaper cost.
- Had shown an efficacy of 90-94% in Ethiopia.

#### B) Sodium Stibogluconate or Meglumin Antimoniate (Monotherapy)

- SSG in monotherapy is administered as intramuscular injection of 20mg/kg/day for 30 days.
- In the absence of or in case of stock ruptures of Paromomycin, Pentavalent antimonials can be used in monotherapy.
- Pentavalent antimonials have been the first-line drug used for the treatment of visceral Leishmaniasis in Ethiopia for the last few decades.
- The generic form of the drug (Sodium Stibogluconate) is widely used, rather than its brand form (Pentostam), mainly due to cost related reasons.

#### C) Liposomal Amphotericin B (LAmb, AmBisome)

- Liposomal Amphotericin B is the first-line treatment for VL in special situations. As the use of antimonials is not safe in pregnant women due to the higher risk of miscarriage, its use is not recommended where there is an alternative drug to use.
- Similarly, the use of antimonials in Leishmania/HIV co-infected patients is found to be less effective with higher and frequent relapse rates and severe (fatal) toxicity.
- Hence, Liposomal Amphotericin B is recommended in those patients with pregnancy, HIV-co-infection, severe illness, severe anemia, severe malnutrition and extremes of age (below 2 years or above 45 years).
- In special situations with severe risk factors for death at the patient's admission, antimonials toxicity has proved to be very high and, therefore, LAmb is preferable if available for these patients.

### **SECOND-LINE TREATMENT FOR PRIMARY VISCERAL LEISHMANIASIS**

- Liposomal Amphotericin B (AmBisome)
- Miltefosine
- Paromomycin (Aminosidine)

## SCHISTOSOMIASIS

- Is caused by five species of the parasitic genus *Schistosoma*:
  - *S. mansoni*,
  - *S. japonicum*,
  - *S. mekongi*, and
  - *S. intercalatum* Cause intestinal disease, and
  - *S. haematobium* causes urogenital disease.
- The infection may cause considerable intestinal, hepatic, and genitourinary morbidity.

### ETIOLOGY

- Is contracted through contact with freshwater bodies harboring infected intermediate-host snails.
- Cercariae, the infective larval stage released from the snail, penetrate intact human skin within a few minutes after attaching to the skin.
- After penetration, the cercariae transform to schistosomula.
- The interval from cercarial penetration to sexual maturation and egg production, termed the **prepatent period**, lasts 5–7 weeks (up to 12 weeks for *S. haematobium*).
- When excreted eggs reach water, they hatch and release a free-swimming larval stage (miracidium), which, after penetrating a host snail, undergoes several rounds of asexual multiplication.
- After ~4–6 weeks, infective cercariae are shed from the infected snails into the water.
- The schistosome egg is the only stage of the parasites' life cycle that can be detected in humans.

### PATHOGENESIS

- Cercarial invasion may be associated with dermatitis.
- Most manifestations of schistosomiasis—in the acute, established, and chronic phases of infection—are due to immunologic reactions to eggs retained in host tissues.
- The eggs induce a granulomatous host immune response composed primarily of lymphocytes, eosinophils, and alternatively activated macrophages.
- Late chronic-stage infections are characterized by accumulation of dead calcified eggs in tissue.

### CLINICAL FEATURES

- In general, disease manifestations of schistosomiasis occur in three stages—acute, active, and chronic—according to the duration and intensity of infection.
- **Cercarial Dermatitis (“Swimmer’s Itch”)**

- Cercarial penetration of the skin may result in a maculopapular rash called **cercarial dermatitis or “swimmer’s itch.”**
- Cercarial dermatitis can develop in people who have not previously been exposed to schistosomiasis (e.g. travelers), whereas it is rare among people living in endemic areas.
- The rash may last for 1–2 weeks.
- This condition normally requires no treatment.
- But systemic antihistamines or topical antihistamines or glucocorticoids can be used to reduce symptoms.
- **Acute Schistosomiasis (Katayama Fever)**
  - Symptomatic acute schistosomiasis, also known as Katayama fever or Katayama syndrome.
  - Is usually seen in travelers who have contracted the infection for the first time.
  - The onset occurs between 2 weeks and 3 months after exposure to the parasite.
  - The symptoms may appear suddenly and include:-
    - fever,
    - myalgia,
    - general malaise and fatigue,
    - headache,
    - nonproductive cough, and
    - Intestinal symptoms such as abdominal tenderness or pain.
  - Many patients recover spontaneously from acute schistosomiasis after 2–10 weeks.

#### **INTESTINAL SCHISTOSOMIASIS (*S. mansoni*, *S. japonicum*, *S. mekongi*)**

- The symptoms tend to be more pronounced with a high intensity of infection and include intermittent abdominal pain, loss of appetite, and sometimes bloody diarrhea.
- The clinical manifestations of *S. intercalatum* and *S. mekongi* infection are generally milder.

#### **HEPATOSPLENIC SCHISTOSOMIASIS**

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- Is caused by schistosome eggs trapped in liver tissue and occurs in *S. mansoni* and *S. japonicum* infections.
- There are two distinct clinical entities:
- Early inflammatory hepatosplenomegaly and
- Late hepatosplenic disease with periportal fibrosis (Symmers clay pipe stem fibrosis).

## EARLY INFLAMMATORY HEPATOSPLENIC SCHISTOSOMIASIS

- It is the main entity seen in children and adolescents.
- The liver is enlarged, especially the left lobe, and is smooth and firm.
- The spleen is enlarged, often extending below the umbilicus, and is firm or hard.
- Generally, ultrasonography shows no hepatic fibrosis.
- This form of hepatosplenic schistosomiasis may be found in up to 80% of infected children.
- Its severity is closely associated with the intensity of infection and may also be associated with concomitant chronic exposure to malaria.

## LATE HEPATOSPLENIC SCHISTOSOMIASIS WITH PERIPORTAL OR SYMMERS FIBROSIS

- May develop in young and middle-aged adults with longstanding, high-level exposure to infection.
- Patients with periportal fibrosis may excrete very few or no eggs in feces.
- During the early stage, the liver is enlarged, especially the left lobe; it is smooth and firm or hard.
- The spleen is enlarged, often massively, and is firm or hard.
- The patient may report a left hypochondrial mass with discomfort and anorexia.
- Ultrasonography reveals typical periportal fibrosis and dilation of the portal vein.
- Other complications include delayed growth and puberty, especially in *S. japonicum* infections, and severe anemia.
- Severe hepatosplenic schistosomiasis may lead to portal hypertension, but hepatic function usually remains normal, even in cases with marked periportal fibrosis and portal hypertension.
- Ascites, attributable both to portal hypertension and to hypoalbuminemia, may be seen, especially in *S. japonicum* infection.
- Patients with severe hepatosplenic disease and portal hypertension may develop esophageal varices detectable by endoscopy or ultrasound.

## UROGENITAL SCHISTOSOMIASIS (*S. HAEMATOBIUM*)

Two stages of infection are recognized: -

- **An active stage**
  - Occurring mainly in children, adolescents, and younger adults.
  - Is characterized by egg excretion in the urine, with proteinuria and macroscopic or microscopic hematuria and deposition of eggs in the urinary tract.
  - A characteristic sign in the active stage is painless, terminal hematuria.

- **A chronic stage**
  - In older individuals.
  - Is characterized by sparse or no urinary egg excretion despite urogenital tract pathology.
  - Egg deposition may cause granulomas and lesions in the genital organs, most commonly in the cervix and vagina in women and the seminal vessels in men.
  - The results may include dyspareunia, abnormal vaginal discharge, contact bleeding, and lower back pain in women and
  - Perineal pain, painful ejaculation, and hematospermia in men.

## DIAGNOSIS

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- Detection of schistosome eggs in stool or urine is indicative of active infection and is the standard diagnostic method.
- Eggs can also be detected in rectal biopsies (both *S. mansoni* and *S. haematobium*) and occasionally in Pap smears and semen samples (*S. haematobium*).
- Polymerase chain reaction (PCR)-based detection of parasite DNA in stool or urine is more sensitive than parasitologic methods and is increasingly used.
- Serology, with detection of specific antibodies to schistosomes, is useful in travelers but less so in people from endemic areas where transmission is ongoing.

## TREATMENT

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- The drug of choice for treatment of schistosomiasis is praziquantel.
- It is administered orally, is available as 600-mg tablets, and is effective against all schistosome species infecting humans.
- The drug is safe and well tolerated.
- In patients who are not cured by initial treatment, the same dose can be repeated at weekly intervals for 2 weeks.
- Since praziquantel doesn't affect the young migrating stages of the schistosomes, it may be necessary to repeat the dose 6–12 weeks later, especially if eosinophilia or symptoms persist despite treatment.
- All patients with acute schistosomiasis should be treated with praziquantel.
- Glucocorticoids can be added in Katayama fever to suppress the hypersensitivity reaction.
- The effect of antischistosomal treatment on disease manifestations depends on the stage and severity of the lesions.
- Early hepatosplenomegaly, mild or moderate fibrosis, and urinary bladder lesions seen during active infection resolve after chemotherapy.

- However, for late-stage manifestations (e.g., severe fibrosis with portal hypertension), praziquantel treatment is only one component of management, since the main complications are due to obstructive pathology.
- Management of portal hypertension and prevention of bleeding from esophageal varices should follow clinical guidelines for treatment of these conditions.

## **PREVENTION AND CONTROL**

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- Avoid water contact—for example, during occupational activities such as fishing and working in rice fields.
- Praziquantel treatment of infected people.
- Control of the intermediate host snails.
- Improved water-quality and sanitation facilities, and health education.

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# CHAPTER EIGHT

## Hematology

Anemia

Pulmonary embolism

Deep venous thrombosis

Bleeding Diathesis

### ANEMIA

#### DEFINITIONS

- Anemia can be defined as:
  - Reduction in RBC mass as determined via blood volume studies
  - Reduction in hemoglobin concentration, hematocrit (HCT), or RBC count.
- In practice, however, a low hemoglobin concentration and/or a low hematocrit are the parameters most widely used to diagnose anemia, with following cut offs
  - **Female**- Hemoglobin<11.9g/dL or hematocrit <36%
  - **Male**- Hemoglobin<13.6g/dL or hematocrit <40%

Table: Normal CBC parameters in adults

Parameter	Males	Females
Hemoglobin, g/dL	13.6 to 16.9	11.9 to 14.8
Hematocrit, percent	40 to 50	35 to 43
RBC count, million/microL	4.2 to 5.7	3.8 to 5.0
MCV (fL)	82.5 to 98	82.5 to 98
MCHC, g/dL of RBC	32.5 to 35.2	32.5 to 35.2
RDW, CV, percent	11.4 to 13.5	11.4 to 13.5
Reticulocyte count, cells/microL	16,000 to 130,000	16,000 to 98,000
Platelet count, cells/microL	152,000 to 324,000	153,000 to 361,000
WBC, cells/microL	3,800 to 10,400	3,800 to 10,400

Values represent the mean and reference intervals (normal range, based on nonparametric 95% confidence interval) for each sex. Reference ranges may vary slightly in different laboratories. There are no sex differences in absolute reticulocyte count, MCV, MCH, MCHC, or RDW.

- Additional information about how these values are determined and variation in cutoff values includes the following:
  - **Hemoglobin** – expressed as grams of hemoglobin per 100 mL of whole blood (g/dL) or per liter of blood (g/L).
  - **Hematocrit** also called packed cell volume, calculated as ( $HCT = [RBC \times MCV]/10$ ).
  - **RBC count** – RBC count is the number of RBCs contained in a specified volume of whole blood, usually expressed as millions of cells per microL of whole blood.
- In patients with anemia, hemoglobin and HCT typically decrease in parallel. RBC also usually parallels the hemoglobin and HCT, except in cases of extreme microcytosis such as thalassemia, in which the RBC count may be increased despite the presence of anemia.
- World Health Organization (WHO) criteria for anemia in men and women are **<13 and <12 g/dL**, respectively.
- The normal ranges specified in the table above may not apply in certain settings:
  - **Causes of lower values**
    - **Intense physical activity** (like Athletes) - due to dilutional anemia from increased plasma volume, IDA and/or march hemolysis.
    - **Pregnancy**- during a healthy pregnancy, maternal red cell mass increase, but plasma volume increase to greater degree, causing a relative decrease in hemoglobin and HCT.
    - **Older age**
  - **Causes of higher values** (may occasionally mask underlying anemia)
    - **Smoking** - it increases in hemoglobin, HCT, and RBC count due to increased levels of carbon monoxide, which reduces oxygen delivery.
    - **Medications**- certain drugs like androgens and Sodium glucose co-transporter 2 (SGLT2) inhibitors can increase hemoglobin conc.
    - **Hemoconcentration**- due to dehydration or hypovolemia
    - **High altitude**- due to relative hypoxia

## RED BLOOD CELL INDICES

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- The RBC indices describe the size, shape, and hemoglobin content of RBCs, as well as the uniformity of the RBC population. Evaluation of these values is an integral part of determining the cause of anemia.
  - **MCV** – Mean corpuscular volume (MCV) is the average volume (size) of the patient's RBCs.
    - It can be measured or calculated ( $MCV \text{ in femtoliters [fL]} = 10 \times HCT \text{ [in percent]} \div RBC \text{ [in millions/microL]}$ ).
    - Anemia can be classified based on whether the MCV is low, normal, or elevated.
  - **MCH** – Mean corpuscular hemoglobin (MCH) is the average hemoglobin content in a RBC.
    - It is calculated ( $MCH \text{ in picograms [pg]/cell} = \text{hemoglobin [in g/dL]} \times 10 \div RBC \text{ [in millions/microL]}$ ).
    - A low MCH indicates decreased hemoglobin content per cell, and is typically reflected in hypochromia on the peripheral blood smear. This may be seen in iron deficiency and hemoglobinopathies like the thalassemias.
  - **MCHC** – Mean corpuscular hemoglobin concentration (MCHC) is the average hemoglobin concentration per RBC.
    - It is calculated as ( $MCHC \text{ in grams [g]/dL} = \text{hemoglobin [in g/dL]} \times 100 \div HCT \text{ [in percent]}$ ).
    - Very low MCHC values are typical of iron deficiency anemia, and very high MCHC values typically reflect spherocytosis or RBC agglutination. Examination of the peripheral blood smear is helpful in distinguishing these findings.
  - **RDW** – Red cell distribution width (RDW) is a measure of the variation in RBC size, which is reflected in the degree of anisocytosis on the peripheral blood smear.
    - A high RDW implies a large variation in RBC sizes, and a low RDW implies a more homogeneous population of RBCs.
    - RDW is calculated as the coefficient of variation (CV) of the red cell volume distribution ( $RDW = [\text{standard deviation}/MCV] \times 100$ ).
    - A high RDW can be seen in a number of anemias, including
      - iron deficiency
      - myelodysplastic syndrome, and
      - hemoglobinopathies
      - patients with anemia who have received transfusions.
    - Review of the peripheral blood smear often is helpful in identifying the cause of large variations in RBC size.

## THE RED BLOOD CELL LIFE CYCLE

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- Erythropoiesis in the adult takes place within the bone marrow under the influence of the stromal framework, cytokines, and the erythroid specific growth factor, erythropoietin (EPO).
- EPO is a true endocrine hormone produced in the kidney by cells that sense the adequacy of tissue oxygenation relative to the individual's metabolic activity.
- EPO enhances the growth and differentiation of the two erythroid progenitors:
  - Burst forming units-erythroid (BFU-E) and
  - Colony forming units-erythroid (CFU-E) into normoblasts of increasing maturity.
- The reticulocyte retains its ribosomal network (and its staining characteristics) for approximately four days, of which three days are generally spent in the bone marrow and one day in the peripheral blood.
- The resulting mature RBC circulates for **110 to 120 days**, after which time it is removed from the circulation by macrophages.
  - Under steady state conditions, the rate of RBC production equals the rate of RBC loss.
  - Reticulocytes normally survive in the circulation for one day; after this time, they lose their reticulum (RNA) and become mature red blood cells.
  - Under steady-state conditions reticulocytes will represent approximately 1 percent of total circulating RBC.
- The rate of red cell production increases markedly under the influence of high levels of EPO.
- A normal bone marrow replete with iron, folate, and cobalamin can increase erythropoiesis in response to EPO approximately fivefold in adults and seven- to eightfold in children.

## VOLUME STATUS

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- Hemoglobin, hematocrit (HCT), and red blood cell (RBC) count are all concentrations and dependent on the red blood cell mass (RCM) as well as the plasma volume.
- As a result, values for all three parameters will be reduced if the RCM is decreased and/or if the plasma volume is increased.
- Similarly, values for all three will be increased if the plasma volume is decreased (i.e., hemoconcentration).

- Three common clinical scenario will help make this point clear.
  - **Acute bleeding**
    - Over the ensuing 36 to 48 hours, most of the total blood volume deficit will be repaired by the movement of fluid from the extravascular into the intravascular space.
    - Only at these later times will the hemoglobin and HCT reflect blood loss.
  - **Late pregnancy**
    - In the third trimester of pregnancy the RBC mass and plasma volume are expanded by 25 and 50 percent, respectively, resulting in reductions in hemoglobin, HCT, and RBC count, often to anemic levels.
    - However, according to the RBC mass, such women are polycythemic. The terms "physiologic" or "dilutional" anemia have been applied to this setting, although such patients are not truly anemic.
  - **Volume depletion**
    - Anemic patients admitted to the hospital in a volume depleted (hemoconcentrated) state may not show abnormally low hemoglobin/HCT values on initial testing.
    - Their underlying anemia may become apparent only after their volume status has been corrected.

## CLINICAL CONSEQUENCES

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### SIGNS AND SYMPTOMS OF ANEMIA

- Are dependent upon the degree of anemia and the rate at which it has evolved, as well as the oxygen demands of the patient.
- Symptoms are much less likely with anemia that evolves slowly because there is time for multiple homeostatic forces to adjust to a reduced oxygen carrying capacity of blood.
- Symptoms related to anemia can result from two factors:
  1. Hypoxia (decreased O<sub>2</sub> delivery to tissue) and
  2. Hypovolemia.

### HYPOXIA INDUCED SIGN & SYMPTOMS

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- Exertional dyspnea,
- Dyspnea at rest,
- Varying degrees of fatigue

- Signs and symptoms of the hyperdynamic state:
  - Bounding pulses
  - Palpitations, and
  - Roaring pulsatile sound in the ears
- More severe anemia may lead to:
  - Lethargy, confusion
  - Congestive failure
  - Angina
  - Arrhythmia, and/or myocardial infarction.

### HYPVOLEMIA INDUCED SIGN & SYMPTOMS

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- Earliest symptoms: easy fatigability, lassitude, and muscle cramps.
- Postural dizziness
- Lethargy
- Syncope
- in severe cases, persistent hypotension, shock, and death.

#### **NOTE**

Anemia by itself is not a disease but rather it is the manifestation of an underlying disease condition.

### CAUSES OF ANEMIA

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- There are two general approaches one can use to help identify the cause of anemia.
  - A kinetic approach, addressing the mechanism(s) responsible for the fall in hemoglobin concentration
  - A morphologic approach categorizing anemias via alterations in red blood cell (RBC) size (i.e., mean corpuscular volume) and the reticulocyte response

#### **1. KINETIC APPROACH**

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- Anemia can be caused by three independent mechanisms:
  - Decreased RBC production,
  - Increased RBC destruction, and
  - Blood loss.
- Patients may have two (or all three) of these mechanisms operating at the same time.

- **Autoimmune hemolytic anemia** (ie, increased RBC destruction) can have a low reticulocyte response (ie, decreased RBC production) as the result of concomitant bone marrow suppression.
- **Aplastic anemia** (decreased RBC production) may have significant hemorrhage as the result of concomitant severe thrombocytopenia (blood loss).
- Acute alcoholism and gastrointestinal hemorrhage (blood loss) may be found to have concomitant folate deficiency associated with ineffective erythropoiesis (decreased RBC production) and shortened RBC lifespan (increased RBC destruction). It would not be unusual for this patient to also be iron deficient.

#### A) DECREASED RBC PRODUCTION

- Anemia will ultimately result if the rate of RBC production is less than that of RBC destruction. In case of:
  - Reduced effective production of red cells, or
  - Destruction of RBC precursors within the bone marrow (ineffective erythropoiesis).
- I. **Decrease in effective red cell production**
  - Indicated by reduced or absent reticulocyte response for the degree of anemia.
  - Reticulocyte production index, will be low ( $<2$ ) when the marrow response inadequate
  - RPI Increased ( $>3$ ) when the marrow is responding normally to the anemia.
  - **common causes**
    - Vitamin B12 and iron deficiency
    - Bone marrow disorders (aplastic anemia, pure RBC aplasia, marrow infiltration)
    - Bone marrow suppression (drugs, chemotherapy, irradiation)
    - Low levels of trophic hormones, (EPO; in chronic renal failure), thyroid hormone (e.g., hypothyroidism), and androgens (e.g., hypogonadism)

### Anemia of inflammation

- Associated with infectious, inflammatory, or malignant disorders
- Characterized by:
  - Reduced availability of iron due to decreased absorption of iron from the gastrointestinal tract and
  - Decreased release of iron from macrophages
  - A relative reduction in EPO levels, and
  - A mild reduction in RBC lifespan.

## II. Presence of ineffective erythropoiesis

- Presence of intense erythroid hyperplasia within the bone marrow along with a relative reduction in reticulocyte production (**Hallmark**)
- In such cases, the erythroid precursors in the bone marrow are not maturing normally and are dying within the bone marrow, usually via the process of apoptosis and/or a *block in maturation*.
- **Common causes**
  - Megaloblastic anemia
  - Alpha and beta thalassemia
  - The myelodysplastic syndromes
  - Sideroblastic anemias
  - Congenital dyserythropoietic anemia in children

## B) INCREASED DESTRUCTION OF CIRCULATING RBCS

- An RBC life span below 100 days is the operational definition of hemolysis.
- When hemolysis is present, laboratory studies show increased levels of lactate dehydrogenase (LDH) along with reduced haptoglobin, often accompanied by increases in indirect bilirubin and clinical jaundice.
- Anemia will ensue in the adult patient when the bone marrow is unable to keep up with the need to replace more than approximately 5 percent of the RBC mass per day, corresponding to an RBC survival of 20 days or less.
- Examples include
  - Inherited hemolytic anemias (eg, hereditary spherocytosis, sickle cell disease, pyruvate kinase deficiency, thalassemia major)
  - Acquired hemolytic anemias (eg, Coombs-positive autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, malaria, paroxysmal nocturnal hemoglobinuria)
  - Increased destruction of normal red cells by an enlarged spleen (ie, hypersplenism).

- **Intravascular hemolysis:** red cells are destroyed while still in the circulation
  - Suggestive clinical parameters
    - passing of darkly colored urine (gold to red to black)
    - (hemoglobinuria) as well as acrocyanosis or livedo reticularis on exposure to cold.
  - Suggestive lab studies
    - The presence of free hemoglobin in the plasma (i.e., hemoglobinemia)
    - The presence of red cell-free hemoglobin in the urine (i.e., hemoglobinuria)
    - The presence of hemosiderin in a stained urine sediment (sloughed renal tubular cells) if the intravascular hemolysis has been ongoing for at least one week
- **Extravascular hemolysis (Most common):** red cells are destroyed in the spleen and liver

**Table: Common causes of intravascular and extravascular hemolysis in adults**

**Extravascular destruction of red blood cells**

- **Intrinsic red blood cell defects**
  - Enzyme deficiencies (eg, deficiencies of G6PD, pyruvate kinase, glucose-phosphate isomerase, 5' nucleotidase)
  - Hemoglobinopathies (eg, sickle cell disease, thalassemias, unstable hemoglobins)
  - Membrane defects (eg, hereditary spherocytosis, elliptocytosis)
- **Extrinsic red blood cell defects**
  - Liver disease
  - Hypersplenism
  - Infections (eg, Bartonella, Babesia, malaria)
  - Oxidant agents (eg, dapsone, nitrites, aniline dyes)
  - Other agents (eg, lead, copper, snake and spider bites)
  - Large granular lymphocyte leukemia
  - Autoimmune hemolytic anemia (warm- or cold-reacting, drugs)
  - Intravenous immune globulin infusion

**Intravascular destruction of red blood cells**

- Microangiopathic hemolytic anemia (eg, TTP, HUS, aortic stenosis, prosthetic valve leak)
- Transfusion reactions (eg, ABO incompatibility)
- Infection (eg, clostridial sepsis, severe malaria)
- Paroxysmal cold hemoglobinuria; cold agglutinin disease (on occasion)
- Paroxysmal nocturnal hemoglobinuria
- Following intravenous infusion of Rho(D) immune globulin
- Following intravenous infusion with hypotonic solutions
- Snake bites
- Exposure to compounds with high oxidant potential (eg, copper poisoning, Wilson disease)

### C) BLOOD LOSS

- The most common cause of anemia
- Iron deficiency in westerns is almost always due to blood loss
- Iron deficiency usually occurs in males and females after losses of  $\geq 1200$  mL and  $\geq 600$  mL, respectively.
  - However, since approximately 25 percent of menstruant females have absent iron stores, any amount of bleeding will result in anemia in this subpopulation.
- Since availability of iron is normally **rate-limiting for RBC production**, iron deficiency associated with chronic bleeding leads to a reduced marrow response, worsening the degree of anemia.

## 2. MORPHOLOGIC APPROACH

- The causes of anemia can also be classified according to measurement of RBC size, as seen on the blood smear and as reported by automatic cell counter indices. The normal RBC has
  - A volume of 80 to 96 femtoliters (fL, 10-15 liter) and
  - A diameter of approximately 7 to 8 microns, equal to that of the nucleus of a small lymphocyte.
- An increased RDW indicates the presence of cells of widely differing sizes, but it is not diagnostic of any particular disorder.

**Table: Differential diagnosis of anemia in the adult**

Low mean corpuscular volume (microcytic anemia: MCV <80 fL)
<ul style="list-style-type: none"> <li>• Iron deficiency anemia</li> <li>• Thalassemic disorders</li> <li>• Anemia of inflammation/anemia of chronic disease (late; uncommon)</li> <li>• Sideroblastic anemia (eg, congenital, lead, alcohol, drugs; uncommon)</li> <li>• Copper deficiency, zinc poisoning (rare)</li> <li>• Hemolysis*</li> </ul>
Normal mean corpuscular volume (normocytic anemia: MCV 80 to 100 fL)
<ul style="list-style-type: none"> <li>• Acute blood loss</li> <li>• Iron deficiency anemia (early)</li> <li>• Anemia of inflammation/anemia of chronic disease (eg, infection, inflammation, malignancy)</li> <li>• Bone marrow suppression (may also be macrocytic)           <ul style="list-style-type: none"> <li>▪ Bone marrow invasion (eg, leukoerythroblastic blood picture)</li> <li>▪ Acquired pure red blood cell aplasia</li> <li>▪ Aplastic anemia</li> </ul> </li> <li>• Chronic renal insufficiency</li> <li>• Endocrine dysfunction</li> </ul>

- Hypothyroidism (most commonly normocytic)
- Hypopituitarism
- Hemolysis\*

#### Increased mean corpuscular volume (macrocytic anemia: MCV >100 fL)

- Excessive ethanol use
- Folate deficiency
- Vitamin B12 deficiency
- Myelodysplastic syndromes
- Acute myeloid leukemias (eg, erythroleukemia)
- Reticulocytosis
  - Response to hemolysis\*
  - Response to blood loss
  - Response to appropriate hematinic (eg, iron, vitamin B12, folic acid)
- Drug-induced anemia (eg, hydroxyurea, AZT, chemotherapeutic agents)
- Liver disease
- Hypothyroidism (less commonly macrocytic)

*This list is not meant to be exhaustive; only the most common causes are mentioned. In addition, two or more of these conditions may be present (eg, combined iron and folate deficiencies), resulting in a misleadingly normal mean corpuscular volume. MCV: mean corpuscular volume; fL: femtoliters; AZT: zidovudine. \**

**Hemolysis** is typically associated with some degree of macrocytosis because reticulocytes, which are larger than mature red blood cells, are increased in hemolysis. However, the MCV can be low, normal, or high depending on the degree of reticulocytosis and the underlying cause of hemolysis, which determines the MCV of the remaining cells.

#### A) MACROCYTIC ANEMIA

- Anemia is considered "macrocytic" when the MCV exceeds 100 fL.

**Table: Causes and mechanisms of macrocytosis**

#### Abnormalities of DNA metabolism

- Vitamin B12 (cobalamin) deficiency
- Folate deficiency
- Drugs
  - Antiretroviral therapies for HIV infection (eg, zidovudine)
  - Azathioprine or 6-mercaptopurine
  - Capecitabine
  - Cladribine
  - Cytosine arabinoside
  - Hydroxyurea
  - Imatinib, sunitinib
  - Methotrexate

#### Shift to immature or stressed red cells

- Reticulocytosis
- Action of erythropoietin - skip macrocytes, stress erythrocytosis

- Aplastic anemia/Fanconi anemia
- Pure red cell aplasia

#### Primary bone marrow disorders

- Myelodysplastic syndromes
- Congenital dyserythropoietic anemias
- Some sideroblastic anemias
- Large granular lymphocyte (LGL) leukemia

#### Lipid abnormalities

- Liver disease
- Hypothyroidism

#### Mechanism unknown

- Alcohol abuse
- Multiple myeloma and other plasma cell disorders

### B) MICROCYTIC ANEMIA

- Anemia is considered "microcytic" when the MCV is less than 80 fL.
- Microcytosis is usually accompanied by a decreased hemoglobin content within the RBC (mean corpuscular hemoglobin, MCH), with a parallel reduction in MCV, producing a hypochromic (low MCH) as well as a microcytic (low MCV) appearance on the blood smear.
- The following pathologic processes lead to the production of hypochromic microcytic red cells:
  - **Reduced iron availability** – Severe iron deficiency, the anemia of inflammation, copper deficiency
  - **Acquired disorders of heme synthesis** – Lead poisoning, acquired sideroblastic anemias
  - **Reduced globin production** – Thalassemic disorders, other hemoglobinopathies
  - Rare congenital disorders including sideroblastic anemias, porphyria, and defects in iron absorption, transport, utilization, and recycling
- The three most common causes of microcytosis in clinical practice are
  - Iron deficiency
  - Alpha or beta thalassemia minor
  - Anemia of inflammation (anemia of chronic disease).

**NOTE:** Since all may have hypochromic and microcytic RBCs, other tests must be used to establish the diagnosis.

- Iron deficiency anemia

**Table: Causes of Iron Deficiency**

**Increased Demand for Iron**

- Rapid growth in infancy or adolescence
- Pregnancy
- Erythropoietin therapy

**Increased Iron Loss**

- Chronic blood loss
- Menses
- Acute blood loss
- Blood donation
- Phlebotomy as treatment for polycythemia vera

**Decreased Iron Intake or Absorption**

- Inadequate diet
- Malabsorption from disease (sprue, Crohn's disease)
- Malabsorption from surgery (gastrectomy and some forms of bariatric surgery)
- Acute or chronic inflammation

- Important discriminating features are
  - ↳ low serum ferritin concentration
  - ↳ Increased total iron binding capacity (transferrin), and
  - ↳ low serum iron concentration, resulting in a low transferrin saturation.

- Alpha or beta thalassemia minor

- Physical examination may reveal splenomegaly
- The peripheral smear shows varying degrees of hypochromia, microcytosis, target cells, tear-drop forms, and basophilic stippling.
- The RBC count may actually be increased
- uncomplicated patients have normal or increased iron stores.

- **Anemia of inflammation**

- The hallmarks of this condition include
  - ↳ low serum iron
  - ↳ low total iron binding capacity (transferrin), and
  - ↳ a normal to increased serum ferritin concentration.

**NOTE:** Although hypochromic and microcytic red cells can be found in these patients, a low MCV is most frequently seen only in those patients with hepatoma or renal cell carcinoma.

**Table: Diagnosis of Microcytic Anemia**

TESTS	IRON DEFICIENCY	INFLAMMATION	THALASSEMIA	SIDEROBLASTIC ANEMIA
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
Serum iron ( $\mu\text{g/dL}$ )	<30	<50	Normal to high	Normal to high
TIBC ( $\mu\text{g/dL}$ )	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin ( $\mu\text{g/L}$ )	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with $\beta$ thalassemia; can be normal with $\alpha$ thalassemia	Normal

### C) NORMOCYTIC ANEMIA

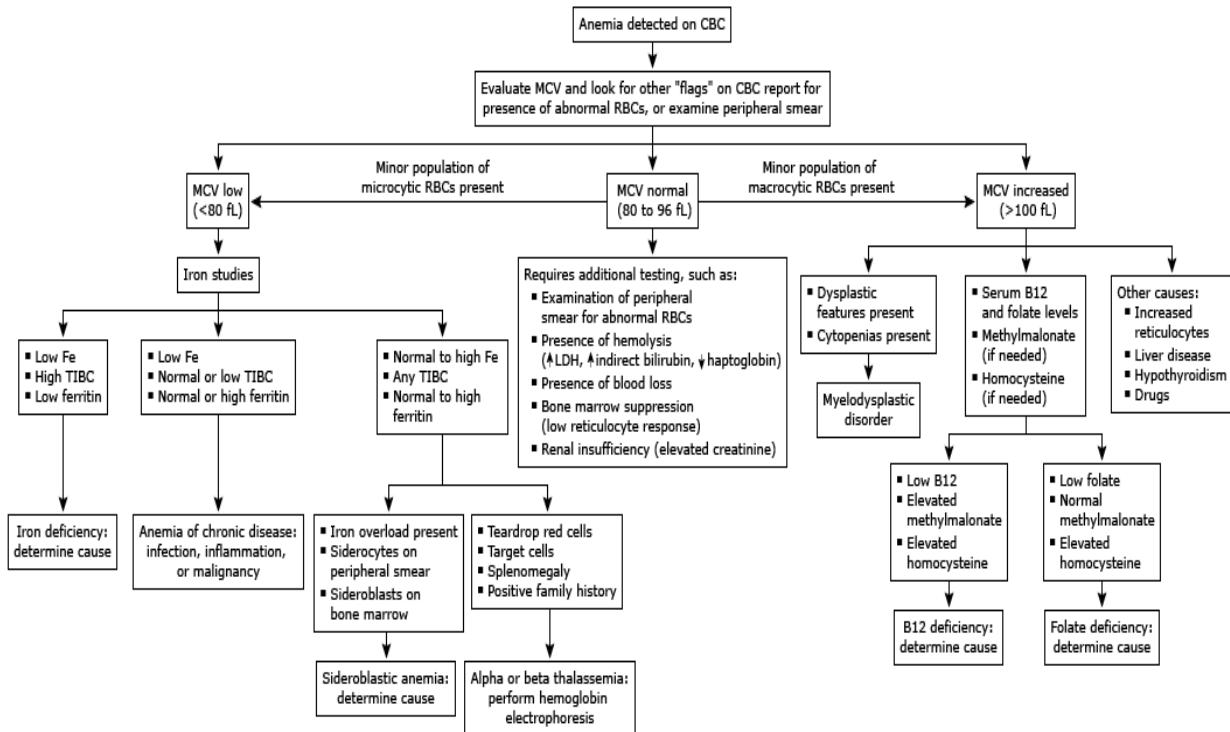
- Definition, MCV between 80 and 100 fl
- **Causes**
  - Anemia of CKD
  - **Cardiorenal anemia syndrome:** refers to the simultaneous presence of anemia, heart failure, and chronic renal disease.
  - Cancer-associated anemia
  - Acquired anemia in hospitalized patients
    - causes such as bleeding following an invasive procedure or surgery, large volumes of blood drawn for diagnostic studies, occult bleeding, hemodilution from intravenous fluid administration, as well as a blunted erythropoietic response associated with critical illness.

## EVALUATION OF THE PATIENT

### APPROACH

- Anemia is one of the major signs of disease. It is never normal and its cause(s) should always be sought. The history, physical examination, and simple laboratory testing are all useful in evaluating the anemic patient
- The workup should be directed towards answering the following questions concerning whether one or more of the major processes leading to anemia may be operative:
  - Is the patient bleeding (now or in the past)?
  - Is there evidence for increased red blood cell (RBC) destruction (either intravascular or extravascular)?
  - Is the bone marrow suppressed? If so, why?
  - Is the patient iron deficient? If so, why?
  - Is the patient deficient in folate or vitamin B12? If so, why?

**Algorithm:** Evaluation of anemia in the adult according to the mean corpuscular volume



**Abbreviation:** CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

## HISTORY

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- There are a number of important components to the history in the setting of anemia:
  - Is there a recent history of loss of appetite, weight loss, fever, and/or night sweats that might indicate the presence of infection or malignancy?
  - Is there a history of, or symptoms related to, a medical condition that is known to result in anemia (e.g., tarry stools in a patient with ulcer-type pain, significant blood loss from other sites, rheumatoid arthritis, renal failure)?
  - Is the anemia of recent origin, subacute, or lifelong? Recent anemia is almost always an acquired disorder, while lifelong anemia, particularly if accompanied by a positive family history, is likely to be inherited (eg, the hemoglobinopathies, thalassemia, hereditary spherocytosis).
- The electronic medical record is very useful in this analysis because one can document quite precisely when the hemoglobin began to fall, as well as when the RBC indices changed and in what direction. One can use this information to determine what, if anything, was occurring prior to the present illness.
- The patient's ethnicity and country of origin may be helpful, as the thalassemias and other hemoglobinopathies are particularly common in patients from the Mediterranean littoral, Middle East, sub-Saharan Africa, and Southeast Asia.
- The use of medications, both prescribed and over-the-counter, should be examined in some detail. Specific questions should be asked about the use of alcohol, aspirin, and nonsteroidal antiinflammatory drugs.
- A past history of blood transfusions, liver disease, treatment of the patient (or other family members) with iron or other hematins, herbal preparations, and exposure to toxic chemicals in the workplace or environment should also be obtained. An assessment of nutritional status is especially important in older adults and alcoholics.

## PHYSICAL EXAMINATION

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- The major aim of physical examination is to find signs of organ or multisystem involvement and to assess the severity of the patient's condition. Thus, the presence or absence of tachycardia, dyspnea, fever, or postural hypotension should be noted. While evaluation for jaundice and pallor is a standard part of the physical examination, such signs may be misinterpreted and are not as reliable indicators of anemia as once thought.
  - **Pallor** — The sensitivity and specificity for pallor in the palms, nail beds, face, or conjunctivae as a predictor for anemia varies from 19 to 70 percent and 70 to 100 percent, respectively, with wide interobserver differences and widely differing conclusions as to the clinical value of the presence or absence of this finding.

- **Jaundice** — Jaundice may be difficult to detect under artificial (nonfluorescent) lighting conditions. Even under optimal conditions, it may be missed.
- **Other physical findings** — Other items to search for on physical examination include the presence or absence of lymphadenopathy, hepatosplenomegaly, and bone tenderness, especially over the sternum. Bone pain may signify expansion of the marrow space due to infiltrative disease, as in chronic myeloid leukemia, or lytic lesions, as in multiple myeloma or metastatic cancer.
  - It is also important to look for signs of other hematologic abnormalities, including petechiae due to thrombocytopenia, ecchymoses, and other signs of bleeding due to abnormalities of coagulation.
  - One should also look for signs and symptoms of recurrent infections secondary to neutropenia or immune deficiency states. Stool obtained during the examination should always be tested for the presence of occult blood.

## LABORATORY EVALUATION

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- CBC
  - This routinely includes hemoglobin, hematocrit (HCT), red blood cell (RBC) count, RBC indices, and white blood cell (WBC) count.
- **Red blood cell indices**
  - Three RBC indices are usually measured by automated blood counters:
    - Mean corpuscular volume (MCV),
    - Mean corpuscular hemoglobin (MCH), and
    - Mean corpuscular hemoglobin concentration (MCHC).
  - The values for MCH and MCHC generally parallel the information obtained from the MCV (i.e., larger or smaller RBCs tend to have higher or lower values for MCH, respectively).
- **Reticulocyte count**
  - Anemia with a high reticulocyte count reflects an increased erythropoietic response to continued hemolysis or blood loss.
  - A stable anemia with a low reticulocyte count is strong evidence for deficient production of RBCs (ie, a reduced bone marrow erythropoietic response to the anemia).
  - Hemolysis or blood loss can be associated with a low reticulocyte count if there is a concurrent disorder that impairs RBC production (eg, infection, prior chemotherapy, other causes for bone marrow suppression).

- **White blood cell count and differential**

- A low total WBC count (leukopenia) in a patient with anemia should lead to consideration of
  - aplastic anemia,
  - bone marrow suppression or replacement,
  - hypersplenism, or
  - deficiencies of cobalamin.
- In comparison, a high total WBC count (leukocytosis) may reflect the presence of
  - infection,
  - inflammation, or
  - a hematologic malignancy.
- Many of the automated cell counters routinely calculate and display the absolute neutrophil count (ANC), total lymphocyte count (TLC), and absolute monocyte count. These values are very useful because they immediately allow distinction between leukopenia caused by a low ANC and leukopenia caused by a low TLC, and the causes are importantly different.
- Examples of causes of increased and decreased ANC and TLC include the following:
  - An increased absolute neutrophil count in infection
  - An increased absolute monocyte count in myelodysplasia
  - An increased absolute eosinophil count in certain infections
  - A decreased absolute neutrophil count following chemotherapy
  - A decreased absolute lymphocyte count in HIV infection or following treatment with glucocorticoids
- **Neutrophil hypersegmentation**
  - defined as the presence of >5 percent of neutrophils with five or more lobes and/or the presence of one or more neutrophils with six or more lobes.
  - This peripheral smear finding, along with macro-ovalocytic red cells, is classically associated with impaired DNA synthesis, as seen in disorders of vitamins B12 and folate.
  - NH can also be seen following the use of drugs interfering with nucleic acid synthesis (e.g., hydroxyurea).

- **Circulating nucleated red blood cells**
  - Nucleated RBCs (NRBCs) are not normally found in the circulation.
  - The appearance of NRBCs usually signifies either stressed erythropoiesis or extramedullary erythropoiesis.
  - NRBCs may be present in patients with
    - known hematologic disease (eg, sickle cell disease, thalassemia major, various hemolytic anemias after splenectomy), or
    - as a part of the leukoerythroblastic pattern seen in patients with bone marrow fibrosis or replacement with tumor cells.
  - In patients without an underlying hematologic disease, NRBCs may reflect the presence of a life-threatening disease, such as sepsis or severe heart failure.
- **Platelet count**
  - Abnormalities in the platelet count often provide important diagnostic information.
  - Thrombocytopenia occurs in a variety of disorders associated with anemia, including aplastic anemia, hypersplenism, marrow involvement with malignancy, autoimmune platelet destruction (either idiopathic or drug-related), sepsis, or folate or cobalamin deficiency.
  - High platelet counts, in comparison, may reflect the presence of a myeloproliferative neoplasm, chronic iron deficiency, and inflammatory, infectious, or neoplastic disorders.
  - Changes in platelet morphology (giant platelets, degranulated platelets) also may be important, suggesting myeloproliferative or myelodysplastic disease.
- **Pancytopenia** — The combination of anemia, thrombocytopenia, and neutropenia is termed pancytopenia.
- **Blood smear**
- **Serial evaluation of hemoglobin and hematocrit**
  - Measuring the rate of fall of the patient's hemoglobin or HCT often provides helpful diagnostic information.
  - Suppose the hemoglobin concentration has fallen from 15 to 10 g/dL in one week. If this were due to total cessation of RBC production (ie, a reticulocyte count of zero) and if the rate of RBC destruction were normal (1 percent/day), the hemoglobin concentration would have fallen by 7 percent over seven days, resulting in a decline of 1.05 g/dL ( $0.07 \times 15$ ). The greater fall in hemoglobin in this patient (5 g/dL) indicates that marrow suppression cannot be the sole cause of the anemia and that blood loss and/or increased RBC destruction must be present.

- **Evaluation for iron deficiency**

- More complete evaluation for iron deficiency is indicated when the history (menometrorrhagia, symptoms of peptic ulcer disease) and preliminary laboratory data (low MCV, low MCH, high RDW, increased platelet count) support this diagnosis. In this setting, the plasma levels of iron, iron binding capacity (transferrin), transferrin saturation, and ferritin should be measured.

- **Evaluation for hemolysis**

- Hemolysis should be considered if the patient has experienced a rapid fall in hemoglobin concentration, reticulocytosis, and/or abnormally shaped RBC (especially spherocytes or fragmented RBCs) on the peripheral smear in the absence of blood loss. The usual ancillary findings of hemolysis are an increase in the serum lactate dehydrogenase (LDH) and indirect bilirubin concentrations and a reduction in the serum haptoglobin concentration.
- The combination of an increased LDH and reduced haptoglobin is 90 percent specific for diagnosing hemolysis, while the combination of a normal LDH and a serum haptoglobin greater than 25 mg/dL is 92 percent sensitive for ruling out hemolysis.
- **Intravascular hemolysis** — Plasma and urinary hemoglobin and urinary hemosiderin should be measured if intravascular hemolysis is a consideration, as with paroxysmal nocturnal hemoglobinuria.

- **Bone marrow examination**

- Examination of the bone marrow generally offers little additional diagnostic information in the more common forms of anemia.
  - If erythropoiesis is increased in response to the anemia, as evidenced by an increased reticulocyte production index, the bone marrow will show erythroid hyperplasia, a nonspecific finding.
  - However, if the reticulocyte response is inadequate and the bone marrow shows erythroid hyperplasia, this suggests the presence of ineffective erythropoiesis.
- Although the absence of stainable iron in the bone marrow had previously been considered the "gold standard" for the diagnosis of iron deficiency, this diagnosis is usually established by laboratory tests alone.
- Indications for examination of the bone marrow in anemic patients include
  - pancytopenia or the presence of abnormal cells in the circulation, such as blast forms. Such patients may have aplastic anemia, myelodysplasia, marrow replacement with malignancy, or a myeloproliferative neoplasm.

- Other findings that may be seen in the marrow in anemic patients include megaloblastic erythropoiesis (folate or cobalamin deficiency), absence of recognizable RBC precursors (pure RBC aplasia), vacuolization of RBC precursors (alcohol or drug-induced anemia), and increased iron-laden RBC precursors (the sideroblastic anemias).

### MULTIPLE CAUSES OF ANEMIA

- It is common in pediatric practice for anemia to be caused by a single identifiable disorder. In comparison, multiple causes are frequently present in adults, particularly hospitalized and/or older adults. Common examples include the following:
  - A patient with gastrointestinal bleeding secondary to colon cancer may also have the anemia of inflammation (anemia of chronic disease), leading to a blunted reticulocyte response.
  - A patient with a chronic hemolytic anemia (eg, sickle cell anemia, hereditary spherocytosis) may develop worsening anemia following acute infection, particularly with parvovirus B19, which may blunt or temporarily ablate erythropoiesis and the reticulocyte response.
  - A patient with autoimmune hemolytic anemia may develop worsening anemia from gastrointestinal blood loss following treatment with glucocorticoids.
  - Anemia, renal failure, and congestive failure are often found together, a condition that has been termed "cardio-renal anemia syndrome." Treatment of the anemia may improve both the renal failure and heart failure.

### MANAGEMENT

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The objective of anemia treatment is improving functional status of the patients by correcting Hgb level and treating underlying causes.

#### 1. TRANSFUSION

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- Indications for transfusion
  - Hgb<=7 for most hospitalized medical or surgical patients
  - Patient with severe symptoms like HF
  - Hgb<=8 for patients with chronic cardiac disease, undergoing orthopedic or cardiac surgery
  - Acutely bleeding patient

## 2. TREAT SPECIFIC CAUSES

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### A. TREATMENT OF IRON DEFICIENCY ANEMIA

- ORAL IRON THERAPY

- Ferrous sulfate, 325 mg( 65mg elemental iron), Po TID
- Ferrous fumarate, 325mg ( 107mg elemental iron),Po BID
- Ferrous gluconate, 325mg ( 39mg elemental iron),Po ,1-2tab, TID for at least three months after correction of anemia.
- If the patients cannot tolerate or prefer syrup:-
  - Iron hydroxide polymaltose syrup, 10ml,Po, BID to TID.
  - Ferrous gluconate syrup, 15ml, Po, TID.
  - Ferrous ammonium citrate syrup, 30ml, Po, TID.
- It should be taken 2hr before or 4hr after meal and foods like,milk,egg, tea and coffee should be avoided when iron is given,b/c they can interfere with iron absorption.
- Encouraging dietary intake of iron-rich foods is also useful. Such foods include:
  - beef liver
  - Whole-wheat bread
  - Tuna
  - Eggs
  - peanut butter
  - brown rice
  - lentils
  - beans
- Complications of oral iron therapy
  - Gastrointestinal distress (15–20% of patients)
  - Abdominal pain, nausea, vomiting, or constipation may lead to noncompliance

- IV IRON THERAPY

- Indications for IV Iron Therapy are:-
  - Intolerance to oral Iron Therapy
  - Anemia 2° to CKD with requirements of EPO
  - No improvement in Hgb after 4 wk of oral therapy
  - Presence of conditions that interfere with absorption of iron from GIT
  - Blood loss difficult to cope with oral therapy
  - Severe anemia during late second or third TM of pregnancy
- For patients not on hemodialysis
  - Iron sucrose, 200mg, IV, over 5min, Q3days for total of 5 doses OR
  - Iron sucrose, 200mg diluted in 100ml of NS, over 30min.
- For patients on hemodialysis
  - Iron sucrose 100mg, over 2-5min, given at early session of dialysis.

## B. TREATMENT OF MELOBLASTIC ANEMIA

- Treatment of folic acid deficiency
  - Folic acid, 1-5mg, Po daily for 1-4month (until full hematologic recovery).
  - Vit B12 level should be checked before giving folic acid alone because it might worsen neurologic manifestation of Vit B12 deficiency.
  - If Vit B12 level is difficult to check, give both folic acid and Vit B12 at the same time.
- Treatment of Vit B12 deficiency
  - Cyanocobalamin, 1mg(1000mcg), IM, daily for one wk, weekly for 1 month( if Hgb level is not corrected, continue weekly therapy)

## C. TREATMENT OF OTHER CAUSES OF ANEMIA

- Anemia of CKD = EPO, 50-150U/kg, IV ,3x/wk.
- Autoimmune hemolytic anemia
  - Prednisone 1mg/kg per day
  - Rituximab 100mg/wk 4 times
  - Splenectomy (refractory to medical therapy)
  - Transfusion of red cells (In LT anemia)

## Reference

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## PULMONARY THROMBO EMBOLISM

- Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE)
- VTE causes cardiovascular death and disability as well as psychological illness and emotional distress
- PE is the most common preventable cause of death among hospitalized patients
- PE: is when venous thrombi dislodge from its site of formation and embolize to the pulmonary arterial circulation or paradoxically to the arterial circulation through a Patent Foramen Ovale or Atrial Septal Defect
  - About 50% of patients with Pelvic Vein Thrombosis or Proximal Leg DVT develop PE: often asymptomatic
  - Isolated calf vein thrombi pose a much lower risk of PE but are the most common source of Paradoxical Embolism
  - Upper Extremity Venous thrombi rarely embolize and cause PE

## PATHOPHYSIOLOGY

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- Virchow's triad of
  - venous stasis
  - hypercoagulability, and
  - endothelial injury leads to formation of thrombi

### Pathophysiologic abnormalities

- The most common gas exchange abnormalities are
  - Arterial hypoxemia and an increased alveolar-arterial O<sub>2</sub> tension gradient
  - Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung
  - Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries
  - Increased pulmonary vascular resistance due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin
  - Impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface
  - Alveolar hyperventilation due to reflex stimulation of irritant receptors

- Increased airway resistance due to constriction of airways distal to the bronchi
- Decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant

## **CLASSIFICATION OF PE AND DVT**

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### **Pulmonary Embolism**

- Massive PE
  - accounts for 5–10% of cases
  - characterized by extensive thrombosis affecting at least half of the pulmonary vasculature
  - Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE
  - Patients may present in cardiogenic shock and can die from multisystem organ failure
- Sub-massive PE
  - accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure
  - The combination of right heart failure and release of cardiac biomarkers indicates a high risk of clinical deterioration
  - Low-risk PE constitutes about 65–75% of cases
  - These patients have an excellent prognosis

## **DEEP VENOUS THROMBOSIS**

- Lower extremity DVT: usually begins in the calf and propagates proximally to the popliteal, femoral, and iliac veins.
  - Leg DVT is about 10x more common than upper extremity DVT
- Upper extremity DVT: is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters
- The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase
- Superficial venous thrombosis usually presents with erythema, tenderness, and a “palpable cord.”
- Patients are at risk for extension of the thrombosis to the deep-venous system
- Not all leg pain is due to DVT, and not all dyspnea is due to PE

DIFFERENTIAL DIAGNOSIS	
DEEP VENOUS THROMBOSIS (DVT)	PULMONARY EMBOLISM (PE)
<ul style="list-style-type: none"> <li>• Ruptured Baker's cyst</li> <li>• Muscle strain/injury</li> <li>• Cellulitis</li> <li>• Acute postthrombotic syndrome/venous insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonia, asthma, chronic obstructive pulmonary disease</li> <li>• Congestive heart failure</li> <li>• Pericarditis</li> <li>• Pleurisy: "viral syndrome", costochondritis, musculoskeletal discomfort</li> <li>• Rib fracture, pneumothorax</li> <li>• Acute coronary syndrome</li> <li>• Anxiety</li> </ul>

## SYMPTOMS

- Symptom of PE-depends on type of PE;
  - Small PE-Cough, Hemoptysis, Pleuritic chest Pain (small PE lodges peripherally near pleural nerves) Normal right heart function and systemic arterial pressure
  - Sub-massive PE: -SOB, cough, RV hypokinesis on ECG
  - Massive PE- SOB, Syncope, change in mentation, change in temperature, Hypotension-shock, cyanosis
  - When occult PE occurs concomitantly, clinical improvement fails to ensue despite standard medical treatment of the concomitant illness
- Symptoms of DVT
  - Acute DVT: unilateral leg swelling and calf pain
  - Chronic DVT:
    - Chronic leg aching-especially after prolonged standing
    - Skin ulceration-especially in the medial malleolus of the leg

## RISK FACTORS:

- Risk factors for DVT, mentioned as component of wells score below
- Wells Point score is used to predict likelihood of DVT and PE; PE is likely if point score exceeds 4

Clinical Decision Rules	
Low Clinical Likelihood of Deep Venous Thrombosis (DVT) If Point Score Is Zero or Less; Moderate Likelihood If Score Is 1 to 2; High Likelihood If Score Is 3 or Greater	
CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery < 12 week	1
Tenderness along distribution of deep veins	1

Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	-2
High Clinical Likelihood of Pulmonary Embolism (PE) if Point Score Exceeds 4	
CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3
Alternative diagnosis less likely than PE	3
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1
Cancer	1

## PHYSICAL EXAMINATION

**Vital sign:** Hypotension, Tachycardia, tachypnea, hypo or hyperthermia

**CVS:** Neck vein Distention, an Accentuated P2

**MSS:** unilateral leg swelling and tenderness, tenderness along deep vein, calf pain on dorsiflexion of affected leg (Homan's sign) – should not elicit Homan's sign.

**I/S:** pitting edema

## INVESTIGATIONS:

### Work up for DVT

- D-dimmer study, the sensitivity of the d-dimer is >80% for DVT and >95% for PE
- D-dimer assay is not specific but a normal d-dimer study is a useful “rule out” test
- Levels increase in patients with MI, pneumonia, sepsis, cancer, second or third trimester of pregnancy, post op state
- Doppler ultrasound: direct visualization of thrombus, loss of vein compressibility (**primary diagnostic criterion for DVT**), dilated vein, loss of collateral channels, loss of normal respiratory variation on venous flow dynamics
- MRI: when ultrasound is equivocal, MR venography is an excellent imaging modality to diagnose DVT

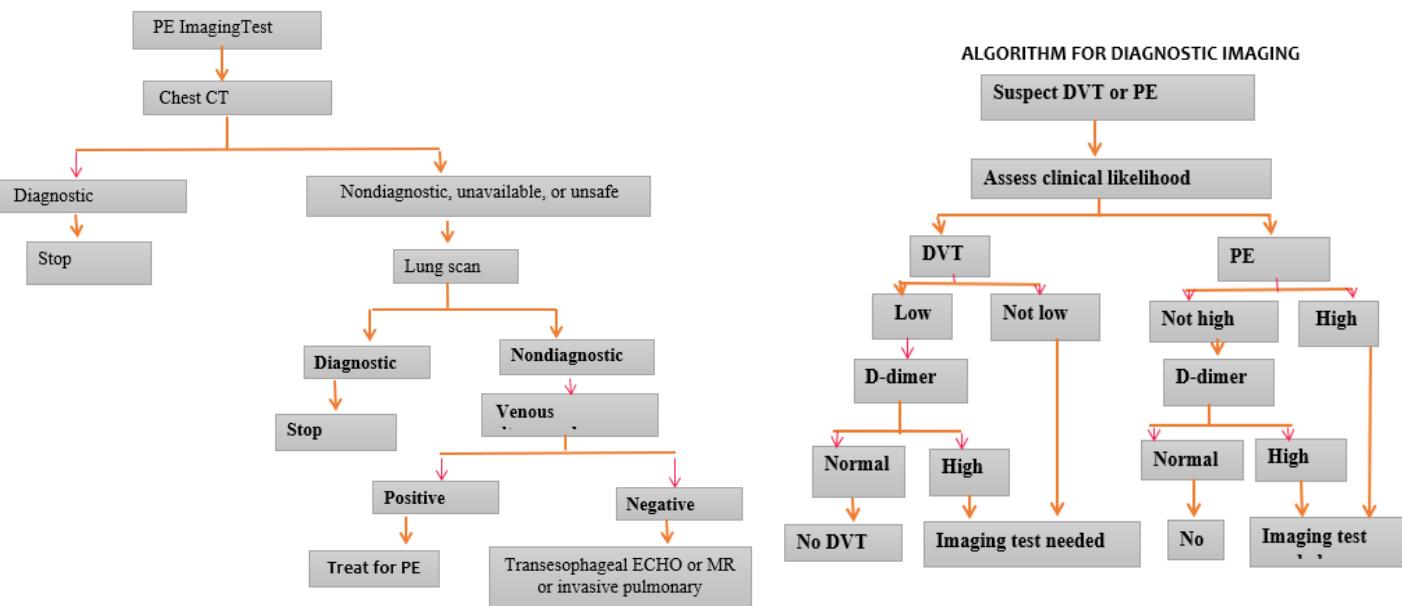
### Work up for PT

- CXR: often normal, but well-established abnormalities include
  - Focal oligemia- Westermark's Sign
  - A peripheral wedged-shaped density above the diaphragm-Hampton's Hump
  - An enlarged right descending pulmonary artery-Palla's Sign
- Chest CT with contrast: Principal/Gold standard imaging test for the diagnosis of PE, can image small peripheral emboli, also provides an excellent four-chamber view of the heart; RV enlargement indicates increased likelihood of death within the next 30 days, in patients without PE, the lung parenchymal images may establish alternative diagnosis that is not apparent on CXR
- Lung scan: second-line diagnostic test for PE, used for patients who cannot tolerate IV contrast, perfusion scan defect-absent/decreased blood flow due to PE
- Pulmonary angiography: for unsatisfactory chest CT and for those in whom procedure like catheter-directed thrombolysis is planned
  - A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection
  - Secondary signs of PE include abrupt occlusion/"cut-off" of vessels, segmental oligemia/avascularity, prolonged arterial phase with slow filling, tortuous and tapering peripheral vessels
- Echo:
  - TTE-McConnell's Sign: Hypokinesis of the RV free wall with Normal Motion of the RV Apex-finding in massive PE
  - TEE-can identify saddle, right main, or left main PE-in massive PE
- ECG: Sinus tachycardia, S1Q3T3 sign(deep S wave in lead1 and Q&T wave In lead 3), T-wave inversion in leads V<sub>1</sub> to V<sub>4</sub>
- Cardiac biomarkers: from myocardial stretch and RV microinfarction

### DIAGNOSIS

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- Clinical: history and physical examination
- Imaging: lung scan, CXR, pulmonary angiography, chest CT



## MANAGEMENT

- Supportive care
- Anticoagulant
- Fibrinolysis: for massive & sub-massive PE
- Pulmonary embolectomy- massive & sub-massive PE
- Prevention of VTE: removal of risk factors for DVT, IVC filter

### Primary therapy

- clot dissolution with pharmaco-mechanical therapy that usually includes low-dose catheter directed thrombolysis
- reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT

### Secondary prevention

- Anti-coagulation or placement of an IVC filter
- when acute DVT of the legs is diagnosed, below-knee graduated compression stockings may be prescribed, usually 30–40 mmHg

## PULMONARY EMBOLISM

### Risk Stratification

- Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level due to RV microinfarction portend a high risk of an adverse clinical outcome despite anticoagulation
- When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone

### Anticoagulation

- Effective anticoagulation is the foundation for successful treatment of DVT and PE
- There are three major strategies:
  - the classical strategy of parenteral anticoagulation with UFH, LMWH, or fondaparinux “bridged” to warfarin
  - parenteral therapy switched after 5 days to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or
  - Oral anticoagulation monotherapy with rivaroxaban or apixaban (both are anti-Xa agents) with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose without parenteral anticoagulation
- In the setting of suspected or proven heparin-induced thrombocytopenia, one can use parenteral direct thrombin inhibitors: argatroban or bivalirudin
- UFH: prevent additional thrombus formation by binding to and accelerating the activity of antithrombin
- UFH is dosed to achieve a target aPTT of 60–80 s
- The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg/h
- UFH has short half-life, which is useful in patients in whom hour-to-hour control of the anticoagulation is desired
- Heparin also has pleiotropic effects that may decrease systemic and local inflammation
- The two principal indications for insertion of an IVC filter are
  - active bleeding that precludes anticoagulation
  - recurrent venous thrombosis despite intensive anticoagulation
- Fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by
  1. dissolving much of the anatomically obstructing pulmonary arterial thrombus
  2. preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension
  3. lysing the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE

- The only Food and Drug Administration-approved indication for PE fibrinolysis is massive PE
- Pulmonary thromboendarterectomy

### CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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- develops in 2–4% of acute PE patients
- PE patients who have initial pulmonary hypertension should be followed up at about 6 weeks with a repeat echocardiogram to determine whether pulmonary arterial pressure has normalized
- Patients impaired by dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy
- Inoperable patients should be managed with pulmonary vasodilator therapy and balloon angioplasty of pulmonary arterial webs
- Prevention of DVT and PE
  - Prophylaxis: Low-dose UFH or LMWH is the most common form

### COMPLICATIONS

- Acute: ARDS, cardiogenic shock
- Chronic: pulmonary hypertension, cor-polmonale-RHF, Post thrombotic syndrome
- Side effect of anticoagulant: - e.g HIT

### HEPARIN INDUCED THROMBOCYTOPENIA

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HIT: - result from autoantibody directed against endogenous platelet factor 4 in complex with heparin

#### Type 1 HIT:

- mild transient drop in platelet count
- occur within the first two days of heparin exposure
- due to direct effect of heparin on platelet causing non immune platelet aggregation
- platelet count typically return to normal with continued heparin use
- The platelet nadir is approximately 100,000/mcl
- Not significant, not associated with thrombosis
- Patient managed expectantly without discontinuation

#### Type 2 HIT:

- Due to antibodies to platelet factor 4 complex to heparin
- Usually occur after 5 days of exposure to heparin
- Can also cause thrombosis along with thrombocytopenia
- Need immediate discontinuation of heparin

## BLEEDING DISORDERS

### INTRODUCTION

#### HEMOSTASIS

- Hemostasis is the process of blood clotting in areas of blood vessel injury.
- Over time, the clot is lysed by the fibrinolytic system, and normal blood flow is restored.
- Hemostasis has 2 major components:
  - Primary Hemostasis: which contains
    - Blood Vessels
    - Platelets
  - Secondary Hemostasis:
    - Coagulation proteins,
    - Anticoagulant proteins, and
    - Fibrinolytic system.

#### THE HEMOSTATIC PROCESS

##### PRIMARY HEMOSTASIS

- Processes involved in the formation of a platelet plug (white thrombus) following endothelial injury.
- Vascular injury results in release of endothelin which causes vasoconstriction and platelet accumulation at the location of injury.
- Platelets undergo 3 main changes
  - Adhesion
    - Platelets bind to vWF via platelet GpIb receptor at the endothelial injury site.
  - Activation
    - After binding to vWF, platelets change their shape and release mediators that lead to activation of more platelets (positive feedback).
    - These are mediated through:
      - Adenosine diphosphate (ADP),
      - Thromboxane A<sub>2</sub> (TXA<sub>2</sub>),
      - Platelet-activating factor (PAF) and Calcium.
  - Aggregation
    - formation of a white thrombus composed of platelets and fibrinogen
    - Mediated by GpIIb/IIIa-receptor and fibrinogen

## SECONDARY HEMOSTASIS

- Processes that lead to stabilization of the platelet plug (white thrombus) by creating a fibrin network.
- It is achieved through two coagulation pathways that merge into a common pathway.
  - I. Extrinsic pathway of coagulation: triggered by endothelial injury
  - II. Intrinsic pathway of coagulation: triggered by tissue factor (exposed collagen, kallikrein, and kininogen (HMWK) activate factor XII).
  - III. Common Pathway

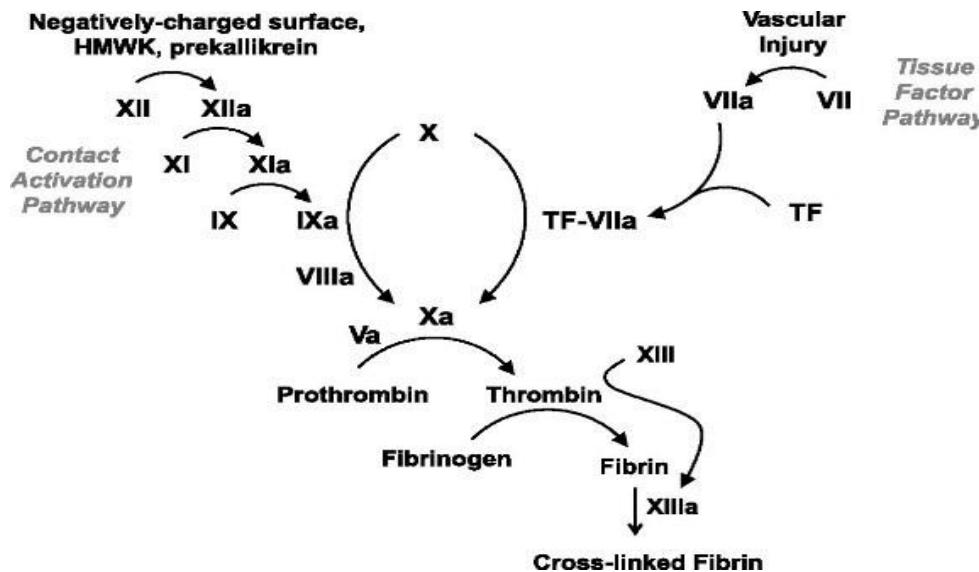


Figure coagulation cascade

## INHIBITION OF HEMOSTASIS

- In order to prevent hypercoagulability as well as excessive bleeding, activation of the coagulation cascade and the processes that inhibit it occur simultaneously in the circulatory system (procoagulant anticoagulant balance).
- These include: -
  - Tissue factor pathway inhibitor: inhibits tissue factor
  - Protein C and protein S: which inhibits factors Va and VIIIa.
  - Antithrombin: Degrades thrombin and factors IXa and Xa
  - Drug-induced: anticoagulant treatment.

## EVALUATION

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- Bleeding that is spontaneous, excessive, or delayed in onset following tissue injury results from a localized pathologic process or a disorder of the hemostatic process, involving a complex interplay among vascular integrity, platelet number and function, coagulation factors, and fibrinolysis.

## HISTORY

- The clinical evaluation of a patient with a bleeding disorder begins with a careful history.
- A history of bleeding is the most important predictor of bleeding risk.
- In evaluating a patient for a bleeding disorder, a history of at-risk situations, including the response to past surgeries, should be assessed.
- Does the patient have a history of spontaneous or trauma/surgery-induced bleeding?
- Spontaneous hemarthroses are a hallmark of moderate and severe factor VIII and IX deficiency and, in rare circumstances, of other clotting factor deficiencies.
- Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease (VWD), termed disorders of primary hemostasis or platelet plug formation.
- Bleeding symptoms that appear to be more common in patients with bleeding disorders include:
  - Prolonged bleeding with surgery, dental procedures and extractions, and/or trauma,
  - Heavy menstrual bleeding (HMB), or postpartum hemorrhage (PPH), and
  - Large bruises (often described with lumps).
- Easy bruising and HMB are common complaints in patients with and without bleeding disorders.
- Easy bruising can also be a sign of medical conditions in which there is no identifiable coagulopathy; instead, the conditions are caused by an abnormality of blood vessels or their supporting tissues.
- In Ehlers-Danlos syndrome, there may be posttraumatic bleeding and a history of joint hyper extensibility.
- Cushing's syndrome, chronic steroid use, and aging result in changes in skin and subcutaneous tissue, and subcutaneous bleeding occurs in response to minor trauma.
- **Epistaxis** is a common symptom, particularly in children and in dry climates, and may not reflect an underlying bleeding disorder.
  - However, it is the most common symptom in hereditary hemorrhagic telangiectasia and in boys with VWD.

- Clues that epistaxis is a symptom of an underlying bleeding disorder include lack of seasonal variation and bleeding that requires medical evaluation or treatment, including cauterization.
- Bleeding with eruption of primary teeth is seen in children with more severe bleeding disorders, such as moderate and severe hemophilia.
- It is uncommon in children with mild bleeding disorders.
- Patients with disorders of primary hemostasis (platelet adhesion) may have increased bleeding after dental cleanings and other procedures that involve gum manipulation.
- HMB is a common symptom in women with underlying bleeding disorders and is reported in the majority of women with VWD, women with factor XI deficiency, and symptomatic carriers of hemophilia.
- PPH is a common symptom in women with underlying bleeding disorders.
- In women with type 1 VWD and symptomatic carriers of hemophilia A in whom levels of VWF and factor VIII usually normalize during pregnancy, PPH may be delayed.
- Gastrointestinal (GI) bleeding and hematuria are usually due to underlying pathology, and procedures to identify and treat the bleeding site should be undertaken, even in patients with known bleeding disorders.
- VWD, particularly types 2 and 3, has been associated with angiodysplasia of the bowel and GI bleeding.
- Hemarthroses and spontaneous muscle hematomas are characteristic of moderate or severe congenital factor VIII or IX deficiency.
- They can also be seen in moderate and severe deficiencies of fibrinogen, prothrombin, and factors V, VII, and X.
- Spontaneous hemarthroses occur rarely in other bleeding disorders except for severe VWD, with associated factor VIII levels <5%.
- Muscle and soft tissue bleeds are also common in acquired factor VIII deficiency.
- Life-threatening sites of bleeding include bleeding into the oropharynx, where bleeding can obstruct the airway, into the central nervous system, and into the retro peritoneum.
- Central nervous system bleeding is the major cause of bleeding-related deaths in patients with severe congenital factor deficiencies.

#### **PROHEMORRHAGIC EFFECTS OF MEDICATIONS AND DIETARY SUPPLEMENTS**

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- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase 1 impair primary hemostasis and may exacerbate bleeding from another cause or even unmask a previously occult mild bleeding disorder such as VWD.
- All NSAIDs, however, can precipitate GI bleeding, which may be more severe in patients with underlying bleeding disorders.

- The effect of other NSAIDs is shorter, as the inhibitor effect is reversed when the drug is removed.
- Inhibitors of the ADP P2Y<sub>12</sub> receptor (clopidogrel, prasugrel, and ticagrelor) inhibit ADP-mediated platelet aggregation and, like NSAIDs, can precipitate or exacerbate bleeding symptoms.
- The risk of bleeding with these drugs is higher than with NSAIDs.
- Many herbal supplements can impair hemostatic function risk than others.
- Fish oil or concentrated omega-3 fatty acid supplements impair platelet function.
- Vitamin E appears to inhibit protein kinase C-mediated platelet aggregation and nitric oxide production.

### **UNDERLYING SYSTEMIC DISEASES THAT CAUSE OR EXACERBATE A BLEEDING**

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- Acquired bleeding disorders are commonly secondary to, or associated with, systemic disease.
- The clinical evaluation of a patient with a bleeding tendency must therefore include a thorough assessment for evidence of underlying disease.
- Bruising or mucosal bleeding may be the presenting complaint in
  - Liver disease,
  - Severe renal impairment,
  - Hypothyroidism,
  - Paraproteinemias or amyloidosis, and
  - Conditions causing bone marrow failure.
- All coagulation factors are synthesized in the liver, and hepatic failure results in combined factor deficiencies.
- This is often compounded by thrombocytopenia associated with liver failure and portal hypertension.
- Coagulation factors II, VII, IX, and X and proteins C, S, and Z are dependent on vitamin K for posttranslational modification.
- Although vitamin K is required in both procoagulant and anticoagulant processes, the phenotype of vitamin K deficiency or the warfarin effect on coagulation is bleeding.
- The normal blood platelet count is 150,000–450,000/ $\mu$ L.
- Thrombocytopenia results from decreased production, increased destruction, and/or sequestration.
- Although the bleeding risk varies somewhat by the reason for the thrombocytopenia, bleeding rarely occurs in isolated thrombocytopenia at counts >50,000/ $\mu$ L and usually not until <10,000–20,000/ $\mu$ L.

- Coexisting coagulopathies, as is seen in liver failure or disseminated coagulation; infection; platelet-inhibitory drugs; and underlying medical conditions can all increase the risk of bleeding in the thrombocytopenic patient.
- Most procedures can be performed in patients with a platelet count of 50,000/ $\mu$ L.
- The level needed for major surgery will depend on the type of surgery and the patient's underlying medical state, although a count of ~80,000/ $\mu$ L is likely sufficient.

## **CLINICAL MANIFESTATIONS**

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- Clinical manifestations of disordered hemostasis can be divided into two major categories:
  1. Those associated with disorders of blood vessels or qualitative or quantitative platelet abnormalities; and
  2. Those associated with disorders of coagulation

## **DISORDERS OF PLATELETS OR BLOOD VESSELS**

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- These conditions are often referred to as disorders of primary hemostasis or the purpuric disorders since they are characteristically associated with mucosal and cutaneous bleeding.
- Mucosal bleeding may be manifest as epistaxis and/or gingival bleeding, and large bullous hemorrhages may appear on the buccal mucosa due to the lack of vessel protection afforded by the submucosal tissue.
- Bleeding into the skin is manifested as petechiae or superficial ecchymoses. Patients with platelet abnormalities tend to bleed immediately after vascular trauma and rarely experience delayed bleeding, which is more common in the coagulation disorders.

## **COAGULATION DISORDERS**

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- The typical manifestations of bleeding in the coagulation disorders are large palpable ecchymoses and large, spreading, deep soft tissue hematomas.
- Hemorrhage into synovial joints (hemarthrosis) most often indicates a severe inherited coagulation disorder, such as hemophilia.
- Postsurgical bleeding can be extensive.
- In some patients with a coagulation disorder, the onset of bleeding after trauma may be delayed.

## **LABORATORY TESTING**

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- Careful history taking and clinical examination are essential components in the assessment of bleeding and thrombotic risk.
- The use of laboratory tests of coagulation complement, but cannot substitute for, clinical assessment.
- No test exists that provides a global assessment of hemostasis.

- Laboratory tests of primary and secondary hemostatic mechanisms are used for two purposes:
  - General screening tests
  - Tests to define specific platelet or clotting factor abnormalities

#### **General screening tests include**

- The platelet count,
- Bleeding time (BT),
- Prothrombin time (PT),
- Activated partial thromboplastin time (aPTT), and
- Thrombin time (TT).

#### **Specific tests include**

- Examination of the peripheral blood smear,
- Platelet aggregation in response to ADP, epinephrine, collagen, and ristocetin;
- Platelet release assays,
- Coagulation factor assays, and Assessment of factor XIII activity via clot solubility testing.
- Tests of fibrinolysis include the measurement of fibrin split products and D-dimer levels.
- Assays for the less commonly seen bleeding disorders include alpha-2-antiplasmin activity, euglobulin clot lysis time, as well as tissue plasminogen activator and plasminogen activator inhibitor-1 antigens.

#### **PLATELET COUNTING AND THE PERIPHERAL SMEAR**

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- Platelets may be counted directly or with the use of fully automated electronic methods.
  - Examination of the peripheral blood smear is essential in patients with low platelet counts to exclude the presence of pseudo thrombocytopenia due to in vitro platelet agglutination in the presence of EDTA.
  - This phenomenon is thought to result from a "naturally occurring" platelet autoantibody directed against a normally concealed epitope on the platelet membrane, which becomes exposed by EDTA.
  - Use of alternative anticoagulants (eg, citrate or heparin), may circumvent this technical problem.

#### **BLEEDING TIME**

- 
- The bleeding time (BT) is a measure of the interaction of platelets with the blood vessel wall.
  - A prolonged bleeding time may occur in-
    - Thrombocytopenia (platelet count usually below 50,000/micro.lt),

- Qualitative platelet abnormalities (eg, uremia),
- Von Willebrand disease (VWD),
- Some cases of vascular Purpura, and severe fibrinogen deficiency, in which it is probably the result of platelet dysfunction.
- Among patients with a normal platelet count who are not taking aspirin, the bleeding time is used primarily to screen patients for inherited disorders of platelet function.
- An abnormal test in a patient with mucocutaneous bleeding would justify further testing for platelet dysfunction or specific tests for von Willebrand disease (VWD).
- However, a normal value for the BT should not preclude testing for VWD.
- The Platelet Function Analyzer is more sensitive for detection of VWD than is the BT.
- **The Platelet Function Analyzer**
  - The commercially-available Platelet Function Analyzer (PFA-100) is an alternative technology that assesses platelet function with greater sensitivity and reproducibility than the bleeding time (BT).
  - Because the BT is insensitive, invasive, time consuming, and subject to variation due to technical factors, many centers have adopted the PFA-100 in place of the BT as their screening test of platelet function

#### PROTHROMBIN TIME

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- The production of fibrin via the extrinsic pathway and the final common pathway (common to both extrinsic and intrinsic cascades) requires tissue thromboplastin (tissue factor), factor VII (extrinsic pathway), and factors X, V, prothrombin (factor II), and fibrinogen.
- The functioning of these pathways is measured by the plasma prothrombin time.
- The test bypasses the intrinsic pathway and uses thromboplastins to substitute for platelets.
- Within this combined pathway, factors VII, X, and prothrombin are vitamin-K dependent and are altered by warfarin.
- For this reason, the PT is used as a measure of the anticoagulant activity of warfarin and other vitamin K antagonists.

#### ACTIVATED PARTIAL THROMBOPLASTIN TIME

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- The activated partial thromboplastin time (aPTT) measures the intrinsic and common pathways of coagulation.
- It is called partial since platelet substitutes are used which are only partial thromboplastins; they are incapable of activating the extrinsic pathway, which requires complete tissue thromboplastin (tissue factor).
- The aPTT is sensitive to inhibitors such as heparin and to deficiencies of all coagulation factors except factors VII and XIII.

- It is less sensitive than the PT to deficiencies of the common pathway (factors X and V, prothrombin, and fibrinogen).
- High levels of a single factor (eg, factor VIII) can shorten the aPTT.

### **THROMBIN TIME AND REPTILASE TIME**

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- The thrombin time (TT) and reptilase time (RT) measure conversion of fibrinogen to fibrin monomers and the formation of initial clot by thrombin and reptilase, respectively.
- Reptilase, a thrombin-like snake enzyme, differs from thrombin by generating fibrinopeptide A but not fibrinopeptide B from fibrinogen and by resisting inhibition by heparin via antithrombin.
- Fibrin strand cross-linking, which is mediated by factor XIII, is not measured by these assays.
- Prolonged thrombin times and reptilase times may be due to
  - Hypofibrinogenemia,
  - Structurally abnormal fibrinogens (dysfibrinogens), or
  - Increased fibrin split products.
- Since heparin prolongs the TT but not the RT, the RT is useful for determining if heparin is the cause of a prolonged TT.

### **FACTOR DEFICIENCIES AND INHIBITORS**

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- A prolonged aPTT can be due to a deficiency (or absence) of a coagulation factor or the presence of a coagulation factor inhibitor.
- A factor deficiency should be correctable by addition of normal plasma to the test reaction tube.
- This is normally done by performing a PT or aPTT on a 1:1 mixture of patient and normal plasma.
- Specific factor deficiencies are then determined by assessing the PT or aPTT in mixes of test plasma with commercially available plasmas deficient in known factors.
- Factor levels can be functionally assessed by comparing test results to standard curves generated by mixtures of serially diluted normal plasma and factor-deficient plasma.
- The presence of a factor inhibitor is suspected when the abnormal test does not correct, or only partially corrects, following an immediate assay of a 1:1 mixture of patient and normal plasma.

### **FIBRINOGEN**

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- Fibrinogen's functional activity is measured as thrombin-coagulable protein, while levels of structural fibrinogen are measured by immunologic assays.
- Immunologic and functional assays of fibrinogen may be discordant in patients with an inherited dysfibrinogenemia.

## TESTS FOR FIBRINOLYSIS

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- Fibrin and fibrinogen degradation products (FDP) are protein fragments resulting from the action of plasmin on fibrin or fibrinogen, respectively.
- Elevated levels are seen in states of fibrinolysis such as disseminated intravascular coagulation (DIC).
- FDP assays do not differentiate between fibrin degradation products and fibrinogen degradation products.
- It is possible to accurately measure the concentration of fibrin D-dimers, which are degradation products of cross-linked fibrin.
- The method of choice is the enzyme-linked immunosorbent assay (ELISA).
- Quantitative FDP levels may be more sensitive than D-dimer levels as an indication of the degree of fibrinolytic activity.
- More specific tests of the fibrinolytic system include assays for plasminogen, tissue plasminogen activator (t-PA), alpha-2 antiplasmin, plasminogen activator inhibitor-1 (PAI-1), and thrombin-activatable fibrinolysis inhibitor (TAFI).

## DIAGNOSTIC APPROACH

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- In many patients with a bleeding diathesis, the likely diagnosis will be apparent from the history and physical examination; the diagnosis can then be confirmed with the appropriate specific tests.
- Individual tests (eg, either PT or aPTT alone) can also be used for monitoring the effect of an anticoagulant or assessing patients with a known condition that has a predictable effect on coagulation.
- When the diagnosis is not immediately apparent, three initial tests should be performed—platelet count, PT, and aPTT—because defects in primary or secondary hemostasis, including intrinsic, extrinsic, and common pathway defects, can all be responsible for bleeding.
- The pattern of results provides a presumptive diagnosis which can then be confirmed with specific testing.

### A. NORMAL PT AND aPTT

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- For patients who have a convincing bleeding history and normal PT and aPTT testing, it is important to evaluate the possibility of a platelet disorder; this is especially true for patients with a mucocutaneous bleeding pattern.
- The first step is measurement of the platelet count, which is done as part of the routine complete blood count (CBC) in most institutions.
- If a platelet count was not performed recently, this should be obtained.

- Spontaneous bleeding generally does not occur with a platelet count greater than 50,000/microL.
- While a finding of thrombocytopenia is helpful in evaluating unexplained bleeding, a normal platelet count does not eliminate the possibility of a platelet abnormality, because the patient may have a condition that affects platelet function rather than number.
- Examples include von Willebrand disease (VWD), in which reduced levels of von Willebrand factor (VWF) lead to impaired binding of platelets to the endothelium; and inherited platelet function disorders, in which platelets do not respond to usual hemostatic cues.
- Appropriate initial testing includes testing for VWD and tests for platelet defects, which may include review of the peripheral blood smear, bleeding time, and/or PFA-100 testing.
- If thrombocytopenia, VWD, and platelet function defects are eliminated as a cause of unexplained bleeding, additional possible causes include factor XIII deficiency, fibrinolytic defects, and disorders of vascular integrity.

## B. NORMAL PT AND PROLONGED aPTT

**1. Factor deficiencies** — A normal PT and a prolonged aPTT is characteristic of disorders of the intrinsic pathway of coagulation.

- Inherited disorders include deficiencies of factors VIII (hemophilia A, von Willebrand disease), IX (hemophilia B), and XI.
- Hemophilia A and B are the most common.
- Patients with these disorders present with life-long recurrent soft tissue and joint bleeding, generally requiring frequent factor replacement therapy.
- Factor XI deficiency, which is relatively common in Ashkenazi Jews, but can be seen in a variety of ethnic groups, presents with a variable and unpredictable bleeding history
- Bleeding in these patients, when present, is most commonly seen following surgical procedures.

**2. Acquired inhibitors** — Acquired inhibitors include antiphospholipid antibodies which, as noted above, may be associated with thrombosis rather than bleeding, and antibodies to factor VIII (acquired hemophilia), IX, and XI, which may be associated with catastrophic bleeding.

- Factor VIII inhibitors have been described in association with malignancy, clonal lympho-proliferative disorders, pregnancy, rheumatologic disorders, as well as in the absence of underlying disease.
- Acquired antibodies to factor IX and XI are rare.

### C. PROLONGED PT AND NORMAL aPTT

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- A prolonged PT with a normal aPTT is indicative of an abnormality in the extrinsic pathway and suggests factor VII deficiency, which can be inherited or acquired.
- This pattern is most commonly seen following warfarin therapy, early liver disease, and vitamin K deficiency, and, less commonly, in certain (early) cases of DIC.
- Inherited factor VII deficiency displays considerable phenotypic and molecular heterogeneity.
- Acquired inhibitors of factor VII are rare.

### D. PROLONGED PT AND aPTT

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- Prolongation of both the PT and the aPTT indicates an inherited disorder of the common pathway or a more complex acquired disorder involving multiple pathways.
- Inherited disorders include deficiency of factor X, factor V, prothrombin (factor II), or fibrinogen (factor 1).
- These deficiencies are extremely rare.
- Supratherapeutic doses of warfarin or heparin (or anticoagulant rodenticide ingestion) can cause prolongation of both the PT and aPTT.
- It is common to see prolongation of both the PT and aPTT when heparin and warfarin are employed simultaneously, as in the initial treatment of venous thromboembolic disease.
- Acquired disorders with multiple abnormalities which produce this pattern include vitamin K deficiency, liver disease, disseminated intravascular coagulation, and fibrinolysis.
- Differentiating among these possibilities may be difficult.
- The first step in the evaluation of patients with a prolonged PT and aPTT should be to exclude or identify an abnormality of fibrinogen.
- This can be achieved by measurement of the plasma fibrinogen concentration and the thrombin time, and testing for increased amounts of D-dimer or fibrin/fibrinogen degradation products (FDP).

# CHAPTER NINE

## Neurology

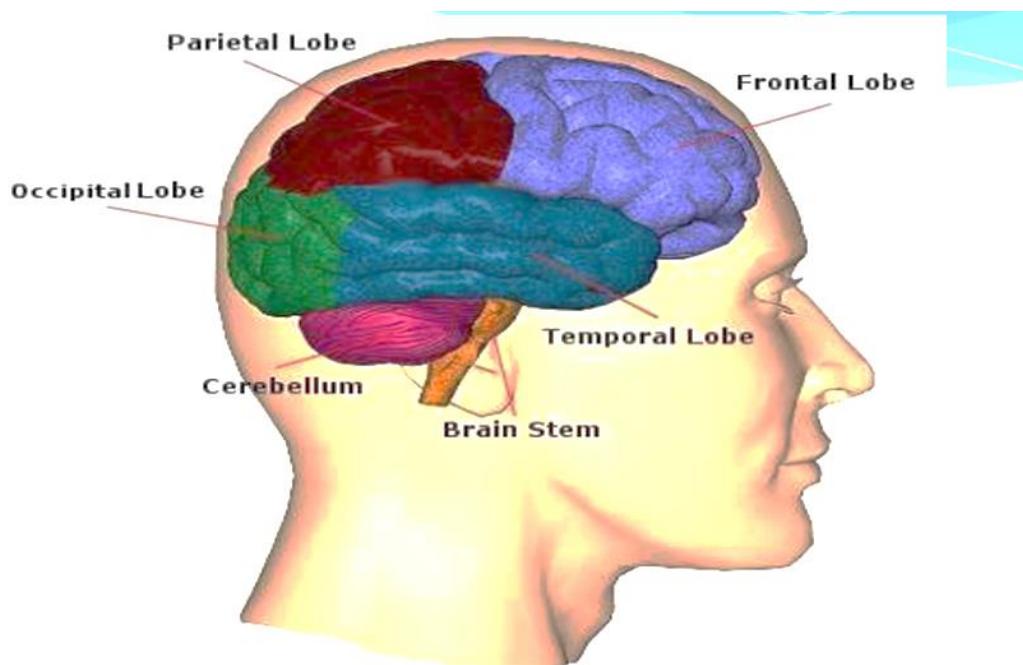
Stroke

Brain Abscess

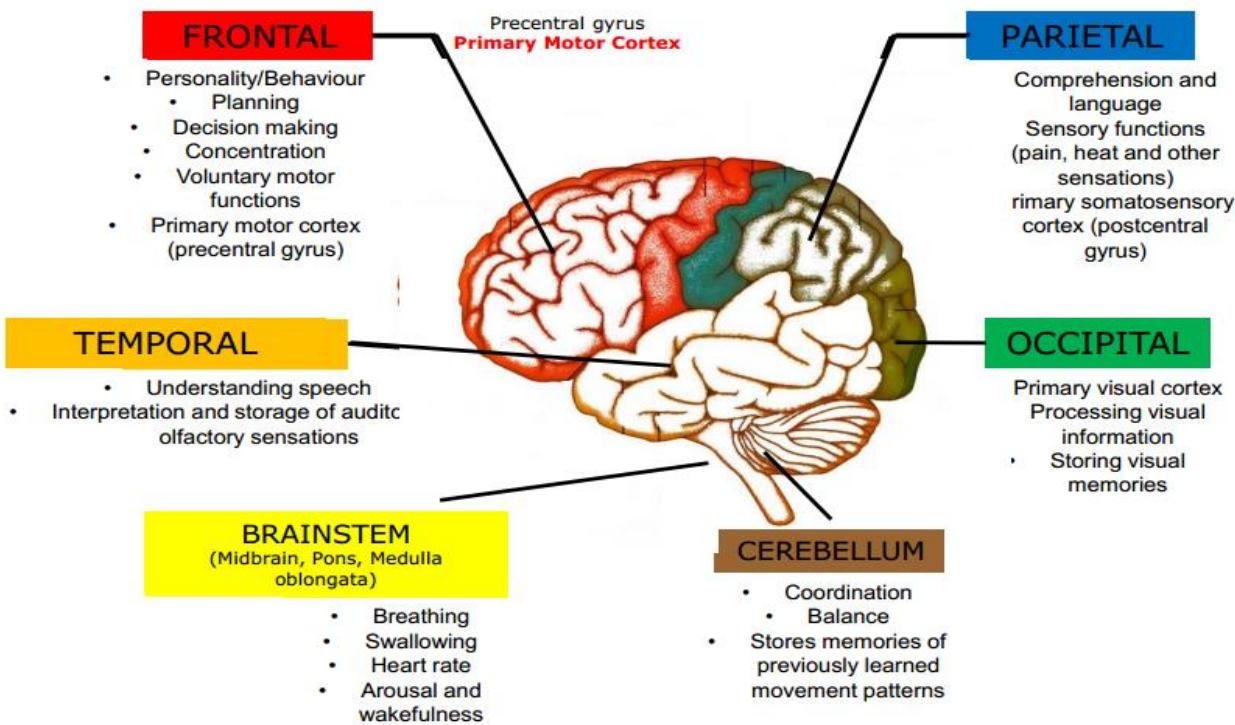
Bacterial Meningitis

### STROKE

#### ANATOMY OF THE BRAIN



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## THE MOST COMMON PRESENTATION OF STROKE

**Hemiplegia**- Is a complete loss of motor function (paralysis) on one half of the body.

**Hemiparesis** – is Partial loss of motor function

## TERMINOLOGIES USED FOR HEMIPLEGIA

- **Crossed hemiplegia** – ipsilateral LMN paralysis of one of the cranial nerves with contralateral (opposite side) hemiplegia.  
Signifies brain stem as the site of the lesion.
- **Uncrossed hemiplegia** – UMN Cranial nerves palsy on the side of hemiplegia (i.e both being opposite to cerebral lesion)
- **Dense hemiplegia** – complete loss of voluntary functions (weakness) of equal magnitude in both upper and lower limbs on the side of the body involved.  
Signifies an internal capsular lesion as corticospinal fibres are condensed there.
- **Pure motor hemiplegia** – because of isolated unilateral involvement of corticospinal tract like in Lacunar (small vessel) infarct of posterior limb of internal capsule.

- **Homolateral hemiplegia** – hemiplegia occurring on the same side of the lesion. It is seen in unilateral cervical spinal cord lesion (Brown sequard's syndrome)

## DIFFERENTIAL DIAGNOSIS

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- Cerebrovascular Accident (stroke)
- Traumatic disorders
- Brain Tumors
- Migraine (acephalic migraine)
- Infective disorders
  - Brain abscess
  - TB
  - Neurosyphilis
- Metabolic encephalopathies
- Todd's paralysis (after epileptic seizure)

## APPROACH TO THE PATIENT

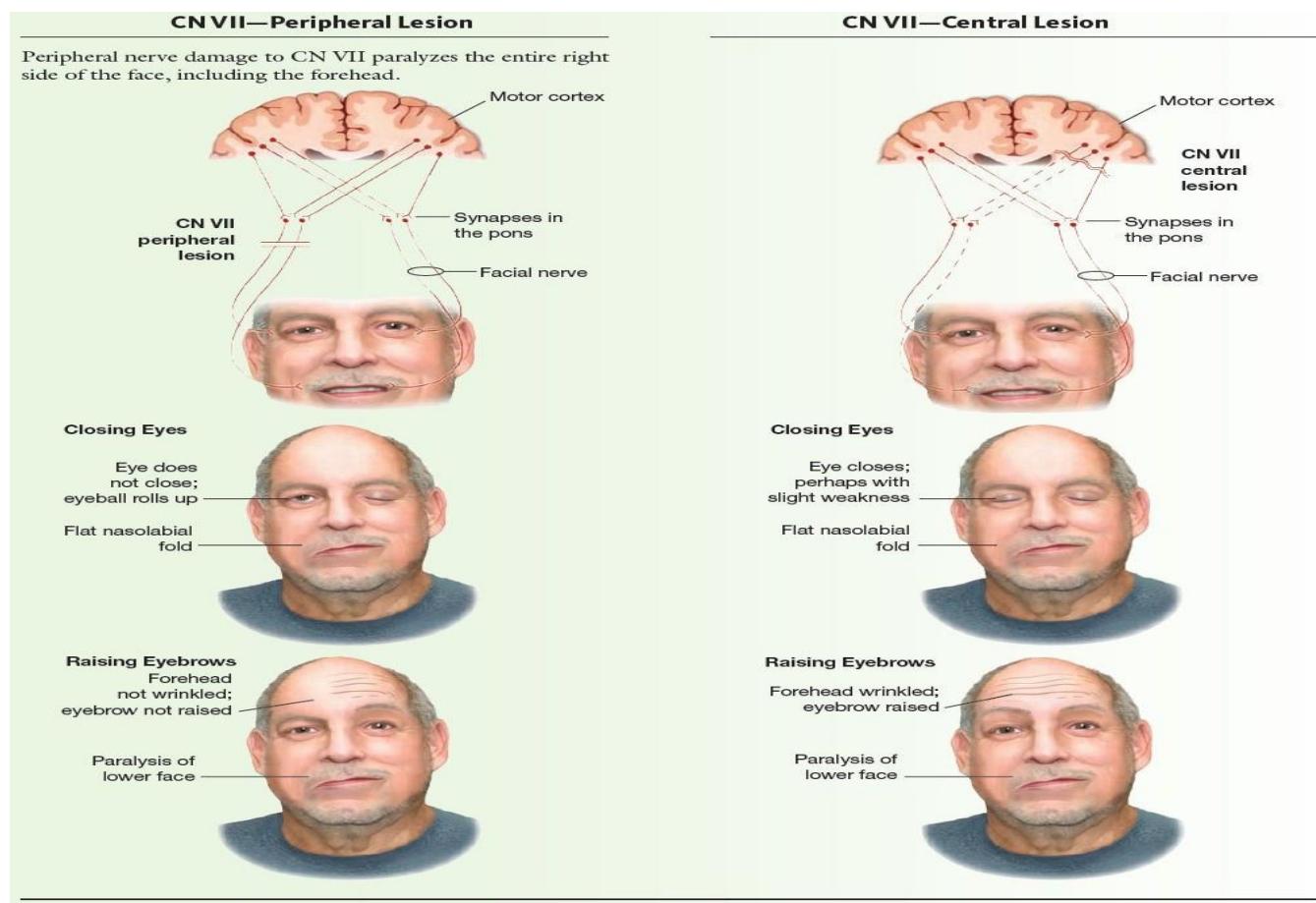
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### History

- **Elaboration of the C/C**
  - Age
  - Date and time of onset
  - Mode of onset (e.g sudden or gradual)
  - Progress or course of paralysis
  - Duration
- **Associated Neurologic symptoms**
  - Any disturbance in Consciousness
  - Speech disturbance
  - Visual disturbance
  - Hearing disturbance
  - Any face deviation
  - Convulsion (history of abnormal body movement)
  - Urinary incontinence
- **Other associated symptoms**
  - Headache history
  - History of fever, Nausea & Vomiting
  - Symptoms of CVS and Pulmonary disease
  - History of trauma
  - History of similar episodes in the past

## PHYSICAL EXAMINATION

- **General Appearance**
  - Is the patient conscious?
  - Posture of the patient
- **Vital Sign**
  - any derangement in v/s (e.g ↓PR could be sign ↑ ICP, abnormal rhythm in AF, ↑BP in HTN patient, fever could be sign of infection)
- **HEENT**
  - **EYE-**
    - Retina (effects of hypertension and cholesterol emboli [Hollenhorst plaques])
    - Arcus senilis (peripheral corneal opacity usually in hypercholesterolemia),
    - Diabetic changes (refer on DM),
    - Hypertensive changes (refer on HTN portion)
- **LGS** – Enlarged LN (could be sign of metastatic tumors)
- **Respiratory system**
  - signs of pulmonary edema (end inspiratory crackles)
  - Signs of respiratory infections
- **CVS**
  - Artery (peripheral pulses and bruits (especially Carotid and subclavian bruit))
  - Venous (raised JVP in HF)
  - Heart rhythm (for atrial fibrillation)
  - Cardiomegally
  - Murmur (could be source of emboli)
- **Abdomen** – palpable bladder (urinary retention)
- **CNS** – (please read NS examination properly from Barbara Bates)
  - **Mental status** – conscious or not
  - **Cognitive** – speech disturbance
  - **CN** – UMN or LMN paralysis of CN-VII
    - Lower part of the face normally is controlled by UMN located on only one side of the cortex – opposite side
    - Upper face is controlled by pathways from both sides of the cortex. (Even though the UMN on the left are destroyed, others on the right remain and the right upper face continues to function fairly well)



- **Motor** – UMN signs ( i.e. Hypertonicity, Hypereflexia, Up going plantar reflex and absence of muscle atrophy & fasciculation ) on the side of the body involved ( i.e opposite to the site of CNC lesion ) if the lesion is above the cervical spinal cord
- **Sensory** – may show hemianesthesia or may be normal

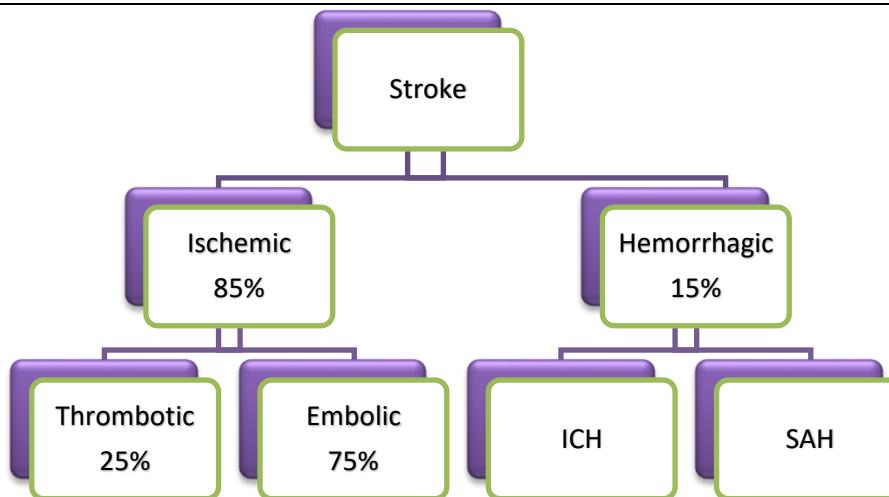
## CEREBROVASCULAR ACCIDENT or STROKE

**Definition:** It is defined as an **abrupt onset** of **neurologic deficit** that is attributable to a **focal vascular cause lasting >24hrs.**

- It is the 2<sup>nd</sup> leading cause of death and the 2<sup>nd</sup> most common disabling condition in individuals aged 50 or older worldwide.

Risk factors	
Non-Modifiable	Modifiable
Age	Hypertension
Gender (M>F)	DM
Race (Afro caribbean > Asian > European)	Smoking
Heredity	Obesity
	Cardiac disorder (AF, HF, Endocarditis)
	Previous TIA or stroke
	Dyslipidemia
	Alcohol, Drug misuse

## ISCHEMIC STROKE



### Embolism can be:-

**Cardioembolism**- account for 20% of all strokes

- Non rheumatic ( non valvular ) **atrial fibrillation** is the most common cause of cerebral embolism
- Others like **MI, RHD, Prosthetic valves, Ischemic cardiomyopathy**
- Paradoxical embolization ( i.e venous thrombus migrating to arterial circulation) usually through PFO or ASD
- Bacterial endocarditis- septic emboli

**Artery to artery** – any diseased vessel maybe an embolic source, including

- Aortic arch
- Common carotid,
- ICA,
- Vertebral and basilar arteries

### ICH (Intracerebral hemorrhage)

– accounts for 10% of all stroke and about 35-45% of patients die within the 1<sup>st</sup> month.

Commonest causes are

- Hypertensive ICH – most common sites are
  - Basal ganglia ( esp Putamen)
  - Thalamus
  - Cerebellum
  - Pons
- Coagulopathy
- Drugs ( Cocaine and amphetamine)
- Cerebral amyloid angiopathy (CAA)

**N.B.** Heavy alcohol consumption increase the risk.

- Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies.
- A decrease in cerebral blood flow to zero causes death of brain tissue within 4–10 min; values <16–18 mL/100 g tissue per minute cause infarction within an hour; and values <20 mL/100 g tissue per minute cause ischemia without infarction unless prolonged for several hours or days.
- *Ischemic penumbra*, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction. The ischemic penumbra will eventually progress to infarction if no change in flow occurs, and hence, saving the ischemic penumbra is the goal of revascularization therapies.

#### TIA (TRANSIENT ISCHEMIC ATTACK) –

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- TIAs are episodes of stroke symptoms that last only briefly; the standard definition of duration is <24 h, but most TIAs last <1 hr.
- It also includes,
  - Transient monocular blindness (aka Amaurosis fugax ),
  - Transient symptoms such as syncope, amnesia, confusion, and dizziness.
- If a relevant brain infarction is identified on brain imaging, the clinical entity is now classified as stroke regardless of the duration of symptoms.
- A normal brain imaging study following a TIA does not rule-out TIA; rather, the clinical syndrome is diagnostic.
- The causes of TIA are similar to the causes of ischemic stroke, but because TIAs may herald stroke, they are an important risk factor that should be considered separately and urgently.
- TIAs may arise from emboli to the brain or from in situ thrombosis of an intracranial vessel. With a TIA, the occluded blood vessel reopens and neurologic function is restored.
- The risk of stroke after a TIA is ~10–15% in the first 3 months, with most events occurring in the first 2 days

Risk of stroke following Transient Ischemic Attack: The ABCD <sup>2</sup> Score	
CLINICAL FACTOR	SCORE
A: Age ≥ 60 years	1
B: SBP > 140 mmHg or DBP > 90 mmHg	1
C: Clinical symptoms	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
>60 min	2
10-59 min	1
D: Diabetes (oral medication or insulin)	1
TOTAL SCORE	SUM EACH CATEGORY
ABCD <sup>2</sup> score Total	3-Month Rate of Stroke (%) <sup>a</sup>
0	0
1	2
2	3
3	3
4	8
5	12
6	17
7	22

## INTRACEREBRAL HEMORRHAGE

Hemorrhages are classified by their location and the underlying vascular pathology. This includes

- Intracerebral hemorrhage (ICH)- Hemorrhage directly into the brain parenchyma,
- Arteriovenous malformations (AVMs) of the brain.
- Other categories of hemorrhage include bleeding into subdural and epidural spaces, usually caused by trauma and subarachnoid hemorrhage due to trauma or the rupture of an intracranial aneurysm
- ICH accounts for ~10% of all strokes, and ~35–45% of patients die within the first month.

## CAUSES OF ICH

- Hypertensive haemorrhage
- Transformation of prior ischemic infarction
- Metastatic brain tumor (i.e. Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma)
- Coagulopathy
- Drugs (Cocaine, amphetamine)
- Arteriovenous malformation
- Amyloid angiopathy- rare in patients <60 years
- Cavernous angioma
- Dural arteriovenous fistula
- Dural sinusthrombosis
- Capillary telangiectasias

Hypertensive ICH usually results from spontaneous rupture of a small penetrating artery deep in the brain.

## CLINICAL PRESENTATION OF STROKE

- Generally, the patient present with
  - Weakness of one half of the body with or without asymmetry of the face.
  - They may also complain sensory and speech disturbance.
  - Sometimes loss of consciousness could be the presenting feature.

Table on Presentation of Ischemic Vs Hemorrhagic stroke

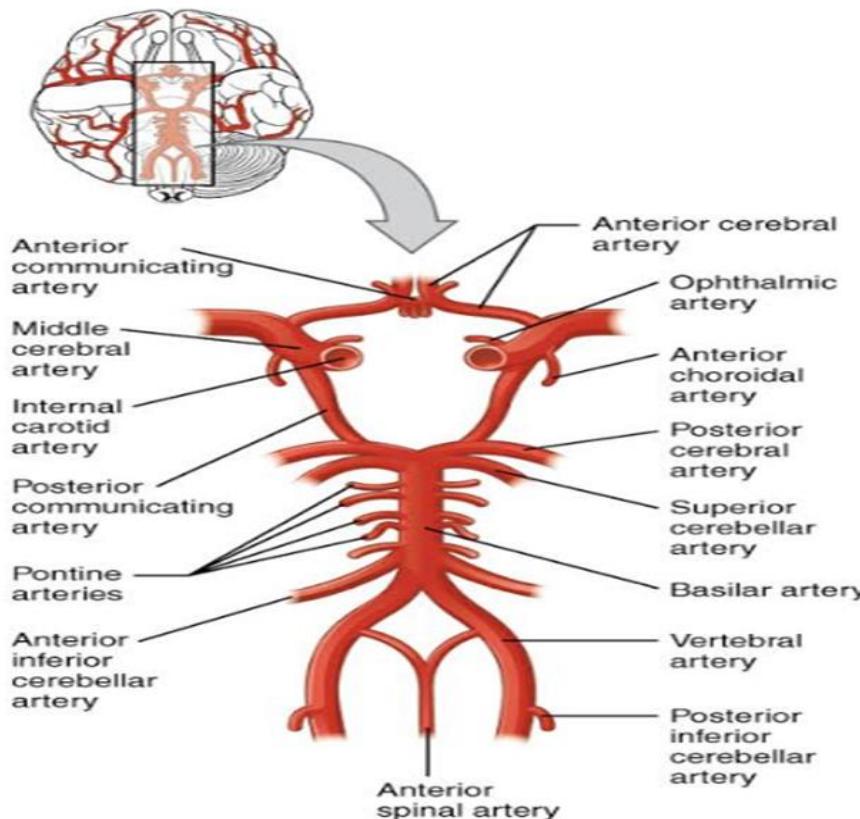
Features	Cerebral thrombosis	Cerebral embolism	Cerebral hemorrhage
<b>Onset</b>	Sudden , may be slow ( stroke in evolution )	Abrupt	Sudden, catastrophic
<b>Consciousness</b>	Preserved or slight confusion	Preserved, sometimes drowsy	Usually semiconscious or unconscious
<b>Headache</b>	Absent but occurs if cerebral edema develops	Absent	Severe, persistent
<b>Neurological deficit</b>	Slowly developing	Maximum at onset, followed by initiation of recovery	Rapidly developing and progressive
<b>Precipitating/ Predisposing condition</b>	HTN, DM, Dyslipidemia, Hypercoagulable state (pregnancy, puerperium, OCP), shock	Evidence of source of embolism; heart disease, aneurysm, thrombosis	Precipitated by stress, exertion, physical activity, sudden rise in BP, AVM
<b>Neck stiffness</b>	Absent	Absent	Present if bleed leaks into subarachnoid space
<b>Premonitory symptoms</b>	Maybe present in the form of TIA	Absent	Maybe present in the form of speech disturbance or attacks of weakness in the limb
<b>Recovery</b>	Slow, maybe partial or complete	Rapid, recovery is the rule	Slow, if patient recovers.

**N.B.** Patients and family members should be counselled to seek for emergency medical service immediately, if they experience or witness any of the following symptoms also known by acronym FAST

- Facial weakness
- Arm weakness
- Speech abnormality
- Time

## STROKES SYNDROMES

A careful history and neurologic examination can often localize the region of brain dysfunction; if this region corresponds to an arterial distribution, the possible causes responsible for the syndrome can be narrowed.



Arterial supply of the brain

Depending on which arterial territory is involved and the size of the lesion Stroke syndromes are divided into

## 1- LARGE VESSEL STROKE WITHIN ANTERIOR CIRCULATION

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- Can be occluded by
  - Intrinsic disease of the vessel (atherosclerosis or dissection)
  - Embolic occlusion from a proximal source
- **MCA (MIDDLE CEREBRAL ARTERY)** – when an entire MCA is occluded at its origin
  - Contralateral hemiplegia
  - Hemianesthesia
  - Homonymous hemianopia
  - Dysarthria
  - Global aphasia – if dominant hemisphere is involved
  - Anosognosia and Neglect – when non dominant hemisphere is affected
- **ACA (ANTERIOR CEREBRAL ARTERY)** –
  - Paralysis of opposite foot and leg
  - Lesser degree of paresis of opposite arm
  - Cortical sensory loss over toes, foot and leg
  - Urinary Incontinence
  - Contralateral grasp reflex, sucking reflex
  - Impairment of gait and stance
- **ANTERIOR CHOROIDAL ARTERY** – syndrome of its occlusion are
  - Contralateral hemiplegia
  - Hemi anesthesia &
  - Homonymous hemianopia

But since this territory is also supplied by other penetrating vessels, minimal deficit may occur and patients frequently recover substantially.

- **ICA (INTERNAL CAROTID ARTERY)** – clinical picture varies depending on whether the cause of ischemia is propagated thrombus, embolism or low flow.
- **COMMON CAROTID ARTERY** – all symptoms of ICA occlusion may also be present

## 2- LARGE VESSEL STROKE WITHIN POSTERIOR CIRCULATION

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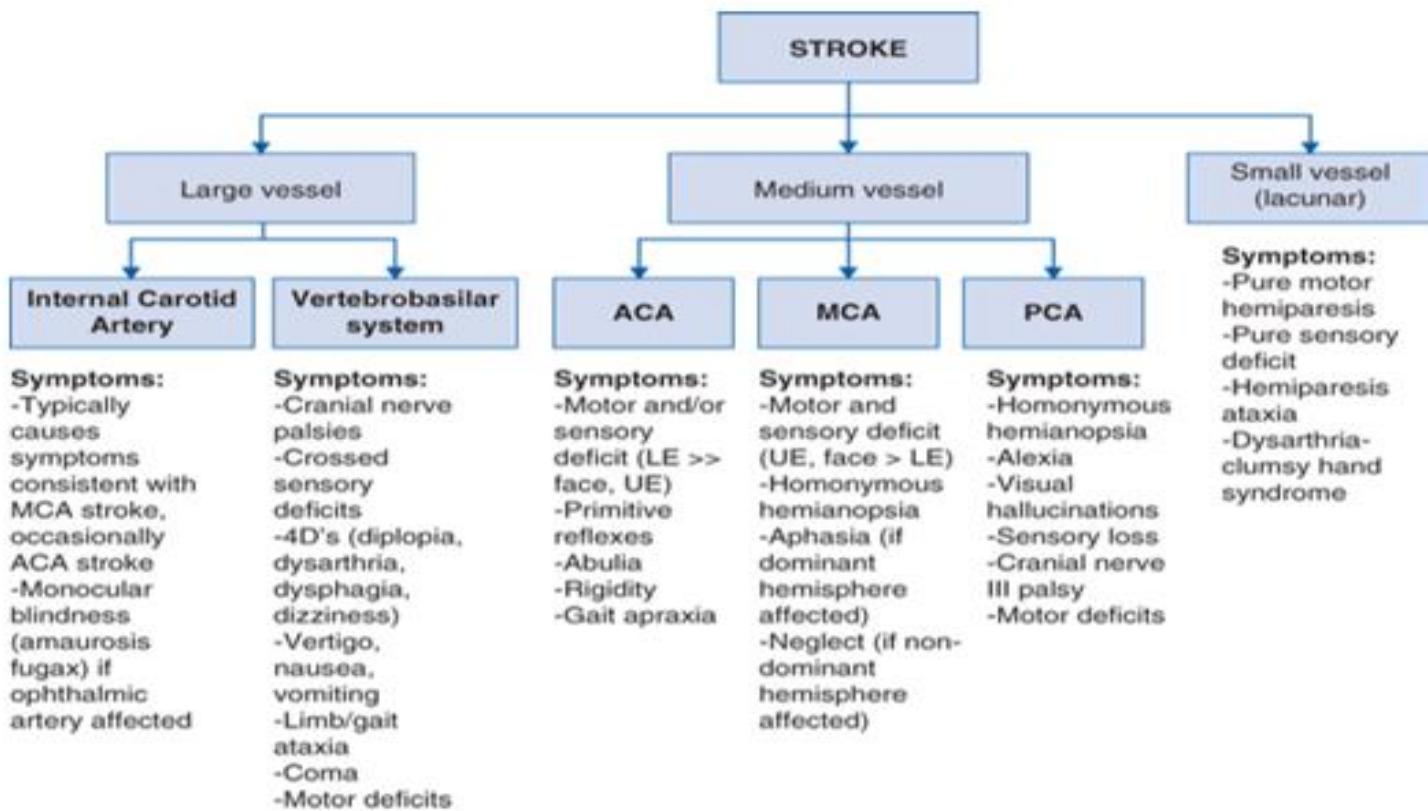
- **PCA (POSTERIOR CEREBRAL ARTERY)** - 2 clinical syndromes are commonly observed
  - **P1 syndrome** – because of disease of proximal P1 segment of PCA or its penetrating branches
    - Midbrain
    - Subthalamic &
    - Thalamic signs are seen

- **P2 syndrome** – because of occlusion of P2 segment distal to the junction of the PCA with post communicating artery
  - Cortical temporal &
  - Occipital lobe signs are seen
- **VERTEBRAL AND POSTERIOR INFERIOR CEREBELLAR ARTERIES (PICA)**
  - **Vertebral** – its 4<sup>th</sup> segment gives rise to branches that supply Brainstem and Cerebellum
    - Lateral Medullary syndrome (Wallenberg's) – embolic occlusion or thrombosis of 4<sup>th</sup> segment causing ischemia of lateral medulla.
  - **PICA** –
    - In its proximal segment supplies lateral medulla
    - In its distal branch Inferior surface of cerebellum
- **BASILAR ARTERY** – its branches supply the
  - Base of the pons &
  - Superior Cerebellum

### 3. SMALL VESSEL DISEASE OF EITHER VASCULAR BED

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- Accounts for 20% of all stroke
- **HTN** and **Age** are its principal risk factor.
- Most common small vessel syndromes are: -
  - Pure motor hemiparesis – infarct in the posterior limb of internal capsule or the pons.
  - Pure sensory stroke – infarct in ventral thalamus
  - Ataxic hemiparesis – infarct in the ventral pons or internal capsule
  - Dysarthria & clumsy hand/ arm- infarction in the ventral pons or in the genu of internal capsule.



### ICH - it is better to look at the clinical presentation for ICH separately

- For hemorrhagic stroke most of their clinical manifestations in each most common site are presented as the following
- The most common sites of hypertensive ICH are the **basal ganglia (especially the putamen)**, **thalamus**, **cerebellum**, and **pons**.

### THE PUTAMEN

- Contralateral hemiparesis is the sentinel sign.
- The face sags on one side over 5–30 min,
- Speech becomes slurred,
- The arm and leg gradually weaken,
- The eyes deviate away from the side of the hemiparesis.
- When haemorrhages are large,
  - Coma, accompanied by deep, irregular, or intermittent respiration,
  - A dilated and fixed ipsilateral pupil, and

- Decerebrate rigidity.
- In milder cases, edema in adjacent brain tissue may cause progressive deterioration over 12–72 h.

### THALAMIC HEMORRHAGES

- Contralateral hemiplegia or hemiparesis
- A prominent sensory deficit involving all modalities is usually present.
- Aphasia, often with preserved verbal repetition, (dominant thalamus) and constructional apraxia or mutism (non dominant hemorrhage.)
- There may also be a homonymous visual field defect.
- Thalamic hemorrhages cause several typical ocular disturbances by extension inferiorly into the upper midbrain. These includes
  - Deviation of the eyes downward and inward so that they appear to be looking at the nose,
  - unequal pupils with absence of light reaction,
  - skew deviation with the eye opposite the hemorrhage displaced downward and medially,
  - ipsilateral Horner's syndrome,
  - absence of convergence,
  - paralysis of vertical gaze, and retraction nystagmus.

### PONTINE HEMORRHAGES

- Deep coma with quadriplegia often occurs over a few minutes.
- prominent decerebrate rigidity
- “pinpoint” (1 mm) pupils that react to light.
- impairment of reflex horizontal eye movements evoked by head turning (doll'shead or oculocephalic maneuver) or by irrigation of the ears with ice water.
- Hyperpnea, severe hypertension, and hyperhidrosis
- Most patients with deep coma from pontine hemorrhage ultimately die or develop a locked-in state,

### CEREBELLAR HEMORRHAGES

- Usually develops after several hours
  - occipital headache,
  - repeated vomiting,
  - ataxia of gait.
  - forced deviation of the eyes to the opposite side

- an ipsilateral sixth nerve palsy.
- As the hours pass, the patient often becomes stuporous and then comatose from brainstem compression or obstructive hydrocephalus
- immediate surgical evacuation before severe brainstem compression occurs may be lifesaving

### **LOBAR HEMORRHAGE**

- The major neurologic deficit in each lobe include
- Occipital hemorrhage - hemianopsia;
- Left temporal haemorrhage - aphasia and delirium;
- Parietal haemorrhage - hemisensory loss; and
- Frontal haemorrhage - arm weakness.
- Large hemorrhages may be associated with stupor or coma if they compress the thalamus or midbrain.
- Most patients with lobar hemorrhages have focal headaches, and more than one-half vomit

### **HOW TO LOCALIZE THE LESION**

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#### **1. CORTICAL OR SUBCORTICAL (CORONA RADIATA)**

- Contralateral hemiplegia of uncrossed type
- Convulsion (Jacksonian) may occur
- Speech disturbance (aphasia): - if dominant hemisphere is involved
- Cortical sensory loss: - Such as,
  - Asterognosis (inability to identify an object by touch)
  - Loss of sense of position
  - Tactile localization
  - Two-point discrimination
- Aosognosia, ( failure to be aware of one's own defect or deficit )
- Visual field defect

#### **2. INTERNAL CAPSULAR LESION**

- Contralateral hemiplegia of uncrossed type
- Contralateral hemi anesthesia
- Dense hemiplegia

#### **NOTE**

Pure motor isolated dense hemiplegia affecting simultaneously the face, arm and leg indicates a lesion in the posterior Limb of internal capsule – **Lacunar Infarct**

### 3. MID BRAIN LESION

- Contralateral hemiplegia of crossed type
- Contralateral hemianesthesia and analgesia
- CN-3 nuclear paralysis with contralateral hemiplegia (weber's syndrome)

### 4. PONTINE LESION

- Contralateral hemiplegia of crossed type
- Contralateral hemianesthesia and analgesia
- Constriction of pupil (Horner's syndrome) on the same side of the lesion due to involvement of sympathetic fibres
- Deep coma with quadriplegia (most patients die or develop a locked in state)

### 5. MEDULLA OBLONGATA LESION

- Medial medullary syndrome
- Ipsilateral: - Paralysis of half of tongue (CN-12 palsy)
- Contralateral:
  - Upper and Lower limbs UMN paralysis sparing face
  - Impaired tactile and proprioceptive sensations
- Lateral medullary syndrome (Wallenberg's syndrome)
  - Ipsilateral: - Facial numbness, Ataxia, Nystagmus (cerebellar involvement), Horner's syndrome (Sympathetic involvement), CN 9 & 10 palsy
  - Contralateral: - spinothalamic (pain, touch, temperature) sensory loss, Hemiparesis

#### 1. Spinal cord (C1-C4) lesion: - Brown sequard syndrome

## INVESTIGATION

### DIAGNOSTIC

- **CT scan:**
  - initial Dx modality because of its rapidity and availability
  - Non contrast CT to identify or exclude hemorrhage as the cause of stroke
  - Scan obtained in the first several hours after an infarction generally show no abnormality and the infarct may not be seen reliably for 24-48 hours



Hemorrhagic lesion on CT (the white parenchymal lesion)

- **MRI** – offer superior imaging but may not identify acute hemorrhage and maybe false negative for small brain stem strokes within the first 3 hour.
  - MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface.
  - It also identifies intracranial hemorrhage and other abnormalities and, using special sequences, can be as sensitive as CT for detecting acute intracerebral hemorrhage.
- **Ultrasound** - Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity (“duplex” ultrasound).

### OTHER Ix (TO ASSESS THE RISK FACTORS)

- Echocardiography (cardiac lesions that can be cause of embolism)
- ECG (arrhythmias, evidence of recent MI)
- CBC, FBS, Lipid profile
- ESR, CRP, VDRL, ANA
- U/A, BUN, Creatinine
- PT, PTT & INR (to identify coagulopathy )
- PICT ( PITC)
- Factor V Leiden, protein C/S, anti-phospholipid Ab,
- Duplex U/S of carotid, MRA, CTA ( not common but used to identify the underlying vascular disease)

## **COMPLICATIONS**

- DVT & PE
- Pressure sore (bed sore)
- Respiratory infection (risk of aspiration)
- Epileptic seizure
- Urinary tract infection
- Depression and Anxiety

## **MANAGEMENT PRINCIPLE**

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### **GOAL OF TREATMENT**

- Minimizing the volume of brain that is irreversibly damaged
- Preventing complications
- Reducing the patient's disability and handicap through rehabilitation
- Reducing the risk of recurrent episodes

### **SUPPORTIVE CARE**

- Begin with ABC of life
- Airway - check that the patient can protect his/her airway and swallow without evidence of aspiration
- Breathing- check that the patient is breathing adequately (checking Oxygen saturation)
- Circulation- check peripheral perfusion, pulse and BP. (treat with fluid replacement, antiarrhythmic and inotropic drugs)
- Blood glucose- check blood glucose level and treat hypoglycemia or hyperglycemia
- Temperature- check for pyrexia and investigate and treat underlying cause. Give antipyretics since raised temperature increase infarct volume.
- Perform an emergency non contrast head CT scan to differentiate between ischemic stroke and hemorrhagic stroke.

- Hydration – check for signs of dehydration and give fluid
- Nutrition- assess nutritional status and provide nutritional supplement if necessary
- Pressure Areas- check pressure areas and introduce measures to reduce the risk of bed sore, turn immobile patients regularly, provide a pressure relieving mattress
- Incontinence- check for constipation and urinary retention and treat appropriately

## **ISCHEMIC STROKE**

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Treatments designed to reverse or lessen the amount of tissue infarction and improve clinical outcome fall within six categories:

- 1) Medical support,
- 2) IV thrombolysis,
- 3) Endovascular revascularization,
- 4) Antithrombotic treatment,
- 5) Neuroprotection, and
- 6) Stroke centers and rehabilitation.

### **MEDICAL SUPPORT**

- When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra.
- Because collateral blood flow within the ischemic brain may be blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely.
- Blood pressure should be reduced
  - if it exceeds 220/120 mmHg,
  - if there is malignant hypertension or
  - if there is concomitant myocardial ischemia,
  - if blood pressure is >185/110 mmHg and thrombolytic therapy is anticipated.
- When faced with the competing demands of myocardium and brain, lowering the heart rate with a  $\beta_1$ -adrenergic blocker (such as esmolol) can be a first step to decrease cardiac work and maintain blood pressure.
- Fever is detrimental and should be treated with antipyretics and surface cooling
- Serum glucose should be monitored and kept  $< 180$  mg/dL and above at least 60 mg/dL.
- Prevent the common complications of bedridden patients such as
  - (DVT) with pulmonary embolism and
  - Infections (pneumonia, urinary, and skin)
- IV mannitol may be used in some cases because 5 to 10% of patients develop enough cerebral edema to cause obtundation and brain herniation.

- Edema peaks on the second or third day but can cause mass effect for ~10 days. The larger the infarct, the greater the likelihood that clinically significant edema will develop.

#### IV THROMBOLYSIS

- Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke (AIS)

INDICATION	CONTRAINDICATION
<ul style="list-style-type: none"> <li>– Clinical diagnosis of stroke</li> <li>– Onset of symptoms to time of drug administration <math>\leq 4.5</math> hr</li> <li>– CT scan showing no hemorrhage or edema of <math>&gt;1/3</math> of the MCA territory</li> <li>– Age <math>\geq 18</math> years</li> </ul>	<ul style="list-style-type: none"> <li>– Sustained BP <math>&gt;185/110</math> mmHg despite treatment</li> <li>– Bleeding diathesis</li> <li>– Recent head injury or intracerebral hemorrhage</li> <li>– Major surgery in preceding 14 day</li> <li>– Gastrointestinal bleeding in preceding 21 days</li> <li>– Recent myocardial infarction</li> </ul>

#### ENDOVASCULAR REVASCULARIZATION

Endovascular mechanical thrombectomy has been studied as an alternative or adjunctive treatment of acute stroke in patients

- Who are ineligible for, or have contraindications to, thrombolytics or
- Who failed to achieve vascular recanalization with IV thrombolytics

#### ANTITHROMBOTIC TREATMENT

- **Platelet Inhibitors**
  - Aspirin is the only antiplatelet agent that has been proven to be effective for the acute treatment of ischemic stroke
  - There are several antiplatelet agents proven for the secondary prevention of stroke
- **Neuroprotection**
  - Neuroprotection is the concept of providing a treatment that prolongs the brain's tolerance to ischemia.
  - Hypothermia is a powerful neuroprotective treatment in patients with cardiac arrest and is neuroprotective in animal models of stroke, but it has not been adequately studied in patients with ischemic stroke and is associated with an increase in pneumonia rates that could adversely impact stroke outcomes.

#### STROKE CENTRE AND REHABILITATION

- Patient care in stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality.
- Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy

## PRIMARY AND SECONDARY PREVENTION OF STROKE AND TIA

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Identification and control of modifiable risk factors, and especially hypertension, is the best strategy to reduce the burden of stroke, and the total number of strokes could be reduced substantially by these means

### ATHEROSCLEROSIS RISK FACTORS

- Hypertension is the most significant of the risk factors; in general, all hypertension should be treated to a target of <130/80 mmHg.
- Several trials have confirmed that statin drugs reduce the risk of stroke even in patients without elevated LDL or low HDL.
- Therefore, a statin should be considered in all patients with prior ischemic stroke.
- Tobacco smoking should be discouraged in all patients
- Diabetes prevention is likely the most effective strategy for primary and secondary stroke prevention.

### ANTIPLATELET AGENTS FOR STROKE PREVENTION

- Aspirin, clopidogrel, the combination of aspirin plus extended-release dipyridamole, and recently ticagrelor are the antiplatelet agents most commonly used for this purpose.
- Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life threatening.

### ANTICOAGULATION THERAPY AND EMBOLIC STROKE PREVENTION

- Several trials have shown that anticoagulation (international normalized ratio [INR] range, 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe
- **Surgery for stroke due to carotid artery disease**

### In our setup

Antiplatelet – Aspirin 81-100 mg as early as possible (ideally within 48 hours of stroke onset)

- Alternative: Clopidogrel 75mg PO daily

High dose statin – Atorvastatin 80 mg PO daily

- Alternative: Rosuvastatin 40mg PO daily

Prophylactic anticoagulation- Unfractionated Heparin 5000 IU SC TID

- Alternative: Enoxaparin (LMWH) 40 mg SC daily

BP control – In general do not give antihypertensive medication in the 1<sup>st</sup> 24 hours unless there is an indication for acute control of BP

## ICH MANAGEMENT

- Approximately 40% of patients with a hypertensive ICH die, but survivors can have a good to complete recovery.
- The ICH Score is a validated clinical grading scale that is useful for stratification of mortality risk and clinical outcome.

**The ICH score (you can remember it with acronym HAGII)**

Clinical or Imaging factor	Point score
Hematoma Volume	
<30 cc	0
= 30cc	1
Age	
<80 years	0
= 80 years	1
GCS	
13-15	0
5-12	1
3-4	2
Intraventricular hemorrhage present	
No	0
Yes	1
Infra tentorial origin of hemorrhage	
No	0
Yes	1

- Thirty-day mortality rates increased steadily with ICH score. The mortality rates were
  - ICH score 1 – 13%

- ICH Score 2 – **26%**
- ICH Score 3 – **72%**
- ICH Score 4 – **97%**
- ICH Score 5 – **100%**

**N.B.** there are multiple clinical scoring systems developed other than ICH score to help approximate the risk of 30-day mortality or likelihood of good functional recovery for patients with acute ICH.

(e.g., FUNC score rates prognosis for good functional (neurologic) outcome at 90 days using an 11-point scale)

#### **ANY IDENTIFIED COAGULOPATHY SHOULD BE CORRECTED AS SOON AS POSSIBLE.**

- If the patient is on anticoagulant or an antiplatelet agent, stop the medications
- For patients taking vitamin K antagonists (VKAs), rapid correction of coagulopathy can be achieved by infusing prothrombin complex concentrates (PCCs), which can be administered quickly, with vitamin K administered concurrently.
- Fresh frozen plasma (FFP) is an alternative.

#### **BP REDUCTION**

- Elevated BP increases ICP and can cause further bleeding. However, hypotension can lower cerebral blood flow, worsening the neurologic deficits. Therefore, BP reduction must be gradual.
- BP reduction is indicated if systolic BP>180 or the MAP > 130
  - Labetalol: IV bolus
    - Initial dose of 10 to 20 mg IV push over 2 minutes, until target is achieved give double the initial dose in 15 minutes (max dose 80 mg/dose )
    - Total maximum dose 300mg

#### **ELEVATED ICP**

- Initial management includes elevating the head of the bed to 30 degrees and appropriate sedation and pain control
- Mannitol (20% solution ) is often used
  - Initial dose 1g/kg/dose, subsequent doses 0.25 to 5g/kg/dose every 6 to 8 hours
  - Administer over 30 to 60 minutes, inspect for crystals prior to administration and if crystals are present, re dissolve by warming the solution

#### **OTHER DIFFERENTIALS**

##### **1. TRAUMATIC DISORDER**

- **HEMIPLEGIA BECAUSE OF CHRONIC SUBDURAL HEMATOMA**
  - Patient have history of injury or fall
  - Patient may have underlying liver disease, bleeding diathesis or maybe on anticoagulant
  - Slow or chronic onset (with fluctuating headache, confusion, seizure, personality changes etc.)
  - There may be lucid interval (weeks, months or more than a year) between the injury and onset of symptoms
  - Sn & Sx of ↑ ICP headache, vomiting, bradycardia,...)
  - Hemiplegia is uncrossed due to compression effect on pyramidal tracts
- **CERVICAL TRAUMA** – if it is unilateral

## 2. BRAIN TUMORS

Cerebral Tumors present with focal neurologic deficit with **slow onset and progressively**.

**N.B** Hemorrhage into a Tumor can present like an **acute stroke**.

The most common **metastatic tumors** associated with **ICH** are:-

- Choriocarcinoma
- Malignant melanoma
- Renal Cell Ca
- Bronchogenic Ca

In addition,

- Glioblastoma multiforme in adults &
- Medulloblastoma in children may also have areas of ICH.

**Brain Tumors Can present with** general or nonspecific symptoms like

- Headache: - classic brain tumor headache predominates in the morning and improves during the day
- Cognitive difficulties
- Personality changes (apathy, withdrawal from social situation)
- Focal or lateralizing findings like
  - Hemiparesis
  - Aphasia
  - Visual defect
- Seizure
- Sn & Sx of ↑ ICP (headache, vomiting, bradycardia,..)

## INVESTIGATION

- MRI – is the preferred Diagnostic test
- CT - for those patients who can't undergo MRI

## 3. MIGRAINE

**ACEPHALGIC MIGRAINE:** - when migraine develops without head pain

- **How to identify?**
  - Prominent sensory disturbance
  - Migrate slowly across a limb over a minute rather than seconds as with stroke
  - Cortical disturbance cross vascular boundaries
  - Scintillating scotomata – classic visual symptom

## 4. INFECTIVE DISORDERS

### i. BRAIN ABSCESS: -

→ Discussed below

- ii. **TUBERCULOSIS** (for TB in detail refer under cough portion)
- CNS TB It could be either: - TB meningitis or Intracranial Tuberculoma
- **TB Meningitis** – present with a subacute febrile illness With **3 Clinical stages**
  - **Stage 1 (Prodromal Phase)** –
    - Patient are lucid with no focal neurologic signs or evidence of hydrocephalus
    - Fever, headache, and nonspecific malaise
  - **Stage 2 (Meningitic phase)** –
    - Worsening headache, nausea, vomiting and early signs of meningismus
    - Patient exhibit lethargy, confusion and may have mild focal signs ( i.e CN palsies or hemiparesis)
  - **Stage 3 (Paralytic phase)** –
    - Advanced illness with delirium, stupor, coma, seizure, multiple CN palsies and/or dense hemiplegia

### Investigation

- LP
- Radiography (CT/MRI)
- **Tuberculomas** – are granulomatous foci within brain parenchyma
- **Present with:** -
  - Seizure

- Headache
- Hemiplegia
- Signs if increased ICP

### Investigation

- CT – on contrast CT
  - early stage lesions: - low density or Isodense
  - Later stage lesion: - well encapsulated, isodense or hyperdense and have peripheral ring enhancement.

#### iii. **SYPHILIS (NEURO SYPHILIS):** - Two types

- **Asymptomatic** – diagnosis is made in patients who lack neurologic Sn & Sx but who have CSF abnormalities (i.e mononuclear pleocytosis, increased protein, VDRL reactive)
- **Symptomatic** – 3 major clinical categories
  - **Meningeal** – headache, CN involvement, N&V, Seizure, Neck stiffness, Change in mental status
  - **Meningovascular** – stroke syndrome involving MCA is the most Common presentation following prodrome of
    - Headache
    - Vertigo
    - Insomnia and
    - Psychological abnormalities
  - **Parenchymatous syphilis** (i.e General paresis and Tabes dorsalis)

## 5. METABOLIC ENCEPHALOPATHIES

### NOTE

In setting of prior stroke or brain injury, a patient with fever or sepsis may manifest a recurrent hemiparesis, which clears rapidly when the infection is treated.

## BRAIN ABSCESS

- Is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule.
- A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~0.3–1.3: 100,000 persons per year

## RISK FACTORS

- Otitis media and mastoiditis,
- Paranasal sinusitis,
- Pyogenic infections in the chest or other body sites,
- Penetrating head trauma or neurosurgical procedures, and
- Dental infections.

## ETIOLOGY

- In immunocompetent individuals the most important pathogens are
  - Streptococcus spp. (anaerobic, aerobic, and viridans [40%]),
  - Enterobacteriaceae (Proteus spp., Escherichia coli sp., Klebsiella spp. [25%]),
  - anaerobes (e.g., Bacteroides spp., Fusobacterium spp. [30%]), and
  - staphylococci (10%)
- In immunocompromised hosts (HIV infection, organ transplantation, cancer, or immunosuppressive therapy),
  - Nocardia spp.,
  - Toxoplasma gondii,
  - Aspergillus spp.,
  - Candida spp., and
  - neoformans.
- A brain abscess may develop
  - By direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection;
  - Following head trauma or a neurosurgical procedure; or
  - As a result of hematogenous spread from a remote site of infection.
- In up to 25% of cases, no obvious primary source of infection is apparent (**cryptogenic brain abscess**).
- Hematogenous abscesses account for ~25% of brain abscesses.
- Hematogenous abscesses are often multiple, and multiple abscesses often (50%) have a hematogenous origin.

## CLINICAL MANIFESTATION

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- The classic clinical triad is present in <50% of cases
  - Headache,
  - Fever, and
  - A focal neurologic deficit
- Headache is the most common symptom ( >75%)
  - It is often characterized as a constant, dull, aching sensation, either hemicranial or generalized
  - It becomes progressively more severe and refractory to therapy.
- Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis.
- The new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients.
- Focal neurologic deficits are the initial presentation in >60% of patients.
  - hemiparesis,
  - aphasia, or
  - visual field defects
- The clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of the intracranial pressure (ICP).
  - Frontal lobe abscess – hemiparesis (mc presentation)
  - Temporal lobe abscess - disturbance of language (dysphasia) or an upper homonymous quadrantanopia.
  - Cerebellar abscess - Nystagmus and ataxia
- Signs of raised ICP— can be the dominant presentation of some abscesses, particularly those in the cerebellum.
  - papilledema,
  - nausea and vomiting, and
  - drowsiness or confusion

## DIAGNOSIS

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- Is made by neuroimaging studies.
- MRI is better than CT for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa.
- On a contrast-enhanced CT scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement with surrounding edema (hypodensity).

- The distinction between a brain abscess and other focal CNS lesions such as primary or metastatic tumors may be facilitated by the use of diffusion-weighted imaging sequences on which a brain abscess typically shows increased signal due to restricted diffusion of the abscess cavity with corresponding low signal on apparent diffusion coefficient images.
- Microbiologic diagnosis of the etiologic agent is most accurately determined by Gram's stain and culture of abscess material obtained by CT-guided stereotactic needle aspiration.
- Lumbar puncture (LP) should not be performed in patients with known or suspected focal intracranial infections such as abscess or empyema; cerebrospinal fluid (CSF) analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.
- Additional laboratory studies may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion.
  - Peripheral leukocytosis, - in about 50% of patients
  - elevated ESR – in 60% of patients
  - elevated CRP - 80% of patients
  - Blood cultures are positive in ~10% of cases overall but may be positive in >85% of patients with abscesses due to Listeria.

#### **DDX**

- subdural empyema,
  - bacterial meningitis,
  - viral meningoencephalitis,
  - superior sagittal sinus thrombosis, and
  - acute disseminated encephalomyelitis
-

## MANAGEMENT

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- Optimal therapy of brain abscesses involves a combination of
  - high-dose parenteral antibiotics and
  - neurosurgical drainage.

**MEDICAL THERAPY** alone is not optimal for treatment of brain abscess and should be reserved for patients

- whose abscesses are neurosurgically inaccessible,
- patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and
- patients whose condition is too tenuous to allow performance of a neurosurgical procedure.
- All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy.
- Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes
  - A third- or fourth generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and
    - Ceftazidime, cefepime, or meropenem should be used when brain abscess complicates a neurosurgical procedure or in cases in which *Pseudomonas aeruginosa* is suspected.
  - Metronidazole – readily penetrates brain abscess and excellent bactericidal activity against anaerobes
  - Vancomycin – should be included until culture and susceptibility results are available when brain abscess follows penetrating head trauma or craniotomy or when *S.aureus* bacteraemia is documented.
- Empirical antibiotic coverage should be modified based on the results of Gram's stain and culture of the abscess contents.

**SURGERY-** most patients require surgical drainage in addition to antibiotics for both diagnostic and therapeutic purposes.

- In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures.
- Corticosteroids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP.

- Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

### **PROGNOSIS**

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- In modern series, the mortality rate is typically <15%.
- The mortality rate of brain abscess has declined in parallel with the development of enhanced neuroimaging techniques, improved neurosurgical procedures for stereotactic aspiration, and improved antibiotics.
- Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% of survivors

## BACTERIAL MENINGITIS

- Meningitis is an inflammatory disease of the leptomeninges (tissue surrounding the brain and spinal cord )
- Bacterial meningitis is an acute purulent infection within the subarachnoid space (SAS)
- The meninges, SAS, and brain parenchyma are all frequently involved in the inflammatory reaction (meningoencephalitis).
- The organisms most often responsible for community-acquired bacterial meningitis are
  - Streptococcus pneumoniae (~50%),
  - Neisseria meningitidis (~25%),
  - group B streptococci (~15%), and
  - Listeria monocytogenes (~10%). (In people >50 years and those who have deficiencies in cell mediated immunity)
  - Haemophilus influenzae type b accounts for <10% of cases
- The major cause of health care associated ventriculitis and meningitis are usually staphylococci and aerobic gram negative bacilli which occurs more commonly after neurosurgical procedure

## ETIOLOGY

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### S. PNEUMONIAE

- Is the most common cause of meningitis in adults >20 years of age,
- Predisposing conditions include
  - pneumococcal pneumonia (the most important)
  - acute or chronic pneumococcal sinusitis or otitis media,
  - alcoholism,
  - diabetes,
  - splenectomy,
  - hypogammaglobulinemia,
  - complement deficiency, and
  - head trauma with basilar skull fracture and cerebrospinal fluid (CSF) rhinorrhea
- The mortality rate remains ~20% despite antibiotic therapy.

### N. MENINGITIDES

- The incidence has decreased with the routine immunization
- N. meningitidis is the causative organism of recurring epidemics of meningitis every 8–12 years.
- Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease.

### **GRAM-NEGATIVE BACILLI**

- In individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with urinary tract infections.
- It can also complicate neurosurgical procedures, particularly craniotomy, and head trauma associated with CSF rhinorrhea or otorrhea.

### **L. MONOCYTOGENES**

- Is an increasingly important cause of meningitis in
  - neonates (<1 month of age),
  - pregnant women,
  - individuals >60 years, and
  - immunocompromised individuals of all ages.

### **H. INFLUENZAE TYPE B (HIB)**

- The frequency in children has declined dramatically since the introduction of the Hib conjugate vaccine.

## **CLINICAL PRESENTATION**

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- Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days.

### **SYMPTOMS**

- The classic clinical triad of meningitis is (occur in >80%)
  - fever,
  - headache, and
  - nuchal rigidity.
- A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma.
- Other common presentations are
  - Nausea,
  - vomiting, and
  - Photophobia
  - Abnormal body movement

### **SIGNS**

- Nuchal rigidity (“stiff neck”)
  - is the pathognomonic sign of meningeal irritation

- is present when the neck resists passive flexion.
- Kernig's sign
  - is elicited with the patient in the supine position.
  - The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present.
- Brudzinski's sign
  - is elicited with the patient in the supine position
  - is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees.
- Jolt accentuation of headache
  - Is a recent and less well recognized physical examination
  - Involves making the headache worse by rotating the head horizontally two or three times per second.
- Signs of increased ICP
  - Cushing reflex (bradycardia, hypertension, and irregular respirations
  - a deteriorating or reduced level of consciousness,
  - papilledema,
  - dilated poorly reactive pupils,
  - sixth nerve palsies,
  - decerebrate posturing
- The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection.

## **DIAGNOSIS**

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- When bacterial meningitis is suspected, blood cultures should be immediately obtained
- Diagnosis is made by CSF examination
- The need to obtain neuroimaging studies (CT or MRI) prior to lumbar puncture (LP) in order to exclude a mass lesion or increased ICP requires clinical judgment
- Indications to perform head CT before LP includes
  - Immunocompromised state (e.g. HIV, immunosuppressive therapy..)
  - History of CNS disease (mass lesion, stroke, or focal infection)
  - New onset seizure (within one week of presentation)
  - Papilledema
  - Abnormal level of consciousness
  - Focal neurologic deficit

*Table on CSF abnormalities in bacterial meningitis*

<b>Opening pressure</b>	>180mmhg
<b>CSF glucose</b>	<40 mg/dl
<b>CSF to serum glc ratio</b>	<=0.4
<b>CSF protein</b>	>200 mg/dl
<b>WBC count</b>	>100 cells with neutrophil predominance
<b>Gram stain</b>	Positive in > 60%
<b>Culture</b>	Positive in > 80%

## TREATMENT

- Bacterial meningitis is a medical emergency.
- The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room.
- Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known

## ANTIBIOTIC REGIMENS

In immunocompetent individuals

- Ceftriaxone 2g IV Q 12 hours
  - Or
- Cefotaxime (where available) 2g IV Q 4-6 hours
  - PLUS
- Vancomycin 15 to 20 mg/kg IV Q 8 to 12 hours
  - PLUS
- Ampicillin 2g IV Q 4 hour In adults >50 years of age

## NEUROLOGIC COMPLICATION

- Impaired mental status
- Increased ICP and cerebral edema
- Seizures
- Focal neurologic deficit
- Cerebrovascular abnormalities
- Sensorineural hearing loss
- Intellectual impairment

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3. UpToDate, Shefner JM (Ed), UpToDate, Waltham, MA. (Accessed on June 23, 2022.)
4. Standard treatment guideline for general hospital, 2020, Ethiopia

# CHAPTER TEN

## Physical Examination and Discussion

Respiratory system

Cardiovascular system

Abdominal examination

Motor examination

### RESPIRATORY SYSTEM PHYSICAL EXAMINATION

Dear reader, especially those starting clinical year, to ease understanding and grasp of each physical examination parts presented in three categories first of all you have to

- ↳ know components; Then how to do; steps and techniques of doing; which is presented under techniques, and interpretation of your finding which is presented under discussion.

### COMPONENTS OF RESPIRATORY SYSTEM EXAMINATION

#### GENERAL ASSESSMENT,

- Respiratory Rate, rhythm (regular, irregular),
- Depth; Is it shallow or deep breathing),
- Clubbing of fingers,

#### INSPECTION

- Symmetry of chest shape,
- Any scar on chest,
- Fracture (flail chest),
- Deformity,
- Noisy breathing (audible wheeze- expiratory; stridor- inspiratory), cyanosis,
- Signs of **Respiratory Distress:** -
  - Nasal flaring,
  - Use of accessory muscles in the neck,
  - SC/IC retractions

#### PALPATION

- Tenderness,
- Tactile fremitus
- Position of trachea,

- Degree of chest expansion,
- Chest lag,
- Subcutaneous emphysema,
- Palpable crepitation (as in pneumonia, rib fracture)

### PERCUSSION

- Abnormal percussion notes (dull, flat, or hyperresonant as in pneumothorax),
- diaphragmatic excursion

### AUSCULTATION

- Vesicular breath sounds
- other character of breath sounds (broncho-vesicular, bronchial),
- Added sounds (rhonchi, crepitation, expiratory wheeze, inspiratory stridor, pleural friction rub),
- Vocal resonance, **egophony**, whispered **pectoriloque**

#### NOTE

Keep this format in mind which easily approach and enables you to memorize easily.  
This format also used while reporting respiratory system physical examination.

### TECHNIQUES OF RESPIRATORY SYSTEM EXAMINATION

Dear reader, techniques of examination of respiratory system have been discussed into following category.

- General Assessment
- Anterior Chest
- Posterior Chest

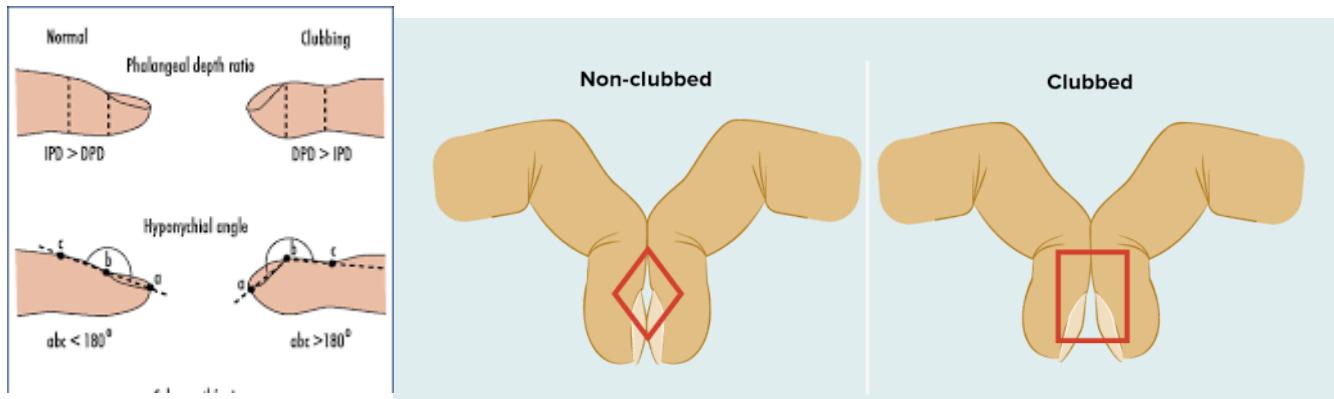
#### NOTE

Each category examination of respiratory system; General Assessment, Anterior Chest Posterior Chest is done distinctly **But**, put whole together in the **respective component**, while reporting respiratory system physical examination findings, as mentioned in the component part.

## TECHNIQUES OF EXAMINATION GENERAL ASSESSMENT

### RESPIRATORY RATE

- Observe the **rate, rhythm, depth, and effort of breathing.**
- Count the number of respirations in 1 minute either by **visual inspection or by subtly listening over the patient's trachea with your stethoscope** during your examination of the head and neck or chest.
- Cyanosis
  - Look for the presence of cyanosis at lips and tongue
- Clubbing
  - When the distal **phalanges** of corresponding fingers of opposite hands are directly **opposed** (place fingernails of same finger on opposite hands against each other, nail to nail),
  - A small **diamond-shaped "window"** is normally apparent between the nailbeds.
  - If this window is obliterated, the test is positive and clubbing is present.



## TECHNIQUES OF EXAMINATION ANTERIOR CHEST

### Prerequisite Before Starting

- Introduce yourself to the patient get permission
- Position of patient: -patient should lying in semirecumbent on bed with arms sufficiently abducted to allow access to axillary region.
- **Exposure:** - expose patient fully from chest until umbilicus
- Start examination from inspection, palpation, percussion and auscultation

### INSPECTION

- Observe the **shape of the patient's chest and the movement of the chest wall.**
- **Note**
  - Deformities or asymmetry
  - Abnormal retraction of the lower interspaces during inspiration.

- Local lag or impairment in respiratory movement

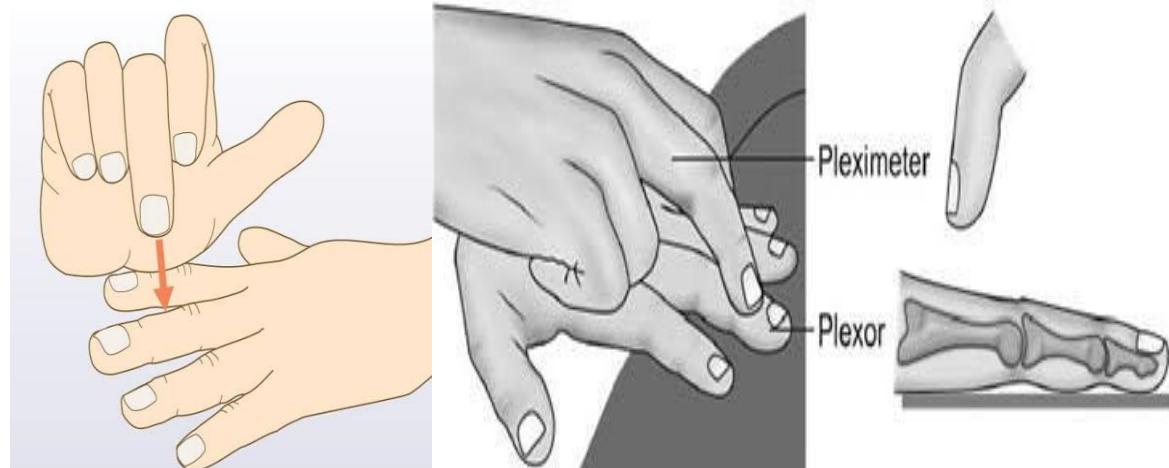
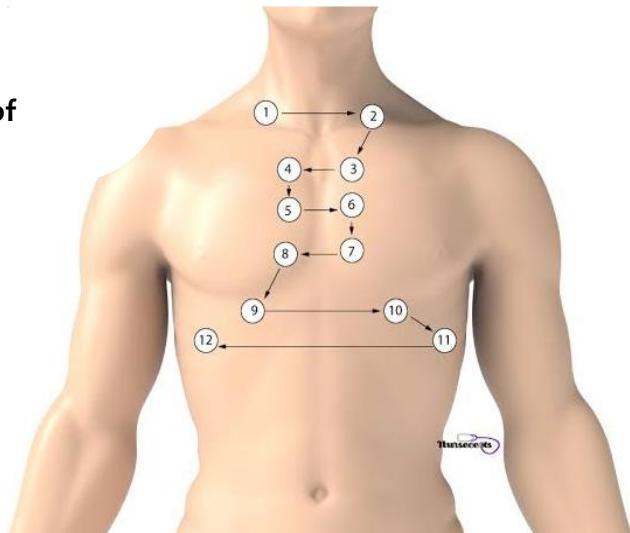
## PALPATION

Palpation has four potential uses:

- a. Identification of tender area
- b. Assessment of observed abnormalities
- c. Trachea: - Assess position of the trachea
  - ⇒ Feel for the trachea by putting the **2nd and 4th fingers** on each edge of sternal notch and **use the 3rd finger** to assess the trachea is central or deviated to one side
    - A slight deviation of the trachea to the right side may be found in healthy individuals
  - ⇒ Assess for the presence of **tracheal tug** in air way obstruction
    - A tracheal tug is demonstrated when the finger resting on the trachea feels it move in interiorly with each inspiration.
    - It is a sign of gross over expansion of the chest because of air way obstruction
- d. **Further assessment of chest expansion.**
  - Place your thumbs along each costal margin, your hands along the lateral rib cage.
  - As you position your hands, slide them medially a bit to raise loose skin folds between your thumbs.
  - Ask the patient to inhale deeply.
  - Observe how far your thumbs diverge as the thorax expands, and
  - feel for the extent and symmetry of respiratory movement
- e. **Tactile fremitus**
  - Assessment of tactile fremitus. Compare both sides of the chest, using the **ball or ulnar surface of your hand**.
    - Fremitus is usually **decreased or absent over the precordium**.
  - When examining a woman, gently displace the breasts as necessary.
- f. **Apical Beat**
  - see under **Cardiovascular examinations**.
    - In certain condition also considered in Respiratory System. For example, COPD patient

## PERCUSSION

- Percuss the anterior and lateral chest, again comparing both sides.
- **The heart normally produces an area of dullness to the left of the sternum from the 3<sup>rd</sup> to the 5<sup>th</sup> interspaces.**
- Percuss the **left lung lateral** to the area of dullness.
- In a woman, to enhance percussion, gently displace the breast with your left hand while percussing with the right.



## AUSCULTATION

- Listen to the chest **anteriorly and laterally** as the patient breathes with mouth open, and somewhat more deeply than normal.
- Compare symmetric areas of the lungs, **using the pattern suggested for percussion and extending it to adjacent areas if indicated.**
- Listen to the breath sounds, noting their intensity and identifying any variations from normal vesicular breathing.
- Identify any added sounds, time them in the respiratory cycle, and locate them on the chest wall. Do they clear with deep breathing?
- If indicated, **listen for transmitted voice sounds.**

## TECHNIQUES OF EXAMINATION POSTERIOR CHEST

### Prerequisite Before Starting

- Introduce yourself to the patient get permission
- **Position of patient:** -patient sitting **upright** with arms folded across chest.
- **Exposure:** - expose patient fully the trunk
- Proceed your physical examination as following:

### INSPECTION

- From a midline position behind the patient, note the shape of the chest and how the chest moves, including:
- Deformities or asymmetry in chest expansion
- Abnormal retraction of the interspaces during inspiration.
  - **Retraction is most apparent in the lower interspaces**
- Impaired respiratory movement on one or both sides or a unilateral lag (or delay) in movement.

### PALPATION

- As you palpate the chest, focus on areas of tenderness and abnormalities in the overlying skin, respiratory expansion, and fremitus.
  - a. **Identify tender areas.** Carefully palpate any area where pain has been reported or where lesions or bruises are evident.
  - b. Assess *any visible abnormalities* such as
    - masses or sinus tracts (blind, inflammatory, tubelike structures opening onto the skin)
  - c. Chest Expansion
    - Place your thumbs at **about the level of the 10th ribs**, with your fingers loosely grasping and parallel to the lateralrib cage.
    - slide them medially just enough to raise a loose fold of skin on each side between your thumb and the spine, As you position your hands
    - Ask the patient to **inhale deeply**,
    - Watch the distance between your thumbs as they move apart during inspiration,
    - feel for the range and symmetry of the rib cage as it expands and contracts. This is sometimes termed lung excursion.

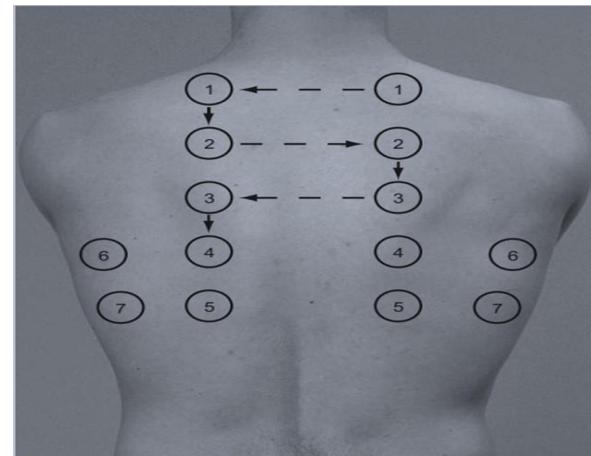
d. Feel for tactile fremitus.

- To detect fremitus, use either the or **the ulnar surface of your hand** /to optimize the vibratory sensitivity of the bones in your hand./
- Ask the patient to repeat the words “**Torbaatamii Torba**” (in Afaan Oromoo), “**Arba Arat**” (in Amharic), “ninety-nine” or “one-one-one.”
- If fremitus is faint, ask the patient to speak more loudly or in a deeper voice.
- *Palpate and compare symmetric areas of the lungs in the pattern shown in the photograph.*
- Identify and locate any areas of **increased, decreased, or absent** fremitus.

## PERCUSSION

### Percussion Note

- Hyperextend the middle finger of your left hand, known as the **pleximeter finger**.
- Press its distal **interphalangeal** joint firmly on the surface to be percussed.
- Position your right forearm quite close to the surface, with the hand cocked upward. The middle finger should be partially flexed, relaxed, and poised to strike
- With a *quick, sharp but relaxed wrist motion*, strike the pleximeter finger **with the right middle finger, or plexor finger. Aim at your distal interphalangeal joint.**
- Strike using the tip of the plexor finger, not the finger pad.
- Your finger should be almost at right angles to the pleximeter.
- A short fingernail is recommended to avoid injuring your knuckle.
- Withdraw your striking finger quickly to avoid damping the vibrations you have created.
- Percuss one side of the chest and then the other at each level in a ladder like pattern, as shown by the numbers below. See Fig. below



### Diaphragmatic Excursion

- First, determine the level of diaphragmatic dullness during quiet respiration.
- Holding the pleximeter finger *above and parallel* to the expected level of dullness, percuss downward in progressive steps until dullness clearly replaces resonance.
- **Confirm** this level of change by percussion near the middle of the hemothorax and also more laterally

### AUSCULTATION

- Listen to the breath sounds with the diaphragm of a stethoscope after **instructing the patient to breathe deeply through an open mouth**.
- Use the ladder pattern suggested for percussion, moving from one side to the other and comparing symmetric areas of the lungs.
- If you hear or suspect abnormal sounds, auscultate adjacent areas to assess the extent of any abnormality.
- Listen to **at least one full breath** in each location.
  - **If the patient becomes light-headed from hyperventilation, allow the patient to take a few normal breathes.**

Listen for any added, or adventitious, sounds that are superimposed on the usual breath sounds.

- If you hear crackles, especially those that do not clear after coughing, listen carefully for the characterize.
- If you hear wheezes or rhonchi, **note their timing and location**.
- If you **hear** abnormally located **bronchovesicular or bronchial breath sounds, assess transmitted voice sounds**. With a stethoscope, listen in symmetric areas over the chest wall

## RESPIRATORY SYSTEM EXAMINATION DISCUSSION

### GENERAL ASSESSMENT

- Respiratory Rate
  - Normally, adults take approximately 20 breaths per minute in a quiet, regular pattern. An occasional sigh is normal.
  - Check to see if expiration is prolonged, **Prolonged expiration is common in COPD.**
- Cyanosis
  - **Cyanosis** is referred as bluish discoloration of the skin and mucus membrane resulting from an increased quantity of deoxygenated hemoglobin (reduced oxygen saturation)
  - Cyanosis becomes evident when the absolute concentration of deoxygenated hemoglobin is  $\geq 5\text{ gm/dl}$  of capillary blood.
  - Cyanosis is usually obvious when the arterial oxygen saturation falls below 90% in a person with a normal hemoglobin level
  - In patients with anemia, cyanosis doesn't occur until even greater levels of arterial desaturation is reached
  - **Central cyanosis:** bluish discoloration of lips and tongue due to hypoxia
  - **Peripheral cyanosis (acrocyanosis):** bluish discoloration of the distal parts of extremities due to vasoconstriction.

Causes of Cyanosis	
Central Cyanosis	Peripheral Cyanosis
<ul style="list-style-type: none"> <li>● <b>Decreased arterial oxygen saturation</b> <ul style="list-style-type: none"> <li>a. Decreased atmospheric pressure—high altitude</li> <li>b. Impaired pulmonary function                             <ul style="list-style-type: none"> <li>➢ Alveolar hypoventilation</li> <li>➢ Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)</li> <li>➢ Impaired oxygen diffusion</li> </ul> </li> </ul> </li> <li>⌚ Anatomic shunts             <ul style="list-style-type: none"> <li>▪ Certain types of congenital heart disease</li> <li>▪ Pulmonary arteriovenous fistulas</li> <li>▪ Multiple small intrapulmonary shunts</li> </ul> </li> <li>⌚ Hemoglobin with low affinity for oxygen</li> </ul>	<ul style="list-style-type: none"> <li>● Reduced cardiac output</li> <li>● Cold exposure</li> <li>● Redistribution of blood flow from extremities</li> <li>● Arterial obstruction</li> <li>● Venous obstruction</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Hemoglobin abnormalities</b> <ul style="list-style-type: none"> <li>⌚ Methemoglobinemia—hereditary, acquired</li> <li>⌚ Sulfhemoglobinemia—acquired</li> <li>⌚ Carboxyhemoglobinemia (not true cyanosis)</li> </ul> </li> </ul>	

- **Clubbing**

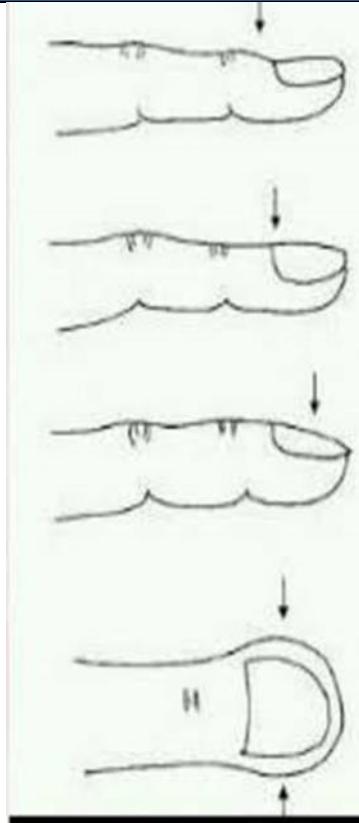
- The selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface.
- Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders

<b>Causes of finger clubbing</b>	
Respiratory system	<ol style="list-style-type: none"> <li>1. Lung cancer</li> <li>2. Lung abscess</li> <li>3. Bronchiectasis</li> <li>4. Pulmonary fibrosis</li> <li>5. LIP (Lymphoid Interstitial Pneumonitis)</li> <li>6. PCP (Pneumocystis Carinii Pneumonia)</li> <li>7. COPD</li> </ol>
CVS	<ol style="list-style-type: none"> <li>1. Cyanotic CHD (congenital heart disease)</li> <li>2. IE (infective endocarditis)</li> </ol>
GIS	<ol style="list-style-type: none"> <li>1. Celiac disease</li> <li>2. Crohn's disease</li> <li>3. Cirrhosis (liver)</li> <li>4. Cystic fibrosis</li> </ol>
*CVS ; Cardiovascular System , GIS; Gastrointestinal system	

- In some instances, it is occupational, for example, **in jackhammer operators**.
- Clubbing in patients with primary and metastatic lung cancer, mesothelioma, bronchiectasis, or hepatic cirrhosis may be associated with hypertrophic osteoarthropathy.
- Although the mechanism of clubbing is unclear, it appears to be secondary to humoral substances that cause dilation of the vessels of the distal digits as well as growth factors released from platelet precursors in the digital circulation.
- In certain circumstances, clubbing is reversible, such as following lung transplantation for cystic fibrosis.

❖ Clubbing Grades

Clubbing grades	
Grade	Description
1	Nail bed fluctuation (softening)
2	Obliteration of the Lovibond's angle (normal angle $160^\circ$ increased to $\geq 180^\circ$ )
3	Increased convexity of the nail fold
4	Thickening of the whole <u>distal</u> (end part of the) finger (resembling a drumstick) Hypertrophic Osteoarthropathy (HOA)



**INSPECTION**

- Signs of respiratory distress:
  - Flaring of ala-nasae
  - Intercostal retraction
  - Subcostal retraction
  - The use of accessory muscles in the neck
- Shape of the chest:
  - The normal chest is bilaterally symmetrical and elliptical incross-section.
  - Diseases of the ribs, spinal vertebra or lungs can distort the shape of the chest. These chest deformities can lead to asymmetry of the chest and may significantly restrict lung movement.

- **Types of abnormal chest shape**
  - ⇒ **Barrel chest:** Increased antero-posterior diameter of the chest in comparison to lateral diameter of the chest (Thoracic ratio: A-P diameter/Lateral diameter > 0.9), often seen in emphysema, chronic asthma, and accompanies normal aging
  - ⇒ **Funnel chest (Pectus excavatum):** Depression in the lower end of the sternum
  - ⇒ **Pigeon chest (Pectus carinatum):** Anteriorly displaced sternum with depressed costal cartilage
  - ⇒ **Harrison's sulcus:** Linear depression of the lower ribs just above the costal margins at the site of attachment of the diaphragm, often seen in rickets and severe childhood asthma
  - ⇒ **Kyphosis:** Exaggerated forward curvature of the spine.
  - ⇒ **Scoliosis:** Lateral curvature of the spine.
  - ⇒ **Kyphoscoliosis:** Forward and lateral bending of the spine

**Movement of the chest:**

- One has to inspect whether both sides of the chest is moving symmetrically or not.

**Causes of asymmetrical chest expansion are:**

- Pleural Effusion
- Pneumothorax
- Extensive Consolidation
- Athlectasis
- Pulmonary Fibrosis

**PALPATION**

- **Tracheal position:**
  - A slight deviation of the trachea to the right side may be found in healthy individuals

### Causes Of Tracheal Displacement

- Mediastinal masses (lymphoma, thymoma, retrosternal goitre) **displace the trachea away from the mass**
- Tracheal deviation **towards the side of lung lesion**
  - Upper lobe collapse
  - Upper lobe fibrosis
  - Pneumonectomy
- Tracheal deviation **away from side of the lung lesion**
  - Massive pleural effusion
  - Tension pneumothorax

- **Reduced** tactile fremitus on affected lung occurs in **pneumothorax, hydrothorax and fibrotic lung disease**
- **Increased** tactile fremitus on affected lung occurs in **lung consolidation due to pneumonia**

### PERCUSSION

❖ **Percussion Note:-**

- In a healthy individual, a resonant noise is produced upon percussion of the chest.
- Resonant sound is of low pitch and clear in character.

Percussion Note		
Causes of dullness to percussion are:	Causes of hyper resonance are:	
	Bilateral causes	❖ Unilateral causes:
<ul style="list-style-type: none"> <li>⌚ Tumors</li> <li>⌚ Lobar pneumonia</li> <li>⌚ hydrothorax</li> <li>⌚ Hemothorax</li> <li>⌚ Empyema</li> <li>⌚ Fibrosis</li> <li>⌚ Athlectasis</li> <li>⌚ Thick chest wall</li> </ul>	<ul style="list-style-type: none"> <li>⌚ Emphysema</li> <li>⌚ Bronchial asthma</li> </ul>	<ul style="list-style-type: none"> <li>⌚ Pneumothorax</li> <li>⌚ Large air filled bulla in the lungs</li> </ul>

❖ **Diaphragmatic Excursion**

→ An **abnormally high level** suggests:-

- Pleural effusion, or
- A high diaphragm as in atelectasis or
- Phrenic nerve paralysis

## AUSCULTATION

→ **Breath sounds**

- Breath sounds have both intensity and quality. The intensity (loudness) of the breathsound may be categorized as normal, reduced or increased.
- The quality of breath sounds have been classified in to three categories:

→ **Vesicular:**

- these are soft and low pitched sounds.
- They are heard through out inspiration, continue without pause in to expiration, and then fade away about one third of the way through expiration.
- Vesicular breath sounds are the normal breathsounds.
- Vesicular breath sounds probably originate in the larger airways and when heard through normal lungs, the attenuating and filtering effect of the alveoli producesrather quiet low pitched rustling sounds

→ **Bronchial:**

- These are louder and higher in pitch.
- There is a short silent period between the inspiratory and expiratory sounds, and the expiratory sound lastslonger than the inspiratory one.
- **Classically they are heard over an area of consolidated lung in cases of pneumonia.**

→ **Bronchovesicular:**

- These are intermediate. Inspiratory and expiratory sounds are about equal in length, and a silent period between them may or may not be present.
- These are often heard in the first and second interspaces anteriorly and between the scapulae.
- Bronchial breath sounds probably originate from the same larger airways but when the lung between these airways and chest wall is airless as a result of consolidation, collapse, or fibrosis.

→ **Added sounds**

- Added sounds may arise in the lung or in the pleura. Sounds resembling pleural friction rubs may be produced by movements of the stethoscope on the patient's skin or of the examiner's hands or cloths against a stethoscope.
- Pleural friction rub is characteristic of pleural inflammation and occurs at a stage when there is pain. It has a rubbing character.
- **Wheezes** are musical sounds associated with airway narrowing. The noise is often inspiratory and expiratory and it is fairly obvious that it originates from the upper airways.

Causes of wheeze on auscultation	
<b>Generalized</b>	<ul style="list-style-type: none"> <li>⇒ Asthma</li> <li>⇒ Chronic Bronchitis</li> <li>⇒ Emphysema</li> <li>⇒ Left ventricular failure</li> </ul>
<b>Localized</b>	<ul style="list-style-type: none"> <li>⇒ Bronchiolitis</li> <li>⇒ Foreign Body</li> <li>⇒ Tumour</li> </ul>

- **Crackles** :- short, explosive sounds often described as bubbling.
  - It is more likely that they are produced by sudden changes in gas pressure related to the sudden opening of previously closed small airways.
  - Crackles may be due to abnormalities of the lungs:-
    - ➔ Pneumonia,
    - ➔ Early congestive heart failure
    - ➔ Theairways (bronchitis, bronchiectasis).

Crackle	
Fine crackle	Coarse crackle
⇒ They don't disappear or change with Coughing	⇒ They either decrease in number disappear or with coughing

NB:-

**Do not confuse with terms:- crackle, rale or crepitation, and rhonchi wheezes**

☞ Older terms such as:-

- ☞ **râles** to describe coarse crackles,
- ☞ **crepitations** to describe fine crackles and
- ☞ **ronchii** to describe wheezes are poorly defined, have led to confusion and are best avoided.

→ **Transmitted voice sounds**

- If you hear abnormally located bronchial breath sounds, continue on to assess transmitted voice sounds

## INVESTIGATION OF RESPIRATORY SYSTEM

- Chest X-ray
  - Pleural Fluid Analysis
  - Pleural biopsy
  - Pulmonary Function Test/PFT/
  - Arterial Blood Gas Analysis
  - Ultrasound
  - CT-Scan
  - Fiberoptic Bronchoscopy
- **Pleural Fluid Analysis**
- Tests **routinely** performed on pleural fluid include cell count, pH, protein, lactate dehydrogenase (LDH), and glucose.
  - **Additional** commonly performed tests in selected patients include amylase, cholesterol, triglycerides, gram and AFB stain, bacterial and AFB culture, and cytology
  - **Pleural effusion** is defined as excess fluid accumulation in the pleural space.
  - It can result from :-
    - Increased pleural fluid formation in the Lung interstitium, Parietal pleura, or Peritoneal cavity, or
    - Decreased pleural fluid removal by the parietal pleural lymphatics.
  - The first step is to determine whether the **effusion is a transudate or an exudate**
    - The primary reason for making this differentiation is that additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

	A transudative pleural effusion	An exudative pleural effusion
	<ul style="list-style-type: none"> <li>occurs when systemic factors that influence the formation and absorption of pleural fluid are altered</li> </ul>	<ul style="list-style-type: none"> <li>occurs when local factors that influence the formation and absorption of pleural fluid are altered</li> </ul>
Leading Causes	4) Left-ventricular failure 5) Cirrhosis.	1. Bacterial pneumonia, 2. Malignancy, 3. Viral infection, and 4. Pulmonary embolism

- Diagnostic Criteria/ The Light's Criteria
  - ⌚ A traditional method of differentiating transudates and exudates that measures serum and pleural fluid protein and LDH.
  - ⌚ According to Light's traditional criteria, if at least one of the following three criteria is present, the fluid is defined as an exudate

The Light's Criteria
<ul style="list-style-type: none"> <li>⌚ Pleural fluid protein/serum protein ratio greater than 0.5</li> <li>⌚ Pleural fluid LDH/serum LDH ratio greater than 0.6</li> <li>⌚ Pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH</li> </ul> <ul style="list-style-type: none"> <li>These criteria misidentify ~25% of transudates as exudates</li> <li>If ≥ 1 of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, measure serum - pleural fluid protein levels.</li> <li>If this gradient is &gt;3.1 g/dL, the exudative categorization by these criteria can be ignored because almost all such patients have a transudative pleural effusion</li> <li>If a patient has an exudative pleural effusion, the following tests on the pleural fluid should be obtained:           <ol style="list-style-type: none"> <li>Description of the appearance of the fluid,</li> <li>Glucose level,</li> <li>Differential cell count,</li> <li>Microbiologic studies, and</li> <li>Cytology.</li> </ol> </li> </ul>

- Factors indicating the likely need for a procedure more invasive ( **chest tube Insertion** ) than a thoracentesis:-

**INDICATIONS: - chest tube Insertion**

1. Loculated pleural fluid
2. Pleural fluid pH <7.20
3. Pleural fluid glucose <3.3 mmol/L (<60 mg/dL)
4. Positive Gram stain or culture of the pleural fluid
5. Presence of gross pus in the pleural space

- **Chest X-Ray**
- **Pulmonary Function Tests**

- These tests aid to assess functional impairment, effect of treatment and progress of the disease.
- Dynamic lung volumes are measured by inhaling to total lung capacity and then exhaling into a spirometer with maximal effort to residual volume.
- The volume exhaled in the first second is the FEV<sub>1</sub> and the total volume exhaled is the FVC.
- Normal predictive values for FEV<sub>1</sub> and FVC are influenced by age, gender, height and race.
- In healthy young and middle-aged adults the FEV<sub>1</sub>/FVC ratio is usually >75%. In the elderly the ratio is usually 70–75%.
- Reduction in the FEV<sub>1</sub>/FVC ratio indicates airway obstruction. The severity of obstruction is represented by the absolute FEV<sub>1</sub> expressed as a percentage of predicted.
  - Airway obstruction that reverses with inhaled  $\beta_2$ -agonist or oral steroid over 5 days or more (an absolute increase in FEV<sub>1</sub> >200 ml that is >15% of baseline) favours a diagnosis of asthma over COPD
  - In interstitial lung disorders, e.g. idiopathic pulmonary fibrosis, pulmonary sarcoidosis or hypersensitivity pneumonitis, there is a decrease in FVC with preservation of FEV<sub>1</sub>/FVC ratio, a restrictive defect

## CVS PHYSICAL EXAMINATION

- As you begin CVS examination, review the BP and HR recorded during the general survey and Vital signs at the start of P/E
- Components of CVS examination
  1. Arterial Examination
  2. Venous examination
  3. Heart (Precordium)

## ARTERIAL EXAMINATION

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- **Arterial Examination Component**
  - Arterial Pulse:-Rate , Rhythm, **Character, Symmetry, Volume**
  - Peripheral arteries Change in condition of arterial walls, Radio femoral delay
  - Blood Pressure
- **Examination Techniques**
  - i. **Arterial Pulse**
    - a. **Pulse Rate.**
      - ⌚ The **radial pulse** is commonly used to assess the heart rate.
      - ⌚ With the pads of your index and middle fingers, compress the radial artery until a maximal pulsation is detected.
      - ⌚ If the rhythm is regular and the rate seems normal, **count the rate for 30 seconds and multiply by 2.**
      - ⌚ If the rate is **unusually fast or slow** count for **60 seconds**.
      - ⌚ The range of normal is **60–100 beats per minute**
    - a. **Rhythm.**
      - To begin your assessment of rhythm, feel the radial pulse.
      - If there are any irregularities, check the rhythm again by listening with your stethoscope at the cardiac apex. Premature beats may not be detected peripherally, and the heart rate can be seriously underestimated.
      - Is the rhythm regular or irregular? If irregular, try to identify a pattern:
        - ii. Do early beats appear in a basically regular rhythm?
        - iii. Does the irregularity vary consistently with respiration?
        - iv. Is the rhythm totally irregular?

### C. Pulse volume (amplitude)

- **Carotid Artery** is the best.
  - Place the patient supine with the head elevated to about 30 degrees.
  - Place your left index and middle fingers (or left thumb) on the right carotid artery in the lower third of the neck, press posteriorly, and
  - Feel for pulsations.
  - Don't palpate both carotids simultaneously.

### D. The peripheral arteries

- Are the carotids, the brachial, the radial, the popliteal, dorsalispedis and posterior tibial arteries.
- ➲ Palpate these arteries symmetrically and orderly to assess: volume symmetry
- **ARTERIAL EXAMINATION DISCUSSION**

Cause Slow and Fast Heart Rate	
Bradycardia (HR < 60/min)	
Sinus bradycardia	Arrhythmic bradycardia
<ul style="list-style-type: none"> <li>- Sleep</li> <li>- Athletic heart</li> <li>- Hypothyroidism</li> <li>- Hypothermia</li> <li>- Second degree AV block</li> <li>- Raised intracranial pressure</li> <li>- Obstructive jaundice</li> <li>- Drugs, e.g. betablockers, calcium channel blocker, digoxin, etc.</li> <li>- Poisoning, e.g. OP compounds</li> </ul>	<ul style="list-style-type: none"> <li>- Carotid sinus hypersensitivity</li> <li>- Sick sinus syndrome</li> <li>- Complete heart block</li> </ul>
Tachycardia (HR > 100/min)	
Sinus tachycardia	Arrhythmic tachycardia
<ul style="list-style-type: none"> <li>- Physiological, e.g. exercise, fever, use of tea, coffee, etc.</li> <li>- Pain</li> <li>- Anxiety/excitement</li> <li>- Thyrotoxicosis</li> <li>- Heart disease, e.g., CHF, congenital heart disease</li> <li>- Drugs, e.g., sympathomimetics, vasodilators</li> <li>- Phaeochromocytoma</li> </ul>	<ul style="list-style-type: none"> <li>- Atrial fibrillation</li> <li>- Atrial flutter</li> <li>- Supraventricular tachycardia (SVT)</li> <li>- Ventricular tachycardia (VT)</li> </ul>

Causes of irregular pulse	
Irregularly Irregular Pulse	Regularly Irregular Pulse
<ul style="list-style-type: none"> <li>- Sinus arrhythmia (respiratory or non respiratory)</li> <li>- Atrial ectopics (extrasystoles)</li> <li>- Ventricular ectopics (extrasystoles)</li> <li>- Atrial fibrillation with variable response</li> <li>- Second degree AV block with variable response</li> </ul>	Ventricular ectopics in bigeminus or trigeminus pattern

- **Arterial Wall:** -
  - Normally vessel wall is not palpable due to resilient arteries but becomes palpable in old age and in **hypertensives** due to stiffness and hardening of arteries (**arteriosclerosis and atherosclerosis**).
- Symmetry of the arterial pulses.
  - A unilateral decrease of amplitude can be due to obstruction or atherosclerosis.
- **Check for radiofemoral delay.**
  - Normally the radial and femoral pulses are simultaneous.
  - **Delay of the femoral pulse** compared to radial pulse is a **sign of aortic coarctation**
- **Pulsus Alternans:**
  - Regular pulse with alternating weak and strong pulse
  - ⇒ **DDx:-**
    - Severe Liver Failure
    - Dilated Cardiomyopathy
- **Pulses Paradoxus:** -
  - Pulse volume increase during expiration and decrease inspiration during

**DDx.**

- Cardiac Tamponade
- Constrictive Pericarditis
- Status Asthamaticus
- Massive Pulmonary Embolism
- Hemorrhagic Shock
- Tension Pneumothorax

## VENOUS EXAMINATION

### Venous Examination Component

- Jugular Venous Pressure/JVP/

### Examination Techniques

- Position the patient
- Elevate head of bed at 45° to maximize visibility of the jugular venous pulsation in the lower half of the neck
- Turn patient's head slightly away from the side you are inspecting
- Use tangential (oblique) lighting and identify the pulsation of internal jugular vein
- Identify the highest point of pulsation of internal jugular vein
- Measure the vertical distance between the highest point of jugular pulsation and sternal angle with a metered ruler and then place tongue blade at an exact right angle to the ruler and read the vertical distance on the ruler

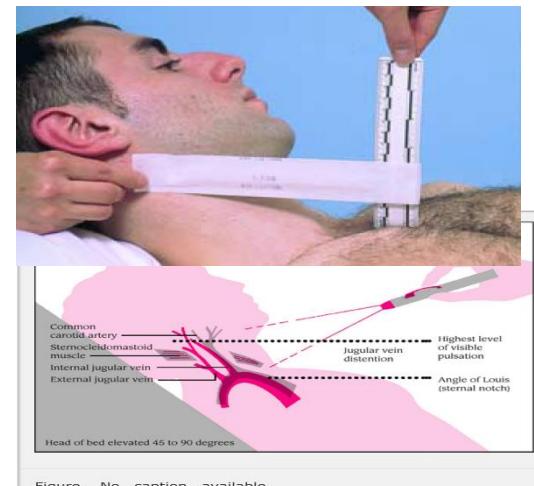


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## VENOUS EXAMINATION DISCUSSION

- **Jugular Venous Pressure (JVP)**
  - Most important because it provides valuable information about the **patients' volume status & cardiac function**
  - Reflects pressure in the **RA or SCVP**
  - Should be assessed from the waveform of the internal jugular vein which lies adjacent to the medial border of the sternocleidomastoid muscle.
  - Best assessed from pulsations in the **Right Internal Jugular Vein**.
  - The normal upper limit is **3 cm** vertically above sternal angle.
  - This is about **8 cm** above right atrium, corresponding to a JVP of **8mmHg**
  - **JVP > 3 or 4 cm** vertically above sternal angle is considered elevated

**NB:** If the internal jugular vein pulsation is not visible, measure the vertical distance of the point above which the external jugular veins appear to be collapsed from the sternal angle.

- **INTERPRETATION:**

**Normal:** - is less than or equal to **3 cm** of water

**Elevated:** - if greater than **3 cm** of water above the sternal angle.

### Causes of elevated jugular venous pressure

- Constrictive pericarditis
- Tricuspid valve disease
- Superior vena cava obstruction
- Pulmonary embolism
- Right ventricular infarction
- Cor pulmonale
- Tamponade
- Congestive heart failure
- Hypertrophic/restrictive cardiomyopathy
- Iatrogenic fluid overload, particularly in surgical and renal patient

Distinguishing Internal Jugular and Carotid Pulsations		
	Internal Jugular Pulsations	Carotid pulsations
<b>Palpation</b>	Rarely palpable	Palpable
<b>Character</b>	Soft, biphasic, undulating quality, usually with two elevations and two troughs per heart beat	A more vigorous thrust with a single outward component
<b>Venous compression</b>	Pulsations eliminated by light pressure on the vein(s) just above the sternal end of the clavicle	Pulsations not eliminated by this pressure
<b>Effect of position</b>	Height of pulsations changes with position, dropping as the patient becomes more upright	Height of pulsations unchanged by position
<b>Effect of Respiration</b>	Height of pulsations usually falls with inspiration	Height of pulsations not affected by inspiration

## EXAMINATION OF PRECORDIUM

### PRECORDIUM EXAMINATION COMPONENT

#### ⌚ INSPECTION:

- Precordial Bulge,
- Deformity,
- Active Or Quiet Precordium,
- Apical Impulse
  - location in no. of ICSs, or in distance (cm) from mid axillary line, or from mid sternal line

#### ⌚ PALPATION:

- PMI (location, character- diffuse or localized, tapping or sustained);
- palpable (accentuated) heart sound;
- Heave (apical & parasternal );
- Thrill (palpable heart murmur)- systolic, diastolic or both

#### ⌚ AUSCULTATION:

- S1 & S2
- murmur (grade 1-6),
- Extra heart sounds (third and fourth)

- Additional sounds (**clicks, snaps and rub**)
- Splitting of the sound (second heart sound)

### PRECORDIUM EXAMINATION TECHNIQUES

- ❑ For most cardiac examination, the patient should be supine with upper body **elevated about 30 degree.**
- ❑ Two other positions
  - Turning to the left side
  - leaning forward
- ❑ Steps in assessing CVS
  - Inspection, palpation, & auscultation

### INSPECTION

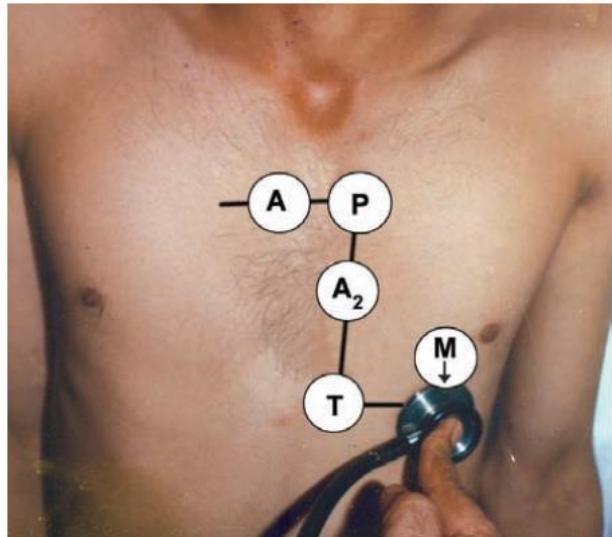
- ➲ Explain that you wish to examine the chest and ask the patient to remove all clothing above the waist.
- ➲ Keep a female patient's chest covered with a sheet as far as possible.
- ➲ Inspect the precordium with the patient sitting at a 45° angle with shoulders horizontal.
- ➲ Look for surgical scars, visible pulsations and chest deformity.

### PALPATION

- ➲ Place your right hand flat over the precordium to obtain a general impression of the cardiac impulse.
- ➲ Locate the apex beat by lying your Fingers on the chest parallel to the rib spaces;
  - ↳ if you cannot feel it, ask the patient to roll on to his left side .
- ➲ Assess the character of the apex beat and note its position.
- ➲ Apply the heel of your right hand firmly to the left parasternal area and feel for a right ventricle heave.
- ➲ Ask the patient to hold his breath in expiration.
- ➲ Palpate for thrills at the apex and both sides of the sternum using the Flat of your Fingers.

## AUSCULTATION

- Aortic Area with diaphragm
- Pulmonic Area with diaphragm
- Lower left sternal border (LLSB) with diaphragm
- Apex with diaphragm and then bell
- Apex - left lateral decubitus position with bell
- Lower left sternal border (LLSB)- sitting, leaning forward



## PRECORDIUM EXAMINATION DISCUSSION

### INSPECTION

#### PRECORDIUM ACTIVITY: -

<b>Quiet: precordium: -</b> ⇒ <b>1 or no visible pulsation</b>	<b>Active precordium: -</b> ⇒ More than two pulsations in more than two intercostal space or ⇒ > 2 cm of single pulse i.e. > 2 finger breadth.
<b>DDx/Cause:-</b> – Normal – Dilated Cardiomyopathy – Pericardial effusion	<b>DDx/Cause; -</b> – Valvular Heart Disease – Ischemic Heart Disease – High output state

### APEX IMPULSE or POINT OF MAXIMAL IMPULSE

- Apical impulse: the lowest and most lateral point at which the cardiac impulse is felt.

The apex beat is neither visible nor palpable on the left side in:

Extreme obesity or thick chest

Large pericardial effusion

Apex beat hidden behind the rib or behind pendulous breast in a female

Asthma or COPD

Dextrocardia

### CAUSES OF SHIFTED APEX IMPULSE

Upward & left: -	Lateral: -	Medially
<ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• High Left Diaphragm</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac Enlargement in CHF,</li> <li>• deformities of thorax &amp;</li> <li>• mediastinal shift,</li> <li>• pneumothorax &amp; pleural effusion</li> </ul>	<ul style="list-style-type: none"> <li>• Due to lung pathology eg collapse, fibrosis</li> </ul>

### PMI = POINT OF MAXIMAL IMPULSE

- The apical impulse is usually the PMI.
- It is normally located in the 4th or 5th intercostals space just medial to the mid clavicular line and properly characterizes the PMI
- Characterization of the Impulse
  - Location: site as intercostal space and medial or later to the midclavicular line,
  - Size: diffuse if more than two intercostals space or not diffuse if otherwise
  - Duration: sustained if more than 2/3 of the systolic time or not if otherwise
  - Amplitude: thrusting if forceful or taping if otherwise.

### PALPATION

- a. Palpable Heart Sound
- b. Heave /Lift
  - sustained systolic lift that results from ventricular hypertrophy.

Apical heave = sustained apical impulse	Parasternal heave
LVH	RVH Severe TR (Tricuspid Regurgitation) with giant right atrium
LVH; Left ventricular hypertrophy RVH; Right Ventricular hypertrophy	

c. **THRILLS:**

- palpable, low frequency vibrations associated with heart murmurs
- timed as systolic or diastolic

Common Thrills and condition associated	
Thrill	Condition
Systolic thrill at apex	Mitral Regurgitation
Diastolic thrill at apex, best heard left lateral position	Mitral stenosis

## AUSCULTATION

a. **1st Heart Sound, S1:-**

- This signals the onset of systole and is caused by the closure of the mitral and tricuspid valves.
- NB The 1st sound can be identified by palpating the carotid pulse while auscultating.
- The upstroke of the carotid pulse closely follows the 1st heart beat.

S1 is loud in	S1 is soft (Muffled) in: -
Mitral stenosis	Mitral Regurgitation
Tachycardia	Bradycardia
Hyperdynamic circulation like e.g.,	LVF
Anaemia	

b. **2nd Heart Sound, S2:**

- This separates systole and diastole.
- The sound is made by the closure of aortic and pulmonary valves.

- The aortic valve closes before the pulmonary valve and this **splitting of the second sound is heard particularly during inspiration**, as more blood is drawn into the right ventricle which is a normal phenomenon

Loud S <sub>2</sub>	Quiet/Feeble S <sub>2</sub>
Systemic hypertension (A <sub>2</sub> is loud)	Low cardiac output
Pulmonary hypertension (P <sub>2</sub> is loud)	Aortic incompetence

#### c. 3rd & 4th Heart Sounds

- These are low pitched sounds. If either S<sub>3</sub> or S<sub>4</sub> is very loud it is often heard as gallop/triple rhythm.
- 3rd Heart Sound, S<sub>3</sub>**
  - This is produced by rapid ventricular filling and occurs in early-mid diastole i.e. soon after S<sub>2</sub> occurs.

Normal/Physiological	Abnormal/Pathological
<ul style="list-style-type: none"> <li>Healthy young adults</li> <li>Athletes</li> <li>Pregnancy</li> </ul>	<ul style="list-style-type: none"> <li><b>CHF</b> <ul style="list-style-type: none"> <li><b>Left heart failure</b> - S<sub>3</sub> heard best in mitral area</li> <li><b>Right heart failure</b> - S<sub>3</sub> heard best in tricuspid area</li> </ul> </li> <li><b>Mitral regurgitation</b></li> <li>Patients with high ventricular filling pressure</li> </ul>

#### d. 4th Heart Sound, S<sub>4</sub>

- This is an *atrial sound*, occurring just before S<sub>1</sub>.
- It is *always abnormal* as it represents atrial contraction against a stiffened ventricle
- e.g. due to *aortic stenosis* or *hypertensive heart disease*.
- It may also occur in heart failure.

#### e. Added Sounds

- Opening snap* may occur in *mitral* or *tricuspid stenosis*. Prosthetic valves make noises on opening and closing.
- A *pericardial friction rub* is a leathery (rubbing) sound heard in systole or diastole, which suggests *pericardial inflammation*.

- Pericardial knock is high pitched sound which is heard in early diastole. **It indicates constrictive pericarditis.**

**f. Murmur**

- abnormal sound due to turbulence of blood flow.
- It may be innocent(Physiologic) e.g. hyperdynamic states like anemia, pregnancy etc. or pathologic e.g. valvular lesions

Characterization of Murmur														
Parameters	Descriptions													
<b>Timing:</b>	systole, diastole, continuous													
<b>Duration</b>	<ul style="list-style-type: none"> <li>● determined the length of systole or diastole that the murmur occupies.</li> <li>● The murmur can be long (eg, it occupies most of systole or diastole), or it can be brief. The following classification is useful:           <ul style="list-style-type: none"> <li>❖ For systolic murmurs:               <ul style="list-style-type: none"> <li>• <b>Midsystolic</b> (or systolic ejection)</li> <li>• <b>Holosystolic</b> (or pansystolic)</li> <li>• <b>Early</b> systolic</li> <li>• <b>Late</b> systolic</li> </ul> </li> <li>❖ For diastolic murmurs:               <ul style="list-style-type: none"> <li>➢ <b>Early</b> diastolic</li> <li>➢ <b>Mid-diastolic</b></li> <li>➢ <b>Late</b> diastolic (or presystolic)</li> </ul> </li> </ul> </li> </ul>													
<b>Location and radiation</b>	<p>The location on the patient's chest where the murmur is loudest is typically described as apical or parasternal.</p> <p>Parasternal murmurs are further described by the intercostal space and right or left side of the sternum</p>													
<b>Intensity (grading)</b>	<table border="1"> <thead> <tr> <th>Grade</th> <th>Volume</th> <th>Thrill</th> </tr> </thead> <tbody> <tr> <td>1/6</td> <td> <ul style="list-style-type: none"> <li>• Very faint, only heard with optimal conditions</li> </ul> </td> <td>No</td> </tr> <tr> <td>2/6</td> <td> <ul style="list-style-type: none"> <li>• Quiet , but heard immediately after placing the stethoscope on the chest</li> </ul> </td> <td>No</td> </tr> <tr> <td>3/6</td> <td> <ul style="list-style-type: none"> <li>• Moderately loud</li> </ul> </td> <td>No</td> </tr> </tbody> </table>		Grade	Volume	Thrill	1/6	<ul style="list-style-type: none"> <li>• Very faint, only heard with optimal conditions</li> </ul>	No	2/6	<ul style="list-style-type: none"> <li>• Quiet , but heard immediately after placing the stethoscope on the chest</li> </ul>	No	3/6	<ul style="list-style-type: none"> <li>• Moderately loud</li> </ul>	No
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	4/6	<ul style="list-style-type: none"> <li>Loud, with palpable thrill</li> </ul>	Yes
	5/6	<ul style="list-style-type: none"> <li>Very loud, with thrill. Can be heard when the stethoscope is partly off the chest</li> </ul>	Yes
	6/6	<ul style="list-style-type: none"> <li>Very loud, with thrill. May be heard with stethoscope entirely off the chest</li> </ul>	Yes
Pitch	<ul style="list-style-type: none"> <li>The frequency of the murmur determines the pitch, which may be high or low.</li> </ul>		
Quality	<ul style="list-style-type: none"> <li>The quality can be described as harsh, rumbling, scratchy, grunting, blowing, squeaky, and musical.</li> <li>Quality and pitch are closely related</li> </ul>		
Shape /configuration	<ul style="list-style-type: none"> <li>⌚ The time course of murmur intensity corresponds to the "shape" of a diagram of murmur intensity over time, as in a phonocardiogram.</li> <li>⌚ A number of configurations or shapes of murmurs are recognized:           <ul style="list-style-type: none"> <li>Crescendo (increasing)</li> <li>Decrescendo (diminishing)</li> <li>Crescendo-decrescendo (increasing-decreasing or diamond shaped)</li> <li>Plateau (unchanged in intensity)</li> </ul> </li> </ul>		
<b>Response to maneuvers</b>			
Maneuvers	Response and significance ( implications )		

a. Clenching Fist	<p style="text-align: center;"><b>Response to Maneuvers</b></p>  <p style="text-align: center;">Clenching Fists → ↑ Afterload</p> <p>Distinguishes between:</p> <ul style="list-style-type: none"> <li>- Mitral Regurgitation (increased intensity)</li> <li>- Aortic Stenosis (decreased or unchanged intensity)</li> </ul>
b. Squatting or supine position	<p style="text-align: center;"><b>Response to Maneuvers</b></p>  <p style="text-align: center;">Valsalva or Abrupt Standing → ↓ Venous Return → ↓ Stroke Volume</p> <p>Distinguishes between:</p> <ul style="list-style-type: none"> <li>- Aortic Stenosis (decreased intensity)</li> <li>- Hypertrophic obstructive cardiomyopathy (HOCM) (increased intensity)</li> </ul>
c. Inspiration	<p style="text-align: center;"><b>Response to Maneuvers</b></p>  <p style="text-align: center;">Inspiration → ↑ RV preload ↓ LV preload</p> <ul style="list-style-type: none"> <li>□ Increases most right sided murmurs</li> <li>□ Decreases most left sided murmurs (except HOCM)</li> </ul>

d. Expiration

#### Response to Maneuvers

Expiration

↑ LV preload  
↓ RV preload

- Increases most left sided murmurs (except HOCM)
- Decreases most right sided murmurs

#### INVESTIGATION OF CARDIOVASCULAR SYSTEM

- Cardiac Biomarker
- ECG
- Chest X-ray
- Echocardiography
- Cardiac Catheterization

## BLOOD PRESSURE

- ❖ Measured, then reported under vital sign, have been brought here for discussion.
- ❖ Measuring position :-
  - ⌚ Supine
  - ⌚ Erect/standing position:- If indicated, assess **orthostatic hypotension, common in older adults**

### Classification of Normal and Abnormal Blood Pressure.

- Categories of BP in Adults

Blood Pressure Stages			
Blood Pressure Category	systolic mmHg(upper)		Diastolic mmHg( lower )
Normal	Less than 120	and	Less than 80
Elevated	120- 129	and	Less than 80
High Blood Pressure/hypertension/ stage 1	130 - 139	or	80- 89
High Blood Pressure/hypertension/ stage 2	140 or higher	or	90 or Higher
Hypertension Crisis	Higher than 180	and/or	Higher than 120

2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults/[A report of the American College of Cardiology](#)

## MEASURING BLOOD PRESSURE.

- I. Selecting the Correct Blood Pressure Cuff
  - ⌚ Width of the inflatable bladder of the cuff should be about **40% of upper arm circumference** (about 12–14 cm in the average adult)
  - ⌚ Length of the inflatable bladder should **be about 80% of** upper arm circumference (almost long enough to encircle the arm).
  - ⌚ The standard cuff is **12 × 23 cm**, appropriate for arm circumferences up to **28 cm**
- II. Making Accurate Blood Pressure Measurements

- Steps To Ensure Accurate Blood Pressure Measurement
  - ➲ In ideal situations, instruct the patient to avoid smoking or drinking caffeinated beverages for 30 minutes before the blood pressure is measured.
  - ➲ Check to make sure the examining room is quiet and comfortably warm.
  - ➲ Ask the patient to sit quietly for at least 5 minutes in a chair with feet on the floor, rather than on the examining table.
  - ➲ Make sure the arm selected is *free of clothing*. There should be no arteriovenous fistulas for dialysis, scarring from prior brachial artery cut downs, or signs of lymphedema (seen after axillary node dissection or radiation therapy).
  - ➲ Palpate the brachial artery to confirm that it has a viable pulse.
  - ➲ Position the arm so that the brachial artery, at the antecubital crease, is *at heart level*—roughly level with the 4th interspace at its junction with the sternum.
  - ➲ If the patient is seated, rest the arm on a table a little above the patient's waist; if standing, try to support the patient's arm at the midchest level
  - ➲ Palpate the radial pulse as the cuff is inflated to a pressure of 20 mmHg above the level at which radial pulsation can no longer be felt.
  - ➲ Place the stethoscope lightly over the brachial artery and reduce the pressure in the cuff at a rate of 2-3 mmHg/second until the first sounds are heard.
    - This is the first Korotkoff sound and correlates with systolic blood pressure as flow is just possible through the pressure applied by the compressive cuff.
    - As the pressure is lowered further, subtle changes in pitch and volume occur; these are the second and third Korotkoff sounds and are not important clinically.
    - With further lowering of the pressure in the cuff, the artery becomes less compressed, flow becomes less turbulent and the sounds over the brachial artery become muffled. This is the fourth Koroktoff sound.
    - Shortly after this (usually 1-10 mmHg lower), the sounds die away completely as flow is unimpeded by the cuff; this is the ffth Korotkoff sound and

- ⇒ correlates most accurately with diastolic blood pressure.
- ⇒ Its identification is also less Objective than the fourth
  - ⌚ Record both systolic and diastolic values.

## ORTHOSTATIC HYPERTENSION

- Orthostatic hypotension is *a drop in systolic blood pressure of 20 mm Hg or greater or in diastolic blood pressure of 10 mm Hg or greater within 3 minutes of standing*
- Common cause of lightheadedness or syncope.
  - Measure blood pressure and heart rate in two positions—supine after the patient is resting from 3 to 10 minutes, then within 3 minutes after the patient stands up.
  - Normally, as the patient rises from the horizontal to the standing position, systolic pressure drops slightly or remains unchanged, while diastolic pressure rises slightly.

### DDx.

- Hypovolemia eg. Dehydration, bleeding
- Drugs, eg. Vasodilator, diuretics, TCAs
- Addison's Disease
- Autonomic Neuropathy, eg. DM, Amyloidosis
- Hypopituitarism

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3. SN Chugh ,Eshan Gupta, clinical methods in medicine: Clinical Skills and Practices Second Edition: 2015
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5. 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults/A report of the American College of Cardiology
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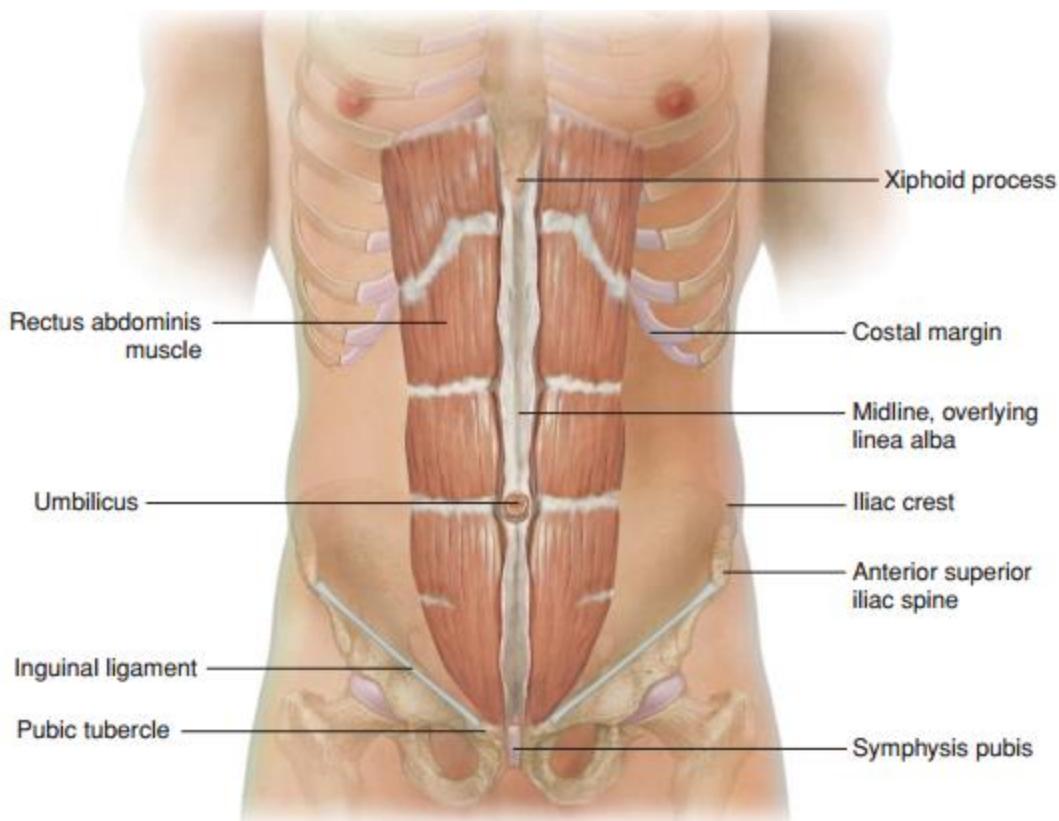
## ABDOMINAL EXAMINATION

### BEFORE EXAMINING

- Ask the patient to keep the arms at the sides or folded across the chest.
- When the arms are above the head, the abdominal wall stretches and tightens, making palpation difficult.
- Move the gown to below the nipple line and the drape to the level of the symphysis pubis.
- Before you begin palpation, ask the patient to point to any areas of pain so that you can examine these areas last.
- Approach the patient calmly and avoid quick, unexpected movements.
- Watch the patient's face for any signs of pain or discomfort.**
- Avoid having long fingernails when examining the patient.

### ANATOMY

**Figure:** Landmarks of the abdomen



## INSPECTION

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You can stand either on the right side or on the side of his/her leg.

### Inspect for:

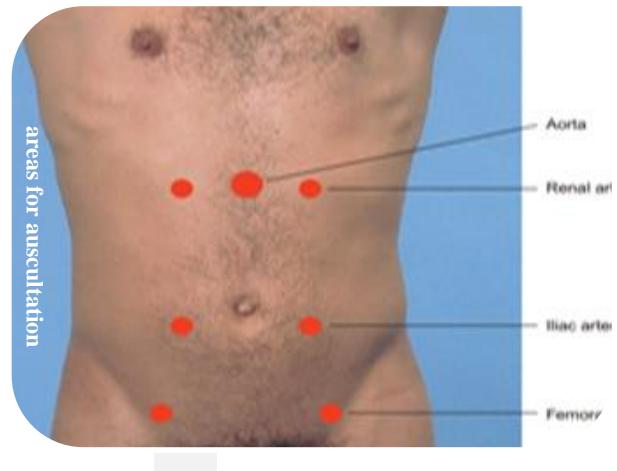
- The contour of the abdomen
  - Flat,
  - Rounded,
  - Protuberant, (DDx. Ascites, Mass)
  - Scaphoid (markedly concave or hollowed)
  - Flanks: full, bulged (Ascites), convex.
  - Symmetry (Asymmetry suggests an enlarged organ or mass)
  - Are there visible organs or masses? Look for an enlarged liver or spleen that has descended below the rib cage.
- The skin
  - Scars
  - Striae; Old silver striae or stretch marks are normal.
  - Dilated vein: Can be from ;
    - Portal hypertension: flow of blood is away from umbilicus
    - Inferior vena cava obstruction:
  - Rashes or ecchymosis: Seen in intraperitoneal or retroperitoneal hemorrhage.
- The umbilicus. Can be:-
  - Inverted(normal)
  - Everted
  - Central
  - Deviated
  - Slit
    - Horizontal (DDx. Ascites)
    - Vertical (DDx. ovarian tumor)
- Pulsations: (DDx. aortic aneurysm or of increased pulse pressure)
- Hernia: see the following areas by asking the patient to strain /cough
  - Epigastric
  - Umbilical
  - Inguinal
  - Femoral

## AUSCULTATION

Listen to the abdomen before performing percussion or palpation because these maneuvers may alter the frequency of bowel sounds.

Place diaphragm of your stethoscope in the Right lower quadrant, because of the presence of iliosecal valve, which will accentuate the bowel sound.

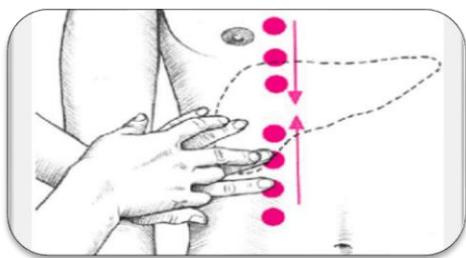
- Bowel sound (5 to 34 per minute; Normoactive), you hear *gurgles*
  - Hypoactive < 5 per minute
  - Hyperactive >35 per minute , you may hear *borborygmi*
- Bruits: Sounds of turbulent arterial flow
  - Aortic (ddx. Aortic aneurysm)
  - Renal (ddx. Renal artery stenosis)
  - Iliac
  - Femoral
  - Liver (ddx Tumors ; resulting in increased vascularity)
  - Spleen
- Friction rubs:
  - Liver ( DDx. hepatoma, gonococcal infection around the liver) and
  - Spleen (DDx. splenic infarction)



## PERCUSSION

### ABDOMEN:

- Tympanic; indicate underlying gas
- Dullness; DDx. (Fluid, tumor and fat)
- Liver: total liver span (8-12 cm for male) and (6-10 cm for Female)



Follow the mid clavicular line.

### DIFFERENTIAL DIAGNOSIS OF HEPATOMEGALY

Acute hepatitis	Malignancy
Viral	Lymphoma
Drug induced	Leukemia
Alcoholic	Metastatic
Chronic liver disease	Metabolic
Early stage of cirrhosis	Diabetes mellitus
Chronic hepatitis	Glycogen storage disease
Hepatoma /HCC	
Parasitic	Congestive hepatomegaly
Amebic liver abscess	Right side heart failure
Hydatid cyst	Constrictive pericarditis
Leishmaniasis	Pericardial effusion
	Budd –chiari syndrome
Bacteria	
Tuberculosis	
Typhoid fever	
Pyogenic liver abscess	

### DDx of tender hepatomegaly

1. Hepatitis
2. Hepatocellular carcinoma(HCC)
3. Amebic liver abscess
4. Payogenic liver abscess
5. Congestive hepatomegaly

**SPLEEN:** we use the following percussion methods:

- **Nixon's method:** The patient is placed on the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in the posterior axillary line and proceeds diagonally along a perpendicular line toward the lower midanterior costal margin.
- **Castell's method:** With the patient supine, percussion in the lowest intercostal space in the anterior axillary line (8th or 9th) produces a resonant note if the spleen is normal in size. This is true during expiration or full inspiration. A dull percussion note on full inspiration suggests splenomegaly.
- **Percussion of Traube's semilunar space:** The borders of Traube's space are the sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. The patient is supine with the left arm slightly abducted. During normal breathing, this space is percussed from medial to lateral margins, yielding a normal resonant sound. A dull percussion note suggests splenomegaly.

#### Differential diagnosis of splenomegaly classified by their Pathogenic Mechanism

Enlargement Due to Increased Demand for Splenic Function	Enlargement Due to Abnormal Splenic or Portal Blood Flow
<b>Reticuloendothelial system hyperplasia (for removal of defective erythrocytes)</b> Spherocytosis Early sickle cell anemia Ovalocytosis Thalassemia major Hemoglobinopathies Paroxysmal nocturnal hemoglobinuria Pernicious anemia <b>Immune hyperplasia</b> <b>Response to infection (viral, bacterial, fungal, parasitic)</b>	Cirrhosis* Splenic artery aneurysm* Hepatic vein obstruction* Hepatic schistosomiasis* Portal vein obstruction, intrahepatic or extrahepatic* Congestive heart failure* Cavernous transformation of the portal vein Hepatic echinococcosis Splenic vein obstruction Portal hypertension (any cause including the above): "Banti's disease"*

Infectious mononucleosis	Infiltration of the Spleen
AIDS	
Viral hepatitis*	<b>Intracellular or extracellular depositions</b>
Cytomegalovirus	<b>Amyloidosis*</b>
Subacute bacterial endocarditis	Gaucher's disease*
Bacterial septicemia	Niemann-Pick disease*
Congenital syphilis	Tangier disease
Splenic abscess	Hurler's syndrome and other mucopolysaccharidoses
Tuberculosis*	Hyperlipidemias
Histoplasmosis	Benign and malignant cellular infiltrations
Malaria*	Leukemias (acute, chronic, lymphoid, myeloid, monocytic)*
Leishmaniasis*	Lymphomas*
Trypanosomiasis	Hodgkin's disease
Ehrlichiosis	Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis)
<b>Disordered immunoregulation</b>	Angiosarcomas
Rheumatoid arthritis (Felty's syndrome)	Metastatic tumors (melanoma is most common)
Systemic lupus erythematosus*	Eosinophilic granuloma
Collagen vascular diseases*	Histiocytosis X
Serum sickness	Hamartomas
Immune hemolytic anemia	Hemangiomas, fibromas, lymphangiomas
Immune thrombocytopenias	Splenic cysts
Immune neutropenias	
Drug reactions	

Unknown Etiology	
Sarcoidosis*	Idiopathic splenomegaly
Thyrotoxicosis (benign lymphoid hypertrophy)	Iron-deficiency anemia
Interleukin 2 therapy	Berylliosis
<b>Extramedullary hematopoiesis</b>	
Myelofibrosis	
Marrow damage by toxins, radiation, strontium	
Marrow infiltration by tumors, leukemias, Gaucher's disease*	

\*Most common ones

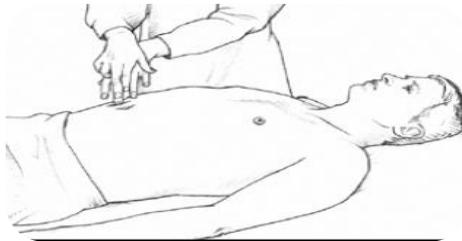
Differential diagnosis of Massive Splenomegaly (> 8cm bellow costal margin)	
Chronic myeloid leukemia	Hyperactive malarial syndrome (HMS)
Lymphomas	Chronic lymphocytic leukemia
Hairy cell leukemia	Sarcoidosis
Myelofibrosis with myeloid metaplasia	Autoimmune hemolytic anemia
Polycythemia vera	Diffuse splenic hemangiomatosis
Gaucher's disease	

DDx of Hepatosplenomegaly	
Kal-azar	Lymphoma
Malaria	CLD with portal hypertension
Chronic myeloid leukemia (CML)	
Myelofibrosis	

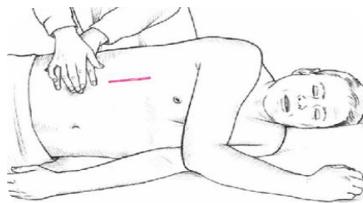
Splenomegaly with ascites
1. CLD
2. Tuberculosis
3. Lymphoma
4. Leukemia

**Shifting dullness;** is a change in the location of dullness to percussion when the patient is turned

- Is positive for accumulation of fluid  $\geq 1500$  ml

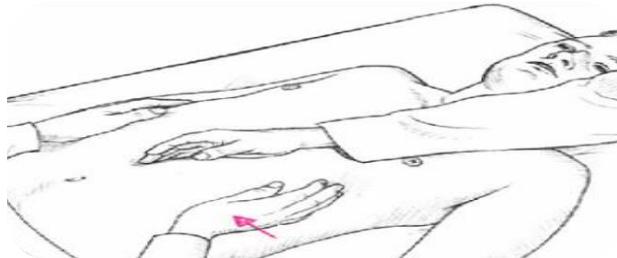


First percus until you rich  
left/right flank



Then hold your pleximeter  
finger their and wait for 5-10  
sec. Then percus and hear for  
dulness

### Fluid trill



Tap by your right/left middle  
finger and feel for a vibration  
by your opposite ball of your  
palm.

Either Positive shifting dullness or fluid thrill indicates the presence of fluid in the abdominal cavity and we call this accumulation of fluid as, **Ascites**.

### PALPATION

**Don't forget:** - To ask for any place where they feel pain.

- To look at your patients face.

### Superficial palpation

- Superficial tenderness
- Superficial mass

### Deep palpation

- Liver; search for palpable liver, starting from right iliac fossa upward.
  - Move hands a few cm up w/each palpation
  - Push down (posterior) & then towards head
  - As approach ribs, palpate while patient inspires deeply (diaphragm brings liver down towards hand)
  - Might feel liver edge in normal (usually not)
- Spleen; search for palpable spleen starting from right iliac fossa obliquely along the umbilicus.
- Bimanual palpation      →



### Differentiation of spleen from kidney, usually during enlargement.

Spleen	Kidney
Has Splenic notch on medial border	Has no notch
Grows oblique and medially	--
Moves with respiration	Not move with respiration
You can't insert your finger below costal margin	You can insert
Bimanually not palpable	Bimanually palpable

### Hyperreactive malarial syndrome (HMS)

Diagnostic feature of hyperreactive malarious splenomegaly (HMS)- Fakunle criteria	
Major criteria	Minor criteria
Splenomegaly > 10cm	Hepatic sinusoidal lymphocytosis
IGM > 2 SD local mean	Hypersplenism
High titers of antimalarial antibodies	Lymphocytic proliferation
Clinical and immunological response to antimalarial drug	Normal cellular and humoral response to antigenic challenge excluding plasmodium
	Occurrence within families and tribes

### Leishmaniasis (for detail refer leishmaniasis portion)

- Demonstration of amastigotes in smears of tissue aspirates is the gold standard for the diagnosis of VL
- The sensitivity of splenic smears is >95%

## INVESTIGATION

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Ascites is the accumulation of fluid in the abdominal cavity.

### Paracentesis

- A bedside procedure in which a needle or small catheter is passed transcutaneously to extract ascitic fluid from the peritoneum.
- The left lower quadrant is preferred because of the greater depth of ascites and the thinner abdominal wall
- Once ascitic fluid has been extracted, its gross appearance should be examined, as follows.

Colour of ascites	Description
Turbid fluid	Infection Or Tumor Cells
White	Chylous Ascites
Dark brown fluid	Biliary tract Perforation.
Black fluid	Pancreatic Necrosis or Metastatic Melanoma.
Heamorrhagic	Malignancy
Straw Colored	Cirrhosis

- Cell count

- WBCS <500/mm<sup>3</sup> and NEUTROPHILS <250/mm<sup>3</sup>: NORMAL
- Neutrophils >250/MicroL: Suggests SBP
- Lymphocytes Predominance : Abdominal Tb Or Malignancy
- SAAG (Serum Ascitic Albumin Gradient)
  - When SAAG >1.1g/dl: strongly suggest portal hypertension
  - When SAAG < 1.1g/dl: non portal hypertensive causes

High (SAAG ≥1.1 g/ dl)	Low (SAAG <1.1 g/ dL)
Cirrhosis	Peritoneal carcinomatosis
Alcoholic hepatitis	Peritoneal tuberculosis
Heart failure	Pancreatitis
Massive hepatic metastases	Serositis
Heart failure/constrictive pericarditis	Nephrotic syndrome
Budd –Chiari syndrome	

- Ascitic Proteins:-When SAAG >1.1g/dl then ,If <2.5g/dL:Transudate ;  
>2.5g/dL:Exudate

## MOTOR EXAMINATION

### MOTOR PATHWAY

Extend from upper motor neurons through long white matter tracts to synapses with lower motor neurons, and continue to the periphery through peripheral nerve structures.

**Upper motor neurons:** lie in the motor strip of the cerebral cortex and in several brainstem nuclei; their axons synapse with motor nuclei in the brain-stem (for cranial nerves) and in the spinal cord, anterior horn (for peripheral nerves).

**Lower motor neurons:** have cell bodies in the spinal cord, termed anterior horn cells; their axons transmit impulses through the anterior roots and spinal nerves into peripheral nerves, terminating at the neuromuscular junction.

### PRINCIPAL MOTOR PATHWAYS

#### 1. Corticospinal (pyramidal) tract

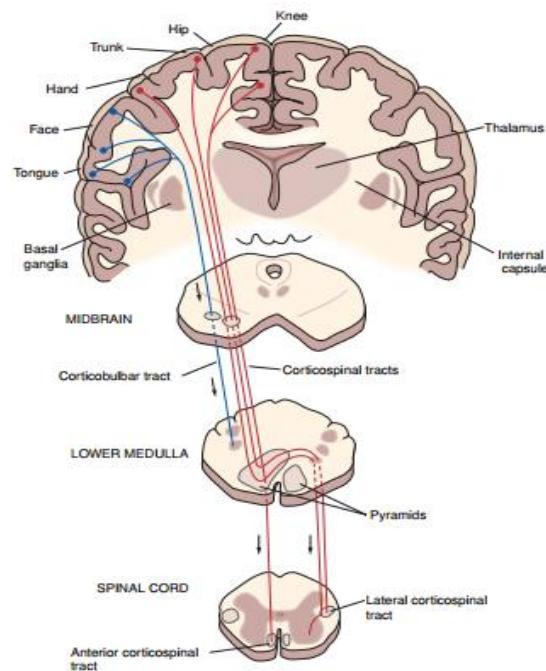
- Mediate voluntary movements and
- Integrate skilled, complicated or delicate mov't

#### 2. Basal ganglia system

- Mainly responsible for gross autonomic movement such as walking

#### 3. Cerebellar system

- Receives both motor and sensory input
- Coordinates motor activity
- Maintains equilibrium
- Helps control posture



Variable	Upper motor neuron	Lower motor neuron
----------	--------------------	--------------------

Atrophy	No	Yes
Fasciculation	No	Yes
Tone	Hypertonic	Hypotonic
Reflex	Hyperactive	Absent or hypo
Plantar reflex	Up-going	Down-going

## EXAMINATION

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### INSPECTION

- Check for visible atrophy
- Visible fasciculation
  - Spontaneous fasciculation
  - Induced fasciculation

### PALPATION

- Muscle bulk: measure 10 cm below the tibial tuberosity or 20 cm above the tibial tuberosity.  $\geq 3\text{cm}$  discrepancy will confirm presence of atrophy for the lower limb
- Muscle tone:
  - Normotonic
  - Hypotonic
  - Hypertonic, may be evident as
    - Spasticity, resistance determined by the angle and velocity of motion; corticospinal tract disease
    - Rigidity, similar resistance in all angles of motion; extrapyramidal disease or
    - Paratonia, fluctuating changes in resistance; frontal lobe pathways or normal difficulty in relaxing.
    - Cogwheel rigidity, in which passive motion elicits jerky interruptions in resistance, is seen in Parkinsonism

- Muscle power (strength): strength is traditionally graded as;

<b>0</b>	no movement
<b>1</b>	flicker or trace of contraction but no associated movement at a joint
<b>2</b>	movement with gravity eliminated (side to side movement)
<b>3</b>	movement against gravity but not against resistance
<b>4</b>	movement against gravity and some resistance
<b>5</b>	movement against full power

**NB:**

- When you examine start from grade 3 and follow accordingly.
- Impaired strength is called weakness, or paresis.
- Absence of strength is called paralysis, or plegia.

### TENDON REFLEX

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Those typically assessed tendons include: -

Upper limb	lower limb
The biceps (C5, C6)	Patellar or quadriceps ( L3, L4)
Brachioradialis (C5, C6)	Achilles ( S1, S2)
Triceps (C6, C7)	

### BASIC TECHNIQUE FOR ASSESSING A REFLEX:

- Clearly identify tendon of muscle to be tested
- Position limb
- Strike tendon briskly
- Observe for muscle contraction & limb movement

REFLEXES ARE GRADED ACCORDING TO THE FOLLOWING SCALE:

<b>0</b>	Absent
<b>1</b>	Reduced(hypoactive)
<b>2</b>	Normoactive
<b>3</b>	Exaggerated (brisk)
<b>4</b>	Clonus

**NB:**

- You will go for clonus if only the reflex is grade 3
- Achilles tendon reflex is graded out of 2



knee reflex at Siting  
position



knee reflex at Supine  
position



Ankle reflex

How can you elicit clonus?

- Patella
  - A sharp downward displacement of the patella may elicit patellar clonus in the extended knee.
- Ankle
  - Support the knee in a partly flexed position. With your other hand, dorsiflex and plantar flex the foot a few times while encouraging the patient to relax, and then sharply dorsiflex the foot and maintain it in dorsiflexion. Look and feel for rhythmic oscillations between dorsiflexion and plantar flexion.
- Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (Jendrassik maneuver), these maneuvers include:
  - Teeth-clenching, for the upper limb reflexes
  - Hooking the flexed fingers of the two hands together and attempting to pull them apart, for the Achilles tendon reflex.

#### PLANTAR REFLEX:

- Gently stroke bottom of foot, starting laterally & near heel –moving up & across balls of feet (metatarsal heads)
  - Could be:
    - Down-going
    - Equivocal
    - Fanning and up-going
      - Shows Upper motor neuron lesion



Plantar reflex

## DISCUSSION

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### HEMIPARESIS

Is weakness of one half of the body

Hemiparesis results from an upper motor neuron lesion above the midcervical spinal cord; most such lesions are above the foramen magnum.

Differential diagnosis of Hemiparesis.

- Acute or episodic hemiparesis
  - Bleeding into brain tumors
  - Stroke
- Subacute hemiparesis; that evolves over days or weeks.
  - Subdural hematoma
  - Infectious or inflammatory disorders
    - Cerebral abscess
    - Fungal granuloma
    - Meningitis
    - Parasitic infections
    - Multiple sclerosis
    - Sarcoidosis
  - In AIDS patient
    - Toxoplasmosis
    - Primary central nervous system (CNS) lymphoma.
- Chronic hemiparesis; that evolves over months.
  - Neoplasm or vascular malformation
  - Chronic subdural hematoma
  - Degenerative disease

### INVESTIGATION

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- Computed tomography (CT): particularly useful for:-
  - Acute change in mental status
  - Focal neurologic findings
  - Acute trauma to the brain and spine
  - Suspected subarachnoid haemorrhage, and
  - Conductive hearing loss
- Magnetic resonance imaging (MRI): particularly useful for evaluation of

- Subacute/chronic haemorrhage
- Suspected mass lesion (with contrast)
- Vascular malformation (MRI ± Angiography)
- Meningeal disease
- Spinal lesions

## MONOPARESIS

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Is weakness of one limb.

Monoparesis usually is due to lower motor neuron disease, with or without associated sensory involvement.

Differential diagnosis of monoparesis

- **Acute monoparesis**
  - Focal cortical ischemia: weakness is predominantly distal and of upper motor neuron type and is not associated with sensory impairment or pain.
- **Sub-acute or chronic monoparesis:** Weakness and atrophy that develop over weeks or months.
  - If weakness is of lower motor neuron origin.
    - Anterior horn cell disease
    - Peripheral causes (associated with sensory symptoms)
      - Nerve lesion
      - Plexus lesion
      - Root lesion
  - If weakness is of the upper motor neuron type.
    - Discrete cortical (precentral gyrus) lesion
    - Cord lesion. e.g. **Brown- sequard syndrome**, characterized by:
      - Ipsilateral spastic weakness (corticospinal tract damage)
      - Segmental LMNS and sensory signs. (anterior horn cell damage)
      - **Loss of pain and temp. Sensation contra lateral to hemi section**
      - Ipsilateral proprioceptive function loss

## INVESTIGATION

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- MRI
- EMG: involves recording compound motor action potentials (CMAPs) over muscles in response to motor nerve stimulation.
  - Fine concentric needle electrodes are inserted into muscle belly and the potentials from individual motor units recorded.
- Nerve conduction studies: involve placing electrodes on the skin overlying peripheral nerves and recording compound action potentials following nerve stimulation as the impulse travels down the nerve
  - Slowing of conduction velocity is suggestive of peripheral nerve demyelination

## QUADRIPAREIS

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Is weakness of all the four limbs.

Although the terms often are used interchangeably, quadriplegia is commonly used when an upper motor neuron cause is suspected, and generalized weakness is used when a disease of the motor units is likely.

Some difference between quadriplegia and generalized weakness.

Variable	Quadriplegia	Generalized weakness
<b>Mental status</b>	changes in consciousness or cognition	Normal
<b>Tone</b>	Spasticity	Hypotonic
<b>Reflex</b>	Hyperreflexia	Hyporeflexia

## ACUTE QUADRIPARESIS

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### DDX

#### 1. Disorders of upper motor neurons

- Anoxia
- Hypotension
- Brainstem or cervical cord ischemia
- Trauma, and
- Systemic metabolic abnormalities

#### 2. Disorder of muscle

- Electrolyte disturbances, certain inborn errors of muscle energy metabolism, toxins, and periodic paralyses

#### 3. in some lower neuron motor lesion

- Guillain Barre syndrome

## SUBACUTE OR CHRONIC QUADRIPARESIS

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#### 1. Disorder of upper motor neuron

- chronic myelopathies
- multiple sclerosis
- brain or spinal tumors
- chronic subdural hematomas, and
- Various metabolic, toxic, and infectious disorders.

#### 2. In some lower neuron motor lesion

- chronic neuropathy ( weakness is often most profound distally), or
- Myopathic weakness (weakness is typically proximal)

## INVESTIGATION

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- CT → for obtunded patient
- MRI → for alert one
- Blood test → for LMNL to check for level of enzyme and electrolyte
- EMG and Nerve conduction test →for LMNL

## PARAPARESIS

Is weakness of both lower limbs.

### Acute paraparesis

- Acute paraparesis is caused most commonly by an intraspinal lesion, but its spinal origin may not be recognized initially if the legs are flaccid and areflexic.
- Imaging the spinal cord may reveal compressive lesions, infarction (proprioception usually is spared), arteriovenous fistulas or other vascular anomalies, or transverse myelitis.

## DIFFERENTIAL DIAGNOSIS

### UPPER MOTOR NEURON LESIONS (UMNL)

1. Diseases of the cerebral hemispheres
  - anterior cerebral artery ischemia
  - superior sagittal sinus or cortical venous thrombosis
  - acute hydrocephalus
2. Disease of spinal lesion (**most common**)

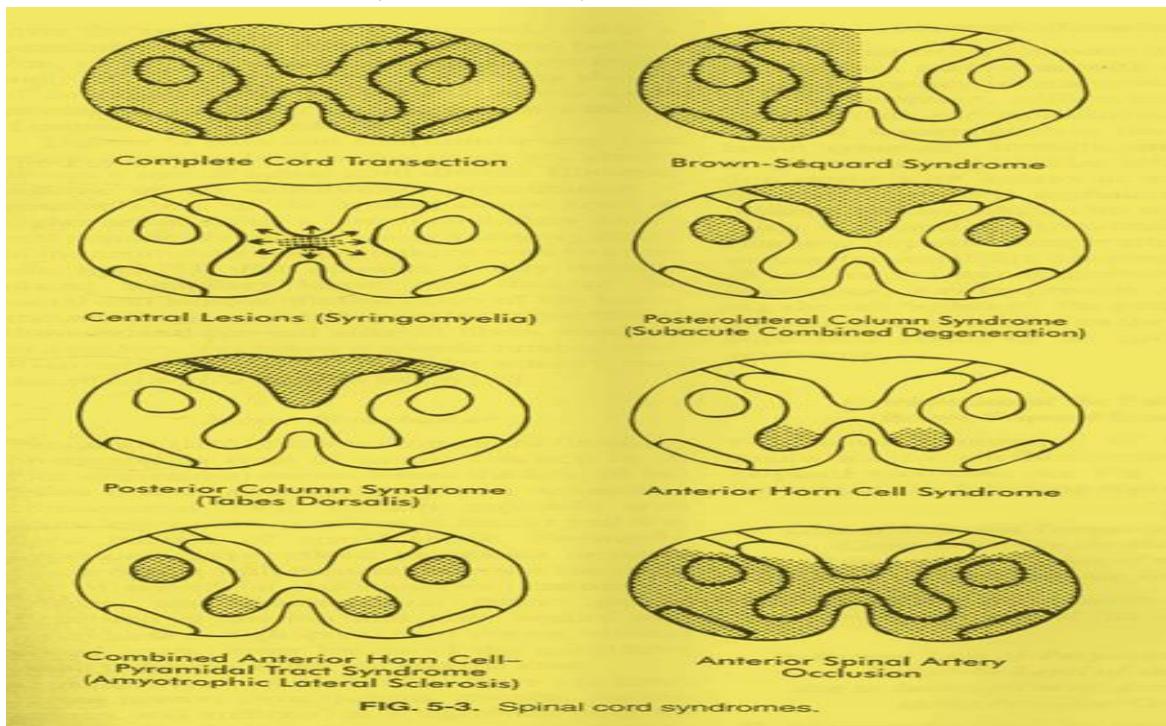


FIG. 5-3. Spinal cord syndromes.

## A. COMPRESSIVE SPINAL CORD LESION

### 1. Epidural Spinal cord compression

- usually neoplastic
  - Breast ca. 20%
  - Lung ca. 20%
  - Prostatic ca. 20%
  - Kidney, Lymphoma,
  - Sarcoma and neuroblastoma: mainly in children
- 20% of Epidural SCC can be the 1st manifestations of Cancers
- Location: **60% in thorax, 30% in lumbosacral, 10% cervical vertebrae**
- Manifestations
  - pain 83-95% at diagnosis (radicular or dull aching pain)
- **Investigation:**
  - Plain spinal X-ray
    - 15-20% chance of missing
    - misses paravertebral lesions in the foramen
  - Myelography
  - CT/CT Myelography
  - MRI
    - High anatomic resolution
    - Seen as hypointense
- **Management**
  - For acutely presented: edema → steroids (dexamethasone 40-100mg stat then 20 mg per day)
  - local radiotherapy
  - surgical decompression
    - if no response to medical treatment
    - if max. radiotherapy is given
    - if compression fracture occurs

## 2. INTRADURAL SPINAL CORD COMPRESSION

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- usually, benign masses
- Intramedullary 10%
  - Ependymomas
  - Hemangioblastomas
  - or low-grade astrocytomas
- Extramedullary 90%
  - Meningioma, lipoma, arachnoiditis
  - frequency is much less than intracranial tumors (1:4)
- symptoms of extramedullary is secondary to:
  - compression of nerve roots or spinal cord
  - compression of spinal cord vessels
- Symptoms of intramedullary is secondary to
  - direct interference with intrinsic structures
  - usually in cervical cord
  - presents as central or hemicord syndrome
  - pain is poorly localized and burning type
  - sacral sparing of sensation
- Management: Surgery

## 3. SPINAL EPIDURAL ABSCESS

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- 2/3rd of them are due to spread from skin/haematogenous
- 1/3rd are due to
  - direct spread from skin
  - osteomyelitis
  - decubitus ulcer
  - iatrogenic (LP, Epidural anaesthesia, spinal surgery)
- Causes: Staph. Aureus 60%
  - G- bacilli
  - Streptococcus
  - Anaerobes
  - Brucella
  - Nocardia
  - Actinomycetes
- Presentation
  - Subacute course

- With triads of: pain, localized tenderness, fever
- Rapidly progressive weakness
- Duration of pain is < 2wks before weakness unless granulomatous
- Risk factors: DM, Renal failure, Alcoholism, malignancy, cellulitis, IV drug users
- Ix: CBC, CT/MRI
- Management: antibiotics, surgical decompression

#### 4. TB SPONDYLITIS

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- infection is initiated in the body of vertebra, anterior or posterior
- common sites: in adults lower thoracic and upper lumbar
- Presentation:
  - Symptom complex often absent (<40%)
  - localized pain
  - weakness
  - spinal deformity: gibbous, kyphoscoliosis
  - +/- sphincter change
- Investigation
  - CBC, ESR, CXR, Spinal X-ray, CT/MRI
  - Abscess analysis
- Treatment
  - Steroid
  - Chemotherapy
  - +/-surgery
  - Rehabilitation

#### B. NON-COMPRESSIVE SPINAL CORD LESIONS

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- Infection (CMV, EBV, syphilis, Borrelia, TB )
- Inflammatory rheumatologic lesions (SLE, MS )
- Vascular (APS, AVM... )
- Metabolic (VB12 deficiency)
- Developmental (meningomyelocele, syringomyelia )

#### LOWER MOTOR NEURON LESION (LMNL)

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1. Anterior horn cell disease
  - poliovirus
  - West Nile virus infection
2. Peripheral neuropathy
  - Hereditary neuropathies

- Charcot-Marie-Tooth disease (Most common)
- Acquired peripheral neuropathy
  - Infections : leprosy(Hansen disease), Borrelia( lyme disease), Diphtheria (diphtheric neuropathy)
  - Inflammatory and /rheumatologic: GBS, SLE ,RA, Sjögren's syndrome, Sarcoidosis.
  - Toxin : medication ( penicillin, isoniazid, zidovudine, stavudine and other)
  - Medical condition : diabetic neuropathy , uremic neuropathy, hypothyroidism
  - Nutritional causes : Vit.B12 ,Cu deficiency , pyridoxine ( vit B6)
  - Cauda-equinia syndrome
- 3. Neuro-muscular junction disorders
  - Myasthenia gravis
  - Hyperparathyroidism
- 4. Muscular disorders
  - Peripheral myopathies: poliomyositis, dermatomyositis, inclusion body myositis.
  - Muscular dystrophies

## SUBACUTE OR CHRONIC SPASTIC PARAPARESIS

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When associated with lower-limb sensory loss and sphincter involvement, a chronic spinal cord disorder should be considered.

DDX

- Vascular malformation
- HIV associated myopathy
- **Tabes dorsalis (tabetic neurosyphilis)**
  - selectively damaged posterior column
  - Impaired vibration and position sense
  - Disturbances in the knowledge of extremity movement and position (temporal and spatial disturbances)
  - Sensory ataxia, noted first at night or in the dark, and a positive Romberg sign
- **Vit.B12 deficiency (subacute combined degeneration)**
  - causes posterolateral column damage
  - Dorsal column dysfunction, sensory ataxia with positive Romberg sign and spasticity
  - Pain &temperature remain intact

- cu deficiency
- Syringomyelia
- Adreno myeloneuropathy
- Spondylopathic myelopathy
  - If hemispheric signs are present, a parasagittal meningioma or chronic hydrocephalus is likely.
  - The absence of spasticity in a long-standing paraparesis suggests a lower motor neuron or myopathic etiology

### TIPS

#### Amyotrophic lateral sclerosis

- Combined ant. Horn cell & pyramidal tract disease
- Diffuse LMN signs superimposed on UMN signs
- Sensory changes are absent
- Bulbar and pseudo bulbar impairment
- Urinary and rectal sphincters unaffected

### INVESTIGATION

- If UMN are associated with drowsiness, seizure or other hemispheric signs → MRI of the brain should be done
- CSF → elevated protein level (1-10g/l) without accompanying Pleocytosis → GBS
- EMG
- Nerve conduction test (NCT)

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