PHARMACOTHERAPY IV

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Integrated Therapeutics IV

Infectious diseases (32 Hrs)

- Principles of antimicrobial regimen selection
- Upper respiratory tract infections
- Lower respiratory tract infections
- Eye infections
- Skin and soft tissue infections
- Infective Endocarditis
- UTI and Prostatitis
- Gastrointestinal infections
- Parasitic infections
- Osteomyelitis and Septic arthritis
- CNS infections
- Tuberculosis
- Sexually Transmitted Infections
- HIV
- Superficial fungal infections
- Invasive fungal infections
- Surgical antibiotic

Integrated Therapeutics IV

- **Immunological Disorders (6 Hrs)**
  - Systemic Lupus Erythematosus
  - Allergic and Pseudoallergic Drug Reactions

Integrated Therapeutics IV

- **ONCOLOGIC DISORDERS (20 Hrs)**
  - Principles of cancer treatment and chemotherapy
  - Breast cancer
  - Lung cancer
  - Colorectal cancer
  - Prostate cancer
  - Lymphomas
  - Ovarian and cervical cancer
  - Acute Leukemias
  - Chronic Leukemias
  - Multiple myeloma
  - Hematopoietic Stem Cell Transplantation
  - Oncologic emergencies

Integrated Therapeutics IV

- **NUTRITIONAL DISORDERS (6 Hrs)**
  - Malnutrition
  - Obesity
  - Parenteral nutrition
  - Enteral nutrition

Delivery Methods

- Interactive presentations
- Group discussions
- Individual and group exercise
- Case studies
- Assignments
- Animation Videos

Methods of Assessment

Continuous Assessment = 40%

Hospital Attachment report = 10%

Final – Exam = 50%

Total =100

References

1. Dipiro JT, Talbert RL, Yee GC, *et.al*. **Pharmacotherapy, A Pathophysiologic Approach**. 10th or later edition.
2. Koda - Kimble MA, Young LY , Kradjan WA, *et.al*. **Applied Therapeutics, The Clinical Use of Drugs**. 11th or later edition.
3. Kasper, Braunwald, et al. **Harrison's Principles of Internal Medicine**, 19th or later edition
4. MoH, **National Malaria Guideline**. fourth edition, FMoH Ethiopia, 2018
5. MoH, Ethiopian. **National Consolidated Guidelines for Comprehensive HIV Prevention, Care and Treatment**. 2018
6. MoH, Ethiopian. **National Comprehensive TB, Leprosy and HIV Training Manual for Healthcare Workers**, **Participant's Manual**, 2016.

INFECTIOUS DISEASES

CHAPTER 1

ANTIMICROBIAL REGIMEN SELECTION

Learning Objectives

- Differentiate between microbial **colonization** and **infection**
- Describe **normal flora** of different parts of the body
- Evaluate drug-specific and patient-specific considerations when selecting antimicrobial therapy.

Introduction

- The discovery of antimicrobials is among the **greatest medical achievements** of the twentieth century.
- Prior to the antimicrobial era, patients who contracted common infectious diseases developed significant morbidity
- The discovery of penicillin in **1927**, followed by the subsequent discovery of other antimicrobials, contributed to a significant decline in infectious disease–related mortality during the next five decades.

Introduction

- The discovery of virtually every new class of antimicrobials has occurred in response to the development of **bacterial resistance** and **loss of clinical effectiveness** to existing antimicrobials
- *Antimicrobials are different from other classes of pharmaceuticals because they exert their action on bacteria infecting the host as opposed to acting directly on the host*

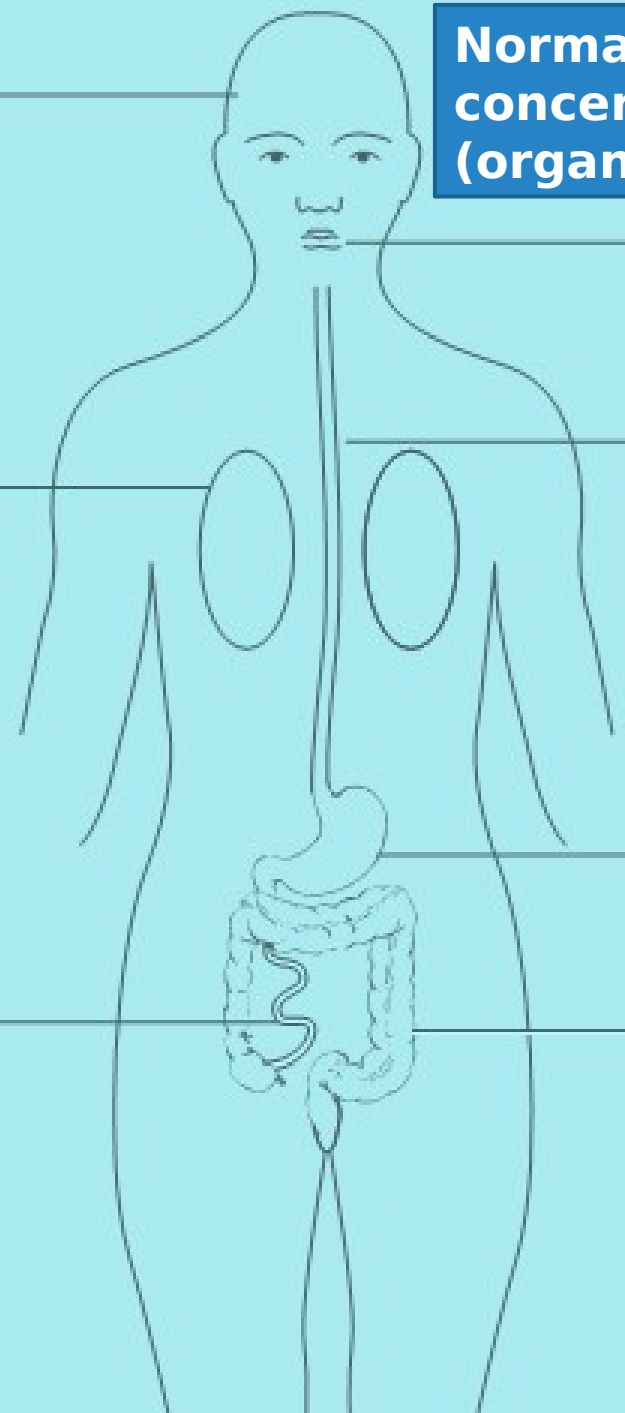
Normal Flora and Endogenous Infection

- Many areas of the human body are colonized with bacteria
  - ***Normal flora***.
- Infections often arise from one's own normal flora
  - ***Endogenous infection***.
- Endogenous infection may occur when:
  - There are alterations in the normal flora (e.g., recent antimicrobial use may allow for overgrowth of other normal flora) or
  - Disruption of host defenses (e.g., a break or entry in the skin).

Colonization versus Infection

- **Infection** refers to the presence of bacteria that are causing disease (e.g., the organisms are found in normally sterile anatomic sites or in nonsterile sites with **signs/symptoms of infection**).
- **Colonization** refers to the presence of bacteria that are not causing disease (could be normal flora).
- Only bacteria that cause disease should be targeted with antimicrobial therapy,
  - Non-disease-producing colonizing flora should be left intact.

Normal flora and concentrations of bacteria (organisms per milliliter)



Skin: 10^5–10^7
Staphylococcus epidermidis
Staphylococcus aureus
Micrococci
Diphtheroids:
Propionibacterium spp

Mouth: 10^8–10^{11}
Viridans streptococci
Oral anaerobes

Upper Respiratory Tract: 10^5–10^9
Oral anaerobes
Streptococcus sp
Staphylococcus sp
Neisseria sp
Diphtheroids
Haemophilus sp
Streptococcus pneumoniae

Lower Respiratory Tract:
Normally sterile

Stomach: Less than 10^3
Streptococcus sp
Lactobacillus

Small Intestine:
Duodenum/jejunum: 10^3–10^5
Lactobacillus
Streptococcus sp
Enterococcus
Enterobacteriaceae
Diphtheroids
Few anaerobes

Ileum: 10^4–10^6 Aerobes
10^5–10^7 Anaerobes
Enterobacteriaceae
Enterococcus sp
Peptostreptococcus
Anaerobes including:
Bacteroides sp
Clostridium sp

Large Intestine: 10^4–10^6 Aerobes
10^5–10^7 Anaerobes
Enterobacteriaceae
Enterococcus sp
Pseudomonas sp
Streptococcus sp
Anaerobes including:
Bacteroides sp
Clostridium sp

Clinical Presentation

- **Patient History**
  - History of present illness
  - Comorbidities
  - Current medications
  - Allergies
  - Previous antibiotic exposure
  - Previous hospitalization or health care utilization
  - Travel history
  - Social history
  - Pets/animal exposure
  - Occupational exposure
  - Environmental exposure

Clinical Presentation

- **Physical Findings**
  - Findings consistent with an infectious etiology
  - Vital signs
  - Body system abnormalities
- **Diagnostic Imaging**
  - Radiographs (x-rays)
  - Computed tomographic (CT) scans
  - Magnetic resonance imaging (MRI)

Clinical Presentation

- **Non-Microbiologic Laboratory Studies**
  - White blood cell count with differential
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein
- **Microbiologic Studies**
  - Gram stain
  - Culture and susceptibility testing

WBC and Differential

Type of Cell	Normal Value (%)	Function	Abnormalities
Neutrophil	Segs: 40–60 (0.40–0.60) Bands: 3–5 (0.03–0.05)	Phagocytic	**Leukocytosis** • Bacterial infections • Fungal infections • Physiologic stress • Tissue injury (e.g., MI) • Medications (e.g., corticosteroids) **Leukopenia** • Long-standing infection • Cancer • Medications (e.g., chemotherapy)
Lymphocyte	20–40 (0.20–0.40)	T cells (cell mediated immunity) B cells (humoral antibody response)	**Lymphocytosis** • Viral infections (mononucleosis) • Tuberculosis • Fungal infections **Lymphopenia**

WBC and Differential

Type of Cell	Normal Value (%)	Function	Abnormalities
Monocyte	2–8 (0.02–0.08)	Phagocytic Precursor to macrophage	Monocytosis • Tuberculosis • Protozoal infections • Leukemia
Eosinophil	1–4 (0.01–0.04)	Antigen-antibody reactions	Eosinophilia • Hypersensitivity reactions, including medications • Parasitic infections
Basophil	Less than 1 (0.01)		Hypersensitivity reactions

Antimicrobial Considerations in Selecting Therapy

- Drug-specific considerations in antimicrobial selection include:
  - Spectrum of activity,
  - Effects on nontargeted microbial flora,
  - Appropriate dose,
  - Pharmacokinetic and pharmacodynamic properties,
  - Adverse-effect and drug-interaction profile, and
  - Cost

Patient Considerations in Antimicrobial Selection

- Age
- Disruption of host defenses
- Site of infection
- History of recent antimicrobial use
- Antimicrobial allergies
- Renal and/or hepatic function
- Concomitant administration of other medications
- Pregnant and nursing women
- Compliance

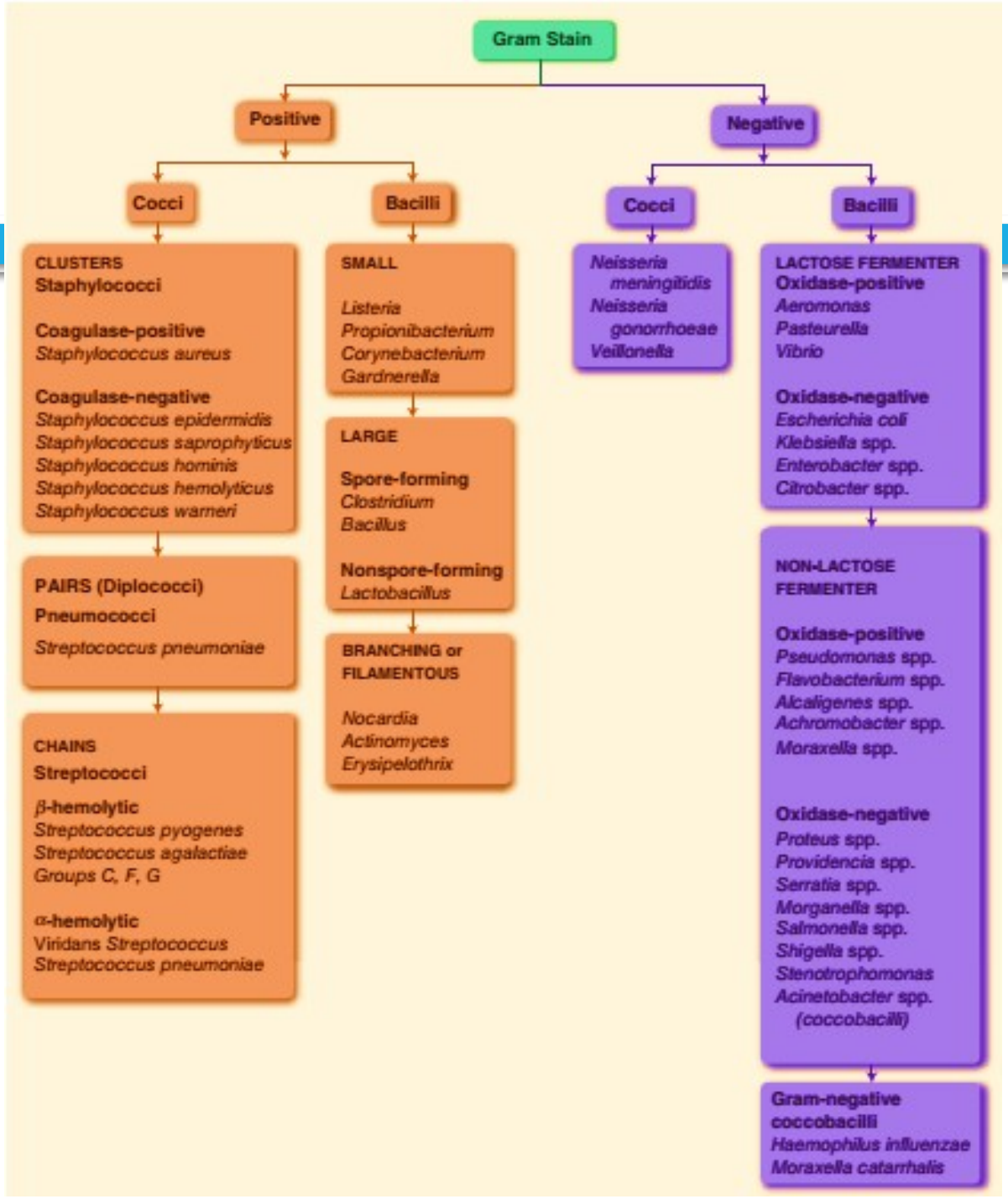
General Approach to Infectious Diseases

- **Step One: Confirm Infection**
  - Temperature > 101^0F
  - WBC > 10 X 10^3 with bands >10%
  - Assess for infection specific signs/symptoms
- **Step Two: Perform diagnostic tests/workup**
  - Obtain culture from the site of infection **before** antimicrobial administration
  - Gram stain and morphology from culture
  - Assess the severity of the infection

General Approach to Infectious Diseases

- **Step Three: Start Empiric Therapy**
  - Review list of likely infection etiologies
  - Start empiric therapy (based on local susceptibility patterns [antibiograms])
- **Step Four: Monitor Response to Therapy**
  - Check for the resolution of sign and symptoms
  - Follow-up culture results/susceptibilities and note MIC
  - Monitor for ADRs
- **Step Five: Streamline/Narrow Antimicrobial Therapy**
  - Use the most narrow spectrum antimicrobial that is susceptible from culture results

Review Your Microbiology Course



UPPER RESPIRATORY TRACT INFECTIONS

Session Objectives

- At the end of this session you will be able to:
  - Identify the different types of URTIs
  - Differentiate the common micro-organisms causing each URTIs
  - Identify the clinical presentations of URTIs
  - Set up the treatment goals for URTIs
  - List out first line and alternative antibiotics for URTIs

URTIs

- Upper respiratory tract infections include:
  - ✓ Otitis media
  - ✓ Pharyngitis
  - ✓ Laryngitis (croup)
- These infections are responsible for the majority of antibiotics prescribed in ambulatory practice and the **cost** is significant.
- Most URIs are caused by viruses, have nonspecific symptoms, and resolve spontaneously

Acute Otitis Media

- **Otitis media** is an inflammation of the middle ear.
- **Acute otitis media** involves the rapid onset of signs and symptoms of inflammation in the middle ear that manifests clinically as one or more of the following:
  - Otalgia
  - Hearing loss
  - Fever
  - Irritability.
- **Otitis media with effusion** differs from acute otitis media in that signs and symptoms of an acute infection are absent

Acute Otitis Media

- Otitis media occurs in all age groups
  - But is most common in children between 6 months and 2 years of age.
- By 3 years of age, up to 85% of children have had at least one episode of otitis media,
- Up to 20% have recurrent infections by 12 months of age.

Acute Otitis Media

Risk factors contributing to increased incidence of AOM include:

- The winter season,
- Attendance at a daycare center,
- Non–breast-feeding in infants
- Early age at first infection,
- Nasopharyngeal colonization with middle ear pathogens,
- Lower socioeconomic status
- Exposure to tobacco smoke
- Use of a pacifier
- Male gender
- Immunodeficiency
- Allergy
- Urban population

Causes

- **Common bacterial causes**
  - ***Streptococcus pneumoniae***: 20% to 35%.
  - ***Haemophilus influenzae****:* >50%
  - ***Moraxella catarrhalis***: 20%
- **Less frequent**: *Staphylococcus aureus, Streptococcus pyogenes,* and *Pseudomonas aeruginosa*
- Viral (with or without concomitant bacteria): 44%
  - Respiratory syncytial virus,
  - Influenza,
  - Parainfluenza,
  - Enteroviruses,
  - Rhinovirus, and
  - Adenoviruses

Pathophysiology

- Nasopharyngeal **viral infections** impair eustachian tube function → mucosal inflammation → impairs mucociliary clearance → promotes **bacterial proliferation** and **infection**.
- Children are predisposed to AOM because:
  - Their eustachian tubes are shorter, more flaccid, and more horizontal than those of adults:
    - Make them less functional for drainage and protection of the middle ear from bacterial entry.
- Clinical manifestations of AOM are the result of host immune response and cellular damage from inflammatory mediators such as TNF and IL that are released from bacteria.

Clinical Presentation

- **Signs and Symptoms**
  - Ear **pain** (>75% of patients)
  - Children may be **irritable**, **tug** on the involved ear, and have **difficulty sleeping**
  - **Fever** is present in less than 25% of patients and, when present, occurs more often in younger children
  - Discolored (gray), thickened, bulging **eardrum**
  - Pneumatic otoscopy or tympanometry demonstrates an immobile eardrum; **50% of cases are bilateral**
  - **Draining** middle ear fluid occurs in less than 3% of patients and usually has a bacterial etiology

Acute Otitis Media

Laboratory tests

- Gram stain, culture, and sensitivities of ear fluid if draining spontaneously or obtained via tympanocentesis

Complications

- **Infectious**: mastoiditis, meningitis, osteomyelitis, intracranial (brain) abscess
- **Structural**: perforated eardrum, cholesteatoma
- **Hearing impairment**

Case, AOM

- A 22-month-old male child presents to the pediatric clinic with 2 days of fever (38.6°C), nasal congestion, and fussiness.
- His mother reports that he was rubbing his left ear throughout the day. She states that he is more irritable than usual and was crying intermittently throughout the night last night. He is not eating as much as usual today.
- He attends daycare 5 days a week and has a 4-year-old sister who recently had a cold.

a) What information is suggestive of acute otitis media (AOM)?

b) What risk factors does this child have for AOM?

c) Is there any additional information you need to know before recommending a treatment plan?

Treatment

Desired Outcome

- Treatment goals include:
  - Pain management
  - Prudent antibiotic use
  - Secondary disease prevention.

General Approach

- Differentiate acute otitis media from **otitis media with effusion** or **chronic otitis media**, as the latter two types do not benefit substantially from antibiotic therapy.
- Address pain with oral analgesics.

Treatment

- **First line**
- **Amoxicillin**,
  - High-dose amoxicillin (80 to 90 mg/kg/day) is preferred over conventional doses (40 to 45 mg/kg/day)
- **Amoxicillin /Clavulanate**, 1000mg BID for 10 days for adults, 312mg/5ml suspension P.O. TID for 10 days OR 156mg/5ml suspension P.O. TID for 10 days for children
  - In cases of **severe illness** or when coverage for β-lactamase -producing organisms is desired,
- **Alternatives**
- **Sulfamethoxazole + trimethoprim,** Adults; 160+800mg. P.O. BID for 10 days, Children 6-12 years of age; 80+400mg P.O. BID for 10 days, OR

Treatment

- **Erythromycin**, Adults; 250mg to 500mg P.O. QID, Children; 30-50mg/kg P.O. QID OR 15-20mg/kg IV Q 4 to 6hours.
- **Azithromycin**
  - 10 mg/kg × 1 day, 5 mg/kg/day × 4 days;
  - 10 mg/kg/day × 3 days;
  - 30 mg/kg single dose
  - adult dose: 500 mg × 1 day, 250 mg × 4 days

Case, cont'd

- On further questioning, his mother states that he is "allergic" to trimethoprim/sulfamethoxazole. He was treated for a urinary tract infection 7 months ago and experienced diarrhea while taking this antibiotic. He has not received antibiotics since that time, and this is his first ear infection.
- **Immunizations**: up-to-date
- **Meds**: Acetaminophen drops 120 mg orally every 4 to 6 hours as needed for fever
- **ROS**: (+) rhinorrhea and fever, (–) vomiting, diarrhea, or
  cough

Case, cont'd

- **PE:**
  Gen: Irritable child but consolable
  VS: BP 100/64 mm Hg, P 130 beats/min, RR 22 breaths/min,
  T 39.1°C (102.4°F)
  HEENT: Erythema and severe bulging of the left tympanic
  membrane with the presence of middle ear fluid; the right
  tympanic membrane is obscured with cerumen.

d) *What are your treatment goals for this child.*

e) *Given this information, what nonpharmacologic and pharmacologic therapy do you recommend?*

Chronic Otitis Media

- Chronic **suppurative** otitis media is characterized by persistent or recurrent **purulent otorrhea** in the setting of **tympanic membrane perforation**.
- Usually, there is also some degree of conductive **hearing loss**.
- Treatment of chronic active otitis media is surgical;
  - Mastoidectomy
  - Tympanoplasty
- Can be performed as outpatient surgical procedures

Acute Pharyngitis

- Pharyngitis is an acute infection of the oropharynx or nasopharynx.
- Although viral causes are most common, **group A β-hemolytic streptococci** (GABHS; also known as *S. pyogenes*), is the primary bacterial cause.

Complications

- **Nonsuppurative complications:**
  - Acute rheumatic fever,
  - Acute glomerulonephritis, and
  - Reactive arthritis
- **Suppurative complications**:
  - Peritonsillar abscess,
  - Retropharyngeal abscess,
  - Cervical lymphadenitis,
  - Mastoiditis,
  - Otitis media,
  - Sinusitis, and
  - Necrotizing fasciitis.

Acute Pharyngitis

- Children ages 5 to 15 years are most susceptible; parents of school-age children and those who work with children are also at increased risk.
- Spread occurs via direct contact (usually from hands) with droplets of saliva or nasal secretions,
- Transmission is thus worse in institutions, schools, families, and areas of crowding

Etiology

- Viruses:
  - Rhinovirus,
  - Coronavirus,
  - Adenovirus,
  - Herpes simplex virus,
  - Influenza virus,
  - Parainfluenza virus, and
  - Epstein-Barr virus
- Bacterial: GABHS

Signs and Symptoms

- Sore throat
- Pain on swallowing
- Fever
- Headache, nausea, vomiting, and abdominal pain
- Erythema/inflammation of the tonsils and pharynx with or without patchy exudates
- Enlarged, tender lymph nodes
- Red swollen uvula, petechiae on the soft palate, and rash

Signs Suggestive of Viral Origin

- Conjunctivitis
- Coryza (nasal congestion)
- Cough
- Diarrhea

Treatment

- Desired Outcome
  - To improve clinical signs and symptoms,
  - Minimize adverse drug reactions,
  - Prevent transmission to close contacts, and
  - Prevent complications

Treatment

- **Supportive care**
  - **Antipyretic medications** and nonprescription **lozenges** and sprays containing menthol and topical anesthetics for temporary relief of pain
  - Analgesics: paracetamol
- **Pharmacologic Therapy**
  - Viral: Only symptomatic therapy
  - Bacterial:
    - Penicillin benzathine IM-single dose
      - 0.6 mIU (if ≤27 kg); 1.2 mIU(if >27 kg), 1.2 mIU for adults
    - Amoxicillin-for 10 days
- Surgical: tonsillectomy

Treatment of complication: ARF

- Acute rheumatic fever (ARF) is a nonsuppurative sequela that occurs two to four weeks following group A streptococcus pharyngitis and may consist of:
  - Arthritis
  - Carditis
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules
- Acute rheumatic fever occurs most frequently in children from 5 to 15 years of age

Treatment of complication: ARF

Jones Criteria:

- The five major manifestations are:
  1. Migratory arthritis (predominantly involving the large joints)
  2. Carditis and valvulitis (pancarditis)
  3. Central nervous system involvement (Sydenham chorea)
  4. Erythema marginatum
  5. Subcutaneous nodules

Treatment of complication: ARF

- The four minor manifestations are:
  1. Arthralgia
  2. Fever
  3. Elevated acute phase reactants (ESR, CRP)
  4. Prolonged PR interval
- Diagnostic criteria: group A streptococcal infection followed by two major manifestations or one major and two minor manifestations

Treatment of complication: ARF

- **Late sequelae — Rheumatic heart disease** is the most severe sequela of acute rheumatic fever.

- It usually occurs 10 to 20 years after the original illness and is the most common cause of acquired valvular disease in the world
- The mitral valve is more commonly involved than the aortic valve

Treatment of complication: ARF

- **Prevention**
  - **Primary prevention:** prompt diagnosis and antibiotic treatment of group A streptococcal tonsillopharyngitis
  - Secondary prophylaxis:
    - Patients who have had an attack of rheumatic fever
    - Prevention of recurrent GAS pharyngitis
    - Requires continuous antimicrobial prophylaxis
    - Penicillin benzathine IM: 0.6 mIU (if ≤27 kg); 1.2 mIU(if >27 kg), 1.2 mIU for adults

Treatment of complication: ARF

- Duration

Category	Duration after last attack
Rheumatic disease with carditis (with valvular disease)	10 years or until 40 years of age (some times life long)
Rheumatic fever with carditis with no valvular disease	10 years or until 21 years of age
Rheumatic fever without carditis	5 years or until 21 years of age

4. Viral croup (laryngotracheitis)

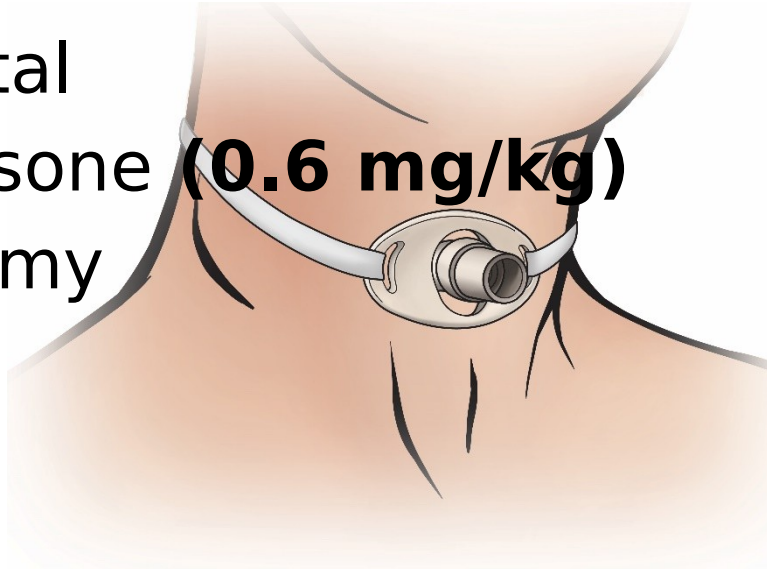
- Usually caused by parainfluenza virus
- It typically occurs in children six months to three years of age
- The viruses infect the nasal and pharyngeal mucosal epithelia initially and then spread locally along the respiratory epithelium to the **larynx** and **trachea**.
- The anatomic hallmark of croup is narrowing of the trachea in the subglottic region
- Inflammation results in **swelling and narrowing** of the airway

Viral Croup (laryngotracheitis)

- Croup causes obstruction of the upper airway, which, when severe, can be life-threatening.
- Most severe episodes occur in children ≤2 years of age.
- **Mild croup** is characterized by:
  - Fever
  - A hoarse voice
  - A barking or hacking cough
  - Stridor that is heard only when the child is agitated.
- **Severe croup** is characterized additionally by:
  - Stridor even when the child is at rest
  - Rapid breathing and lower chest indrawing
  - Cyanosis or oxygen saturation ≤90%

Treatment

- Mild Croup
  - Can be managed at home with supportive care, including encouraging oral fluids, breastfeeding or feeding, as appropriate.
- Severe Croup
  - Should be admitted to hospital
  - One dose of oral dexamethasone **(0.6 mg/kg)**
  - Intubation and/or tracheostomy



LOWER RESPIRATORY TRACT INFECTIONS

PNEUMONIA

Definition

- Pneumonia is an infection of the pulmonary parenchyma
- To **the pathologist**, pneumonia is an infection of the alveoli, distal airways, and interstitium of the lung that is manifested by:
  - Increased weight of the lungs,
  - Replacement of normal lung's sponginess by consolidation, and
  - Alveoli filled with white blood cells, red blood cells and fibrin.

Definition

- To **the clinician**, pneumonia is a constellation of symptoms and signs:
  - Fever, chills, cough, pleuritic chest pain,
  - Sputum production,
  - Increased respiratory rate,
  - Dullness to percussion, bronchial breathing,
  - Crackles, wheezes, pleural friction rub
- In combination with at least one opacity on chest radiography.

Classification

1. Etiologic

- Infections
- Inhalation of gastric contents
- Immunological reactions
- Inhalation of other toxic substances

2. Anatomic

- **Lobar or segmental**: process is confined to the division of the lung
- **Bronchopneumonia**: small areas of the lung alveoli and lobule around small terminal bronchi are affected

Classification

- **Revised Classification System**

1. Community-acquired pneumonia (CAP):

- Cases of infectious pneumonia in patients living independently in the community
- Patients who have been hospitalized for other reasons for **less than 48 hours** before the development of respiratory symptoms

2. Health care-associated pneumonia (HCAP)

a) Hospital-acquired pneumonia (HAP)

- Patients who have been hospitalized for **at least 2 days**

b) Ventilator-associated pneumonia (VAP)

- Patients contracting pneumonia **>48 hours** after the institution of **endotracheal intubation** *and* **mechanical ventilation**

Pathogenesis

- **Routes of Infection**
  - **Gross aspiration**: postoperative, seizure, stroke patients
  - **Microaspiration** of oropharyngeal secretions colonized with pathogenic microorganisms
  - **Hematogenous spread** from a distant infected site
  - **Direct spread** from a contiguous infected site
- ***Host Factors***
  - Hypogammaglobulinemia
  - Defects in phagocytosis or ciliary function, neutropenia, functional or anatomical asplenia, or a reduction in $CD4^+$ T lymphocyte counts
  - Anatomical defects such as obstructed bronchus, bronchiectasis

Community-Acquired Pneumonia

- **Epidemiology**: With an annual cost of $9.7 billion, CAP affects 4 million adults per year in the United States.
- Rates of pneumonia are higher for men than for women and for black than for white persons.
- **Risk factors**: Independent risk factors for CAP include
  - Alcoholism [RR 9],
  - Asthma (RR 4.2),
  - Immunosuppression (RR 1.9), and
  - Age of >70 years (RR 1.5 vs. age of 60 to 69 years).

Etiology

- Most cases of pneumonia are caused by a few common respiratory pathogens, including
  - S. *pneumoniae*, H. *influenzae*, S. *aureus*, M. *pneumoniae*, C. *pneumoniae*, *Moraxella catarrhalis*, *Legionella* spp., aerobic gram-negative bacteria,
  - Influenza viruses, adenoviruses, and respiratory syncytial virus.
- Overall, S. *pneumoniae* accounts for 50% of all cases of CAP requiring admission to the hospital

Microbial Causes of CAP, by Site of Care

Outpatients	Hospitalized Patients	
	Non-ICU	ICU
S. pneumoniae	*S. pneumoniae*	*S. pneumoniae*
M. pneumoniae	*M. pneumoniae*	*S. aureus*
H. influenzae	*C. pneumoniae*	*Legionella* spp.
C. pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses	*Legionella* spp.	*H. influenzae*
	Respiratory	

Clinical Manifestations

- **Signs and symptoms**
  - Abrupt onset of fever, chills, dyspnea, and productive cough
  - Rust-colored sputum or hemoptysis
  - Pleuritic chest pain
- **Physical examination**
  - Tachypnea and tachycardia
  - Dullness to percussion
  - Increased tactile fremitus
  - Chest wall retractions and grunting respirations
  - Diminished breath sounds over affected area
  - Inspiratory crackles during lung expansion

Investigations

- **Chest radiograph**
  - Dense lobar or segmental infiltrate
- **Etiologic diagnosis**
  - Gram stain of sputum
  - Culture of sputum (≤50%)
  - Blood culture (5–14%)
  - Antigen tests
  - PCR
  - Serology
  - Bronchoscopy

Treatment

- **Goals of Therapy**
  - Eradication of the offending organism through selection of the appropriate antibiotic
  - Complete clinical cure

General Approach to Treatment

- **Oxygen** or, in severe cases, mechanical ventilation and fluid resuscitation
- Administration of **bronchodilators** (albuterol) when bronchospasm is present,
- Chest physiotherapy with postural drainage if evidence of retained secretions
- **Adequate hydration** (IV if necessary), optimal nutritional support, and **control of fever**

Pharmacologic Therapy

- **Selection of Antimicrobial Agents**
  - Initially involves the empirical use of a relatively broad-spectrum antibiotic that is effective against probable pathogens
  - **Therapy should be narrowed to cover specific pathogens after the results of cultures are known.**
- **Factors to define the potential pathogens:**
  - Patient age,
  - Previous and current medication history,
  - Underlying disease(s),
  - Major organ function, and
  - Present clinical status.

Severity-of-illness scoring: CURB-65 Scoring

Symptom	Points
Confusion	1
Urea > 19 mg/dL	1
Respiratory rate ≥ 30 breaths/minute	1
SBP < 90 mm Hg, DBP ≤ 60 mm Hg	1
Age ≥ 65 yr	1

Score	Risk of Death at 30 Days (%)	Location of Therapy
0	0.7	Treat as outpatient
1	2.1	Treat as outpatient
2	9.2	Outpatient or inpatient
3	14.5	Inpatient (± ICU)
4	40.0	Inpatient (± ICU)
5	57.0	Inpatient (± ICU)

Empirical Antibiotic Treatment of CAP

- **Outpatients**
  - **Previously healthy and no antibiotics in past 3 months**
    - **A macrolide** [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg qd)] ***or***
    - **Doxycycline** (100 mg PO bid)
  - **Comorbidities or antibiotics in past 3 months:**
    - **A respiratory fluoroquinolone** (moxifloxacin [400 mg PO qd], gemifloxacin [320 mg PO qd], levofloxacin [750 mg PO qd]) **or**
    - **A β-lactam** (high-dose amoxicillin [1 g tid] or amox/clavulanate [2 g bid] or ceftriaxone [1–2 g IV qd] cefpodoxime [200 mg PO bid] or cefuroxime [500 mg PO bid]) plus **a macrolide**

Empirical Antibiotic Treatment of CAP

- **Inpatients, non-ICU**
  - **A respiratory fluoroquinolone** [moxifloxacin, gemifloxacin, levofloxacin]

    OR
  - **A β-lactam** [cefotaxime, ceftriaxone, ampicillin] *plus* **a macrolide** [clarithromycin or azithromycin]
- **Inpatients, ICU**
  - A **β-lactam** [cefotaxime, ceftriaxone, ampicillin-sulbactam]

    PLUS
  - azithromycin or a fluoroquinolone

Switch from IV to PO Antibiotics

- Switching from IV to PO antibiotics can be done safely when:
  - The white blood cell count is returning toward normal,
  - There are two normal temperature readings (37.5 ^{0}C) 16 hr apart, and
  - There is improvement in cough and shortness of breath.



Case study, Pneumonia

- M.R. is a 33-year-old man presenting to the ED with fevers, chills, and chest pain. His symptoms have persisted for 3 days, and he has a productive cough with rusty-colored sputum and dyspnea with exertion. He has had no recent illnesses and no known sick contacts, but he was recently released from a 2-year period of incarceration. He has tried ibuprofen to alleviate his fever and chest pain
- Past medical history is positive for asthma, for which he is prescribed fluticasone and albuterol, and depression, for which he takes sertraline

Case study, Pneumonia

- Vital signs reveal a temperature of 40.1◦C, heart rate of 128 beats/minute, blood pressure of 130/76 mm Hg, and respiratory rate of 32 breaths/minute with accompanying oxygen saturations of 85% on 5 L of oxygen by nasal cannula. The remainder of the physical examination is notable for orientation to person but not place or time and for diffuse crackles bilaterally, which are most apparent on the right side.
- Laboratory results include: **WBC**, 15,500 cells/**μ**L; **Hematocrit**, 29.3%; **Sodium**, 133 mmol/L; **Potassium**, 3.8 mmol/L; **BUN**, 23 mg/dL; **SCr**, 0.8 mg/dL; **Glucose** 148, mg/dL; **pH** 7.42; **PO2**, 61 mm Hg; **PCO2**, 46 mm Hg; **HCO3**, 28 mEq/L

Case study, Pneumonia

- A test for human immunodeficiency virus is negative. Chest radiograph reveals a right lower lobe infiltrate.

1. What signs, symptoms, and tests are consistent with CAP in M.R.?
2. Which antimicrobial agent(s) should be chosen for the initial management of M.R?
3. What is the appropriate length of therapy for M.R.?
4. What are the monitoring parameters for treatment outcome?

Health Care-Associated Pneumonia (HCAP)

- **Hospital-acquired pneumonia (HAP)**
  - Patients who have been hospitalized for *at least 2 days*
- **Ventilator-Associated Pneumonia (VAP)**
  - Patients contracting pneumonia *greater than 48* hours after the institution of *endotracheal intubation and mechanical ventilation*

HCAP

- Endotracheal intubation increases the risk of pneumonia in several ways.
  - The tube serves as a direct conduit for bacterial introduction into the lower respiratory tract,
  - Prevents effective coughing to clear lower respiratory secretions,
  - Damages the tracheal epithelium, and
  - Allows the accumulation of oropharyngeal secretions

Microbiologic Causes of VAP

Non-MDR Pathogens	MDR Pathogens
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	MRSA
Haemophilus influenzae	*Acinetobacter* spp.
MSSA	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	✓ *Enterobacter* spp.
✓ *Escherichia coli*	✓ ESBL-positive strains
✓ *Klebsiella pneumoniae*	✓ *Klebsiella* spp.
✓ *Proteus* spp.	✓ *Legionella pneumophila*
✓ *Enterobacter* spp.	✓ *Burkholderia cepacia*

HCAP Treatment

Patients without Risk Factors for MDR Pathogens	Patients with Risk Factors for MDR Pathogens
Ceftriaxone or cefotaxime or	***1. A β-lactam:***
Moxifloxacin, ciprofloxacin, or levofloxacin ***or***	Ceftazidime (2 g IV q8h) or cefepime (2 g IV q8–12h) ***or***
Ampicillin/sulbactam (3 g IV q6h) ***or***	Piperacillin/tazobactam, ***plus***
Ertapenem (1 g IV q24h)	***2. A second agent active against gram-negative bacteria:***
	Gentamicin (7 mg/kg IV q24h) ***or***
	Ciprofloxacin or levofloxacin ***plus***
	3. An agent active against gram-positive bacteria:
	Vancomycin (15 mg/kg q12h) or Linezolid

Duration of Antimicrobial Therapy

- Adult outpatient CAP:
  - 5-day duration of therapy: levofloxacin (the 750-mg dose) and azithromycin
  - 7 to 10 days for other therapies
- Admitted to the hospital: 7 to 10 days
- HCAP, HAP, or VAP: 10 to 21 days.

PNEUMONIA IN PEDIATRICS

Etiologies

AGE GROUP	PATHOGENS
Neonates (<3 wk)	GBS, *E coli,* other Gram-negative bacilli, *S pneumoniae, H inflenzae*
3 wk-3 mo	RSV, other respiratory viruses (rhinoviruses, parainflenza virus, inflenza virus, adenovirus), *S. pneumoniae, H. inflenzae*;
4 mo-4 yr	RSV, other respiratory viruses (rhinoviruses, parainflenza virus, inflenza virus, adenovirus), *S. pneumoniae, H. inflenzae*, *M. pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, C. pneumoniae, H. inflenzae*, inflenza viruses, adenovirus, *Legionella pneumophila*

Pneumonia in Pediatrics

- Pneumonia is classified as severe or non-severe on the basis of clinical features,
- The management is based on the classification.

Severe Pneumonia

- Diagnosis: Cough or difficulty in breathing, plus at least one of the following:
  - Central cyanosis or oxygen saturation < 90% on pulse oximetry
  - Severe respiratory distress (e.g. grunting, very severe chest indrawing)
  - Signs of pneumonia with a general danger sign:
    - Inability to breastfeed or drink,
    - Lethargy or unconscious,
    - Convulsions.

Treatment

- Admit the child to hospital.
- Oxygen therapy
- Antibiotic therapy
  - Give intravenous ampicillin (or benzylpenicillin) and gentamicin.
    - Ampicillin 50 mg/kg IM or IV every 6 h for at least 5 days
    - Gentamicin 7.5 mg/kg IM or IV once a day for at least 5 days
  - If no improvement within 48 h and staphylococcal pneumonia is suspected, switch to gentamicin 7.5 mg/kg IM or IV once a day and cloxacillin 50 mg/kg IM or IV every 6 h
  - Use ceftriaxone (80 mg/kg IM or IV once daily) in cases of failure of first line treatment.
- Supportive Care
  - If the child has fever (≥ 39 °C), give paracetamol.
  - If wheeze is present, give a rapid-acting bronchodilator, and start steroids when appropriate.

Pneumonia

Diagnosis

- Cough or difficult breathing plus at least one of the following signs:
  - Fast breathing:
    - age 2–11 months, ≥ 50/min
    - age 1–5 years, ≥ 40/min
  - Lower chest wall indrawing
  - Crackles or pleural rub

Pneumonia

Treatment

- Treat child as outpatient.
- Advise parents to give normal fluid requirements plus extra breast milk or fluids if there is a fever.
- Antibiotic therapy
  - Oral amoxicillin 40 mg/kg per dose twice a day for 5 days

No pneumonia: cough or cold

- No signs of pneumonia or severe pneumonia
- Home care
  - Soothe the throat and relieve cough with safe remedy.

OUTCOME EVALUATION

- Improvement of symptoms (within 24 to 72 hours)
  - resolution of cough, sputum production, and presence of constitutional symptoms (malaise, nausea or vomiting, and lethargy)
- Assess WBC, chest radiograph, and blood gas determinations

TUBERCULOSIS

Pharmacotherapy

Objectives

- Identify the etiology and pathophysiology of TB
- Recognize the transmission mechanism of TB
- Identify clinical manifestation and diagnosis of TB
- Recommend the appropriate treatment regimens for PTB and extrapulmonary TB
- Identify drugs important for the management of MDR TB
- Manage adverse effects of anti-TB drugs

Epidemiology

- Tuberculosis (TB) is one of the top 10 causes of death worldwide??
- Every year, 10 million people fall ill with tuberculosis
- 1.5 million people die from TB each year – making it the worlds infectious killer
- Tuberculosis is the leading cause of death of people with HIV.
  - In 2016, 40% of HIV deaths were due to TB.
- About half of all people with tb can be found in 8 countries: Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines, and South Africa.

Etiology

- TB is caused by M. *tuberculosis*, an aerobic, non–spore-forming bacillus that resists decolorization by acid alcohol after staining with basic fuchsin.
  - An **acid-fast bacillus (AFB)**.
- It is also different from other organisms in that it replicates slowly once every 24 hours instead of every 20 to 40 minutes as do some other organisms.
- M. *tuberculosis* thrives in environments where the oxygen tension is relatively high, such as the apices of the lung, the renal parenchyma

Transmission

- Transmitted through the air by aerosolized droplet nuclei that are produced when a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings.
- These droplet nuclei, which contain one to three M. *tuberculosis* organisms, are small enough (1–5 µg) to remain airborne for long periods of time and reach the alveoli within the lungs when inhaled.

Transmission

- Several factors influence the likelihood of transmission of *M. tuberculosis*, including:
  - The number of organisms expelled into the air
  - The concentration of organisms in the air determined by the volume of the space and its ventilation
  - The length of time an exposed person breathes the contaminated air
  - The immune status of the exposed individual
  - Family household contacts, especially children, and persons working or living in an enclosed environment (e.g., hospitals, nursing homes, prisons) with an infected person

Pathogenesis

- **TB develops in the human body in two stages:**
  - Individual who is exposed to micro-organisms from an infectious case becomes infected, (TB infection)
  - Infected individual develops the disease.
- **What happens after infection?**
  - Most (80-90%) will never become ill unless their immunity is seriously compromised.
  - About 5% are likely to develop disease immediately following infection
  - The remaining 5% will have a risk of developing TB in their life time

Risk factors for active TB among persons who have been infected with Tubercle Bacilli

Factor	Relative Risk/Odds
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidity	
✓ HIV infection	100
✓ CKD/hemodialysis	10–25
✓ Diabetes	2–4
✓ Intravenous drug use	10–30
✓ Immunosuppressive treatment	10
✓ Gastrectomy	2–5
✓ Jejunoileal bypass	30–60
✓ Posttransplantation period (renal, cardiac)	20–70
✓ Malnutrition and severe	2

Clinical Manifestations

- Tuberculosis is classified as:
  - **Pulmonary**,
  - **Extrapulmonary**, **or**
  - **Both**
- Before the advent of HIV infection, **80%** of all new cases of tuberculosis were limited to the lungs.
- However, up to **two-thirds** of HIV-infected patients with tuberculosis may have both pulmonary and extrapulmonary disease or extrapulmonary disease alone.

TB Diagnosis

A TB suspect:

- Any person who presents with symptoms and signs suggestive of TB, in particular cough of ≥ 2 weeks duration.

A case of tuberculosis:

- A patient in whom TB has been bacteriologically confirmed, or who has been diagnosed by a clinician.

Case-finding - Pulmonary TB

Symptoms of Pulmonary TB:

- TB in the lungs cause **cavities** which lead to:
  - **Cough**: this is the commonest symptom of pulmonary TB.
    - It is usually of long duration (≥ 2 weeks).
  - **Blood stained sputum (haemoptysis)**
  - **Chest pain**
  - **Shortness of breath**

Case-finding

- **General, systemic symptoms of TB:**
  - **Fever**: often at night & night sweat
  - **Loss of appetite & malaise**
  - **Weight loss**

Diagnostic methods

A. History and physical examination:

- Signs and symptoms
- History of anti-TB treatment previously.
- Check lymph nodes, lungs and other systems as appropriate.

Diagnostic methods

B. Microscopic examination of sputum smears:

- Most important and reliable.
- 3 sputum specimens must be collected
- Spot - Early morning - spot

✍ Smear-positive PTB is confirmed when there are **at least two** AFB positive smear results.

✍ In HIV positive individual, smear- positive PTB is diagnosed when **one** AFB positive smear result is found.

Diagnostic methods

C. Radiological examination:

- X-ray may be helpful in the diagnosis of PTB, miliary TB and childhood TB when interpreted in conjunction with presenting signs and symptoms
- **It is a major error to omit sputum examination and diagnose TB based on X-ray findings alone!**

Diagnostic methods

D. Culture

- A complex and sophisticated tool.
- It takes up to 6 weeks to yield results.
- It is required for drug sensitivity testing.
- Not routinely practiced.

Diagnosis of Latent *M. tuberculosis* Infection

Tuberculin Skin Testing (TST)

- Mantoux method
- A positive skin test is not necessary for the diagnosis of active TB disease.
- The skin test is performed by injecting 0.1 mL of solution containing purified protein derivative (PPD) intracutaneously into the surface of the forearm.
- A discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter should be produced when the injection is performed correctly

TREATMENT AND FOLLOW-UP OF TB

- **Desired Outcomes**
  - To cure the patient
  - To decrease disease transmission
  - To prevent death from active TB
  - To prevent relapse
  - To prevent the development of drug resistance

Anti-TB drugs

Anti-TB	Adult Dose	Pediatrics Dose
Isoniazid (H)	5mg/kg	10-15mg/kg
Rifampicin (R)	10mg/kg	10-20mg/kg
Ethambutol (E)	15mg/kg	15-20mg/kg
Pyrazinamide (Z)	25mg/kg	15-30mg/kg
Streptomycin (S)	15mg/kg	20-40mg/kg

Anti-TB drugs

- **Drugs available in FDC in Ethiopia:**
  - HRZE – 75/150/400/275 mg
  - RHZ – 150/75/400 mg
  - HRE – 75/150/275 mg
  - RH – 150/75 mg
- **Drugs available as loose form are:**
  - Ethambutol 400mg
  - Isoniazid 100mg, 300mg
  - Streptomycin 1gm vial

Anti-TB drugs

- Pediatric formulations available
  - RH: 60mg+30mg (dispersible)
  - RH: 60mg+60mg (dispersible)
  - RHZ: 60mg+30mg+150mg (dispersible)
  - RHZ: 75mg+50mg+150mg (dispersible)
- Pediatric drugs as loose form
  - Ethambutol: 100mg tab
  - Isoniazid: 100mg tab

Phases of Chemotherapy

- **There are two phases:**

1. Intensive (initial) phase

- Consists of 4 drugs
- Duration
  - 8 wks
- The drugs must be swallowed daily under DOT
- **Rapid killing** of actively growing and semi dormant bacilli.
- It renders the patient non infectious

Phases of Chemotherapy

2. Continuation phase

- Immediately follows the intensive phase
- Consists of 2 drugs
- Duration is 4 months
- Except for re-treatment cases drugs must be collected every month.
- Eliminates bacilli that are still multiplying.
- Reduces failures and relapses.

1. New Patients

ew patients **presumed** or **known** to have drug-susceptible T

New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: **2HRZE/4HR**

Wherever feasible the optimal dosing frequency for new patients with pulmonary TB is **daily** throughout the course of therapy

2(RHZE)/4(RH)

Wt in KG	Regimen	
	Intensive Phase 2(RHZE) (150/75/400/275)	Continuation phase 4(RH) (150/75)
20-29	1 ½	1 ½
30-39	2	2
40-54	3	3
≥55	4	4

New, Pediatric FDC dosing for children using RHZ 75/50/150mg

Weight bands	Intensive phase (2 months)		Continuation phase (4 months)
	RHZ 75/50/150mg tablet	E 100mg tablet	RH 75/50mg tablet
4-7kg	1	1	1
8-11kg	2	2	2
12-15kg	3	3	3
16-24kg	4	4	4
25+kg	Adult dosages recommended		

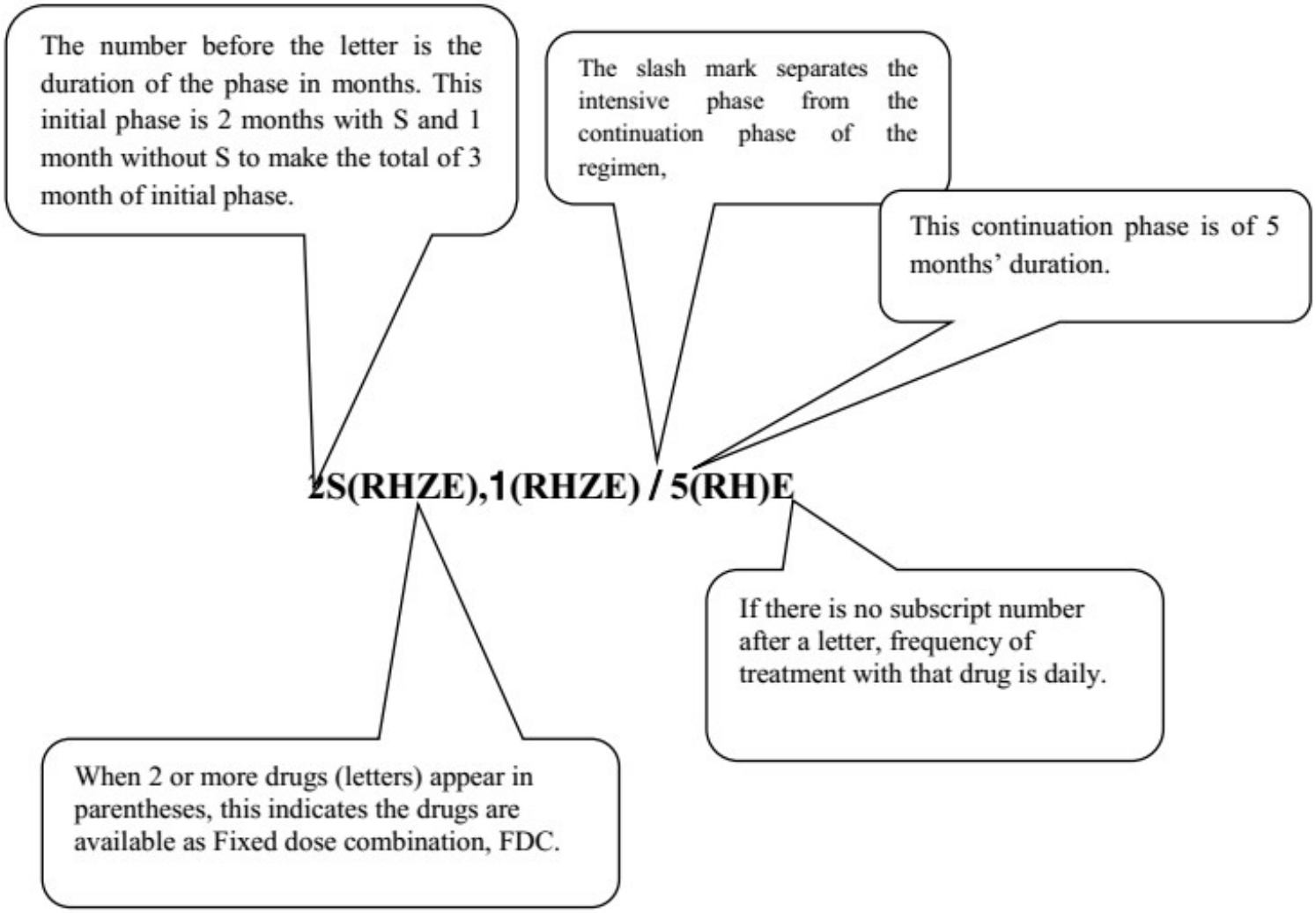
Old, Pediatric FDC dosing for children using RHZ 60/30/150mg

Weight band (Kg)	Numbers of tablets		
	Intensive phase		Continuation phase
	RHZ 60/30/150	E 100	RH 60/30
4-6	1	1	1
7-10	2	2	2
11-14	3	2	3
15-19	4	3	4
20-24	5	4	5
25+	Adult dosages recommended		

2. Previously Treated Patients

- Patients eligible for retreatment should be referred for a rapid molecular test or drug susceptibility testing to determine at least rifampicin resistance, and preferably also isoniazid resistance status.
- On the basis of the drug susceptibility profile, a standard first-line treatment regimen (2HRZE/4HR) can be repeated if no resistance is documented; and if rifampicin resistance is present, an MDR-TB regimen should be prescribed
- In patients who have had treatment interruption, the reason for the interruption, such as medication stock-outs, adverse effects from medicines or need for greater patient/provider education should be addressed.

Codes


The number before the letter is the duration of the phase in months. This initial phase is 2 months with S and 1 month without S to make the total of 3 month of initial phase.
The slash mark separates the intensive phase from the continuation phase of the regimen,
This continuation phase is of 5 months' duration.
2S(RHZE),1(RHZE) / 5(RH)E
If there is no subscript number after a letter, frequency of treatment with that drug is daily.
When 2 or more drugs (letters) appear in parentheses, this indicates the drugs are available as Fixed dose combination, FDC.

Co-Management of HIV and Active TB

- The first priority for HIV-positive TB patients is to initiate TB treatment, followed by co-trimoxazole and ART

• TB patients with known positive HIV status and all TB patients living in HIV prevalent settings should receive daily TB treatment at least during the intensive phase
• It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV negative TB patients

Co-Management of HIV and Active TB

Co-trimoxazole preventive therapy

- In all HIV-positive TB patients, co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment.

Antiretroviral Therapy

- ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count.
- TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment

Co-Management of HIV and Active TB

- The recommended first-line ART regimens for TB patients are those that contain efavirenz (EFV)
- For those who are unable to tolerate EFV or who have contraindications to an EFV-based regimen, the lead-in dose of nevirapine is not necessary.
- For PI regimen with RTV boosted:
  - Rifampicin → rifabutin,
  - If rifabutin is not available, ↑ RTV dose

Treatment during Pregnancy and Breast-Feeding

- ***Streptomycin*** is ototoxic to the fetus and should not be used during pregnancy.
- A breastfeeding woman who has TB should receive a full course of TB treatment
- After active TB in the baby is ruled out, the baby should be given 6 months of **isoniazid preventive therapy**, followed by BCG vaccination.
- Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid

Comorbid states

- **Leprosy**
  - Rifampicin will be common to both regimens and it must be given in the doses required for TB.
- **Renal failure**
  - Avoid *streptomycin* and *Ethambutol*
  - Give ***2RHZ/4RH***.
- **Liver disease**
  - Do not give *Pyrazinamide* because this is the most hepatotoxic anti-TB drug.
  - Recommended regimens are:
    - ***2SERH/6EH or 2SEH/10EH***

Treatment of Extrapulmonary TB

- Lymphatic, pleural, and bone or joint disease are the **most common**, while **pericardial**, **meningeal** and ***disseminated*** (miliary) forms are more likely to result in a fatal outcome.
- Pulmonary and extrapulmonary disease should be treated with the same regimens.
- **Note** that some experts recommend 9–12 months of treatment for **TB meningitis** given the serious risk of disability and mortality, and 9 months of treatment for TB of **bones** or

Extrapulmonary TB

- **Pericardial TB**
  - Same regimen of anti-TB as Pulmonary TB
  - Corticosteroid as adjuvant therapy for 11 weeks

Week of Rx	Dose
1-4	60mg/day
5-8	30mg/day
9-10	15mg/day
11th	5mg/day

- **Pleural TB**
  - Same regimen of anti-TB as Pulmonary TB
  - No adjuvant corticosteroid
  - Surgical drainage

Extrapulmonary TB

- **TB Meningitis**
  - Associated with high mortality and sequale
  - High risk for RVI patients
  - Anti-TB:
    - **Intensive phase**: RHZE for 2 months
    - **Continuation phase**: RH for 7 to 10 months
  - Adjuvant corticosteroids
    - **Dexamethasone** 8 mg/day for <25kg or 12mg/day for >25kg for 3 weeks,
      - Then tapered off gradually over the following 3 to 4 weeks.

Management of Common Side Effects

Hepatotoxicity

- **INH**, **R** and **Z** are all associated with hepatitis.
- **E** is the only safe drug to use in people with liver disease.
- Risk factors for medicine induced liver disease:
  - Preexisting liver disease (cirrhosis, hepatitis), co-infection with Hepatitis B/C
  - Concomitant hepatotoxic drugs such as amiodarone, paracetamol, cotrimoxazole, statins
  - HIV associated hepatobiliary disease
  - History of alcohol abuse
  - Patients older than 35 years

Hepatotoxicity

- Hepatotoxicity occurs most commonly in first 2 mons but occasionally can occur later.
- Patient may present with nausea, vomiting and abdominal discomfort.
- They may or may not have jaundice and could present with fulminant hepatic failure.
- Investigations
  - ALT/AST, > 5 times upper limit of normal (ULN), it indicates liver cell damage (**hepatitis**)
  - Disproportional increase in alkaline phosphatase (ALP) and total bilirubin levels is most commonly seen in **Rifampicin**.

Hepatotoxicity

- Management
  - Rule out other causes
  - Conduct liver function tests, serological testing for Hepatitis A, B and C
  - Stop all medicines the patient is taking
  - Monitor the clinical symptoms until they resolve
  - Monitor the ALT until the levels are less than 100 IU/l and bilirubin levels normal.
  - Start Rifampicin, repeat ALT on day 3,
  - If normal, add H on day 4 to 6, repeat ALT on day 7,
  - If normal, add E on day 8-10, check ALT on day 10,
  - If normal add Z, repeat ALT weekly for a month

Gastro-intestinal intolerance

- The drug most commonly associated with gastro-intestinal intolerance is **rifampicin**.
- The symptoms usually occur within the first few weeks of treatment and are:
  - Nausea, vomiting
  - Poor appetite
  - Mild abdominal pain
  - Diarrhea occurs less frequently.

Gastro-intestinal intolerance

Management

- Exclude other possible causes of GI intolerance such as alcohol intake, non-steroidal anti-inflammatory drugs
- Ask patient about history of gastritis, gastric ulcers, gastro-esophageal reflux, pancreatitis etc
- These are managed symptomatically as they are mild.
- Consider changing the time for drug administration, taking medication just before or after a meal or with a light snack or at bedtime
- Give antacid, anti-emetic, antidiarrheal depending on the severity of symptoms. Patient should be advised not to take the antacid 1 hour before and 2 hours after taking treatment as the aluminium reduces INH bioavailability.

Peripheral neuropathy

- The main cause of peripheral neuropathy is **Isoniazid**.
- It occurs more commonly in patients who are malnourished, diabetics, abuse alcohol, patients with renal failure, pregnant women and breastfeeding mothers and HIV positive patients, including those patients on ART

Symptoms and signs

- Tingling/ burning sensation and numbness of the hands and feet

Management

- This can be treated by giving the patient Pyridoxine **50 – 75mg** daily, the recommended dose for HIV positive patients is **100mg** daily.

Prevention

- In the high risk groups, peripheral neuropathy can be prevented by adding Pyridoxine to the TB treatment.
- The recommended dose is **25 mg** daily.

Optic neuritis

- Progressive loss of vision caused by retrobulbar neuritis usually manifests first as loss of color vision and usually presents after the patient has been on treatment for at least two months.
- This is usually caused by excessive doses of **ethambutol**.
- **Ethambutol** should not be given if there is pre-existing optic neuritis.

Symptoms and signs

- Reduced red-green color discrimination
- Blurred vision
- Difficulty in reading
- These may occur in one or both eyes

Management

- Stop the treatment immediately and introduce individual drugs (excluding Ethambutol)

Rash

All TB drugs can cause rash.

RASH TYPE	MANAGEMENT
Mild itching rash	1) Give antihistamine 2) Prednisone may be added 3) A topical cream may be added
Petechial rash	1) Mainly due to Rifampicin 2) Conduct Platelet count 3) If below normal range, stop Rifampicin . 4) Monitor platelet count until it returns to normal
Erythematous rash with fever	1) Stop all drugs 2) Rule out anaphylaxis reaction 3) If treatment cannot be interrupted due to severity of disease, a regimen comprising other drugs the patient has not used can be started 4) If rash improves, the drugs can be reintroduced one by one every 2-3 days starting with Rifampicin Isoniazid pyrazinamide and ethambutol.

PREVENTION

- By far the best way to prevent tuberculosis is to diagnose and isolate infectious cases rapidly and administer appropriate treatment until patients are rendered noninfectious and the disease is cured.
- BCG vaccination and
- Treatment of persons with *latent tuberculosis infection* who are *at high risk of developing active*

Drug	Interval and duration
Isoniazid	**Daily for 9 months**
Rifampin	**Daily for 4 months**

INH PROPHYLACTIC THERAPY (IPT)

Rationale of IPT

1. At least 30% of the world population is latently infected with tuberculosis (TB) worldwide
2. The risk of active TB disease is greatly elevated in HIV+ persons
   - 10% annual risk; 50% lifetime risk
   - TB accounts for up to 40% of all AIDS deaths
3. IPT reduces risk of TB in PLWH by 33-67%, reduces risk of death by 26%;
4. Prevent further transmission of TB in the community

Indication of IPT

- HIV positive with no clinical, bacteriologic or radiological evidence of active TB

Administration of INH

- Daily self-administered INH at a dose of 5mg/kg (a maximum dose of 300mg/day) for

Body weight	Dosage
Adults < 30 kg	150 mg = half tablet for 6 months
Adults > 30 kg	300 mg = one tablet for 6 months

Plus **pyridoxine** at a fixed daily dose of 25mg

9 months

Contraindications of IPT

- Active TB confirmed clinically, bacteriologically or by radiology:
- Abnormal CXR
- Diagnosis of TB in the past 3 years
- Active hepatitis [Clinical or Lab]
- Prior allergy or intolerance to INH
- Known or reported high daily alcohol consumption
- History of poor compliance with treatment

Follow up of patients on IPT

- Monitor patients monthly, including:
  - Provision of a one-month supply of isoniazid
  - Counseling about adherence
  - Clinical evaluation for toxicity (especially hepatitis) [nausea, vomiting, abdominal pain, jaundice]
  - Clinical evaluation for active TB disease
  - Educate at each visit about the importance of adherence, signs of toxicity (hepatitis), signs of active tuberculosis, and HIV-prevention

Alternative TB Preventive

- Isoniazid (INH) and rifapentine (RPT) known as **3HP**:
  - Adult: 900mg INH/900mg RPT for **three months**
- Rifampicin and isoniazid (**3RH**):
  - Adult and pediatric FDC for **three months**

DRUG RESISTANT TUBERCULOSIS

Rifampicin Resistant TB (RR-TB)	Resistance to rifampicin, with or without resistance to other TB medicines. This maybe mono, poly, multi or extensive drug resistance.
Multi Drug Resistant TB (MDR-TB)	Resistance to at least both rifampicin and isoniazid
Extensive Drug Resistant TB (XDR-TB)	Resistance to any **fluoroquinolone** and to at least one of the **three second line injectable** drugs (capreomycin, kanamycin and amikacin), in addition to multi drug resistance.
Mono resistance TB	Resistance to one of the first line TB medicines (rifampicin, isoniazid, pyrazinamide or ethambutol)
Poly Drug Resistant TB	Resistance to more than one first line TB medicines. This excludes resistance to both

Treatment of Drug-Resistant Tuberculosis

Group	Drugs (abbreviations)
Group 1: First-line oral agents	• Pyrazinamide (Z) • Ethambutol (E) • Rifabutin (rfb)
Group 2: Injectable agents	• Kanamycin (Km) • Amikacin (Am) • Capreomycin (Cm) • Streptomycin (S)

Group 3: fluoroquinolones	• Levofloxacin (Lfx) • Moxifloxacin (Mfx) • Ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• Para-aminosalicylic acid (PAS) • Cycloserine (Cs) • Terizidone (Trd) • Ethionamide (Eto) • Protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• Clofazimine (Cfz) • Linezolid (Lzd) • Amoxicillin/clavulanate (Amx/Clv) • Thioacetazone (Thz) • Imipenem/cilastatin (Ipm/Cln) • High-dose isoniazid (high-dose

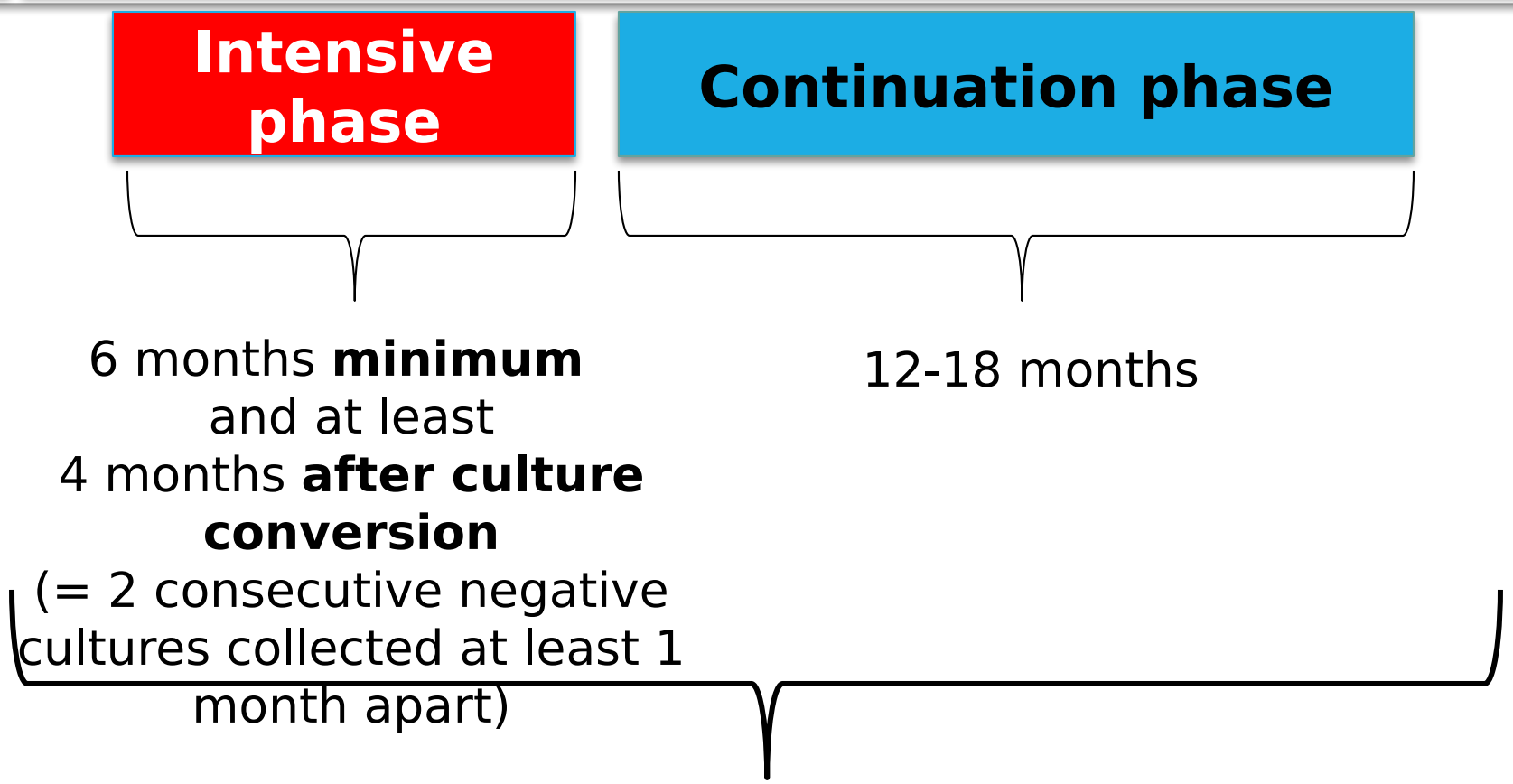
General Principles for Designing MDR-TB Treatment Regimens

- Treatment regimens should consist of at least four drugs
- Use any of the first-line oral agents (group 1) that are likely to be effective.
- Use an effective aminoglycoside or polypeptide by injection (group 2).
- Use a fluoroquinolone (group 3).
- Use the remaining group 4 drugs to complete a regime at least four effective drugs.
- For regimens with fewer than four effective drugs, consider adding two group 5 drugs.

Designing Regimen

- **Intensive phase:** An injectable agent (an aminoglycoside or capreomycin) and oral drugs are used.
  - The injectable is given for a **minimum of six months and at least four months after culture conversion.**
- **Continuation phase:** Oral drugs are given.
  - The minimum length of treatment is **18 months after culture conversion**. Extension to 24 months may be indicated in chronic patients with extensive pulmonary damage.

Duration of MDR-TB Therapy



Standardized MDR-TB Regimen

Intensive phase

- **8 Z-Cm_6-Lfx–Pto-Cs**

Continuation phase

- **12 Z-Lfx–Pto-Cs**

Review Question

1) A 34-year-old woman currently on treatment for tuberculosis disease comes to the pharmacy and states she shows a positive pregnancy test despite being on oral contraceptives. Which one of the following drugs most likely caused her to become pregnant?

A. Pyrazinamide

B. Isoniazid

C. Ethambutol

D. Rifampin

Review Questions

2) A-month ago, a 10-kg and 8-month male baby with active tuberculosis infection was put on 2 tabs of RHZ (75/50/150) and 2 tabs of E (100mg). Today, the baby was clinically stable with good appetite and gained 3 kgs. How do you refill these anti-Tb's for this baby?

A. 2 tabs of RHZ and 2 tabs of E

B. 3 tabs of RHZ and 3 tabs of E

C. 3 tabs of RHZ and 2 tabs of E

D. 4 tabs of RHZ and 4 tabs of E

Review Questions

3) Which extrapulmonary TB patients need to be treated with corticosteroids?

4) Put these antiTB drugs in the order of hepatotoxicity:

Rifampicin, Ethambutol, Pyrazinamide, Isoniazid

5) What is the indication of IPT in Ethiopia?

INFECTIVE ENDOCARDITIS

Objectives

- Upon completion of this topic you will be able to:
  - Describe the most likely causative organisms of IE.
  - Identify the clinical presentation and laboratory evaluation for IE.
  - Develop appropriate pharmacologic treatments for IE.
  - Define appropriate pt populations requiring prophylactic treatment & differentiate appropriate drug regimens.
  - Devise a monitoring plan for pts with IE.

Introduction

- **Endocarditis** is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves.
- **Infectious Endocarditis** (IE) is an infection of the heart's endocardial surface
- Endocarditis may be classified according to:
  - The temporal evolution of disease,
  - The site of infection,
  - The cause of infection, or
  - A predisposing risk factor such as injection drug use.

Epidemiology

- 10,000 to 20,000 new cases annually in US
- Considered the 4th leading cause of serious infections following:
  - **Sepsis** 2⁰ UTI
  - **Pneumonia**, and
  - **Intraabdominal infections**
- More than 50% of cases occur in patients older than 50 year

Classification

- Classified into four groups (causes):
  - Native Valve IE
  - Prosthetic Valve IE
  - Intravenous drug abuse (IVDA) IE
  - Nosocomial IE

Classification

Acute

- Affects normal heart valves
- Rapidly destructive
- Metastatic foci
- Commonly Staph.
- If not treated, usually fatal within 6 weeks

Subacute

- Often affects damaged heart valves
- Indolent nature
- If not treated, usually fatal by one year

Risk factors

- Presence of a prosthetic valve (highest risk)
- Previous endocarditis (highest risk)
- Congenital heart disease
- Chronic intravenous access
- Diabetes mellitus
- Healthcare-related exposure
- Acquired valvular dysfunction (e.g., rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with regurgitation
- IVDA
- Poor oral hygiene

Infecting Organisms

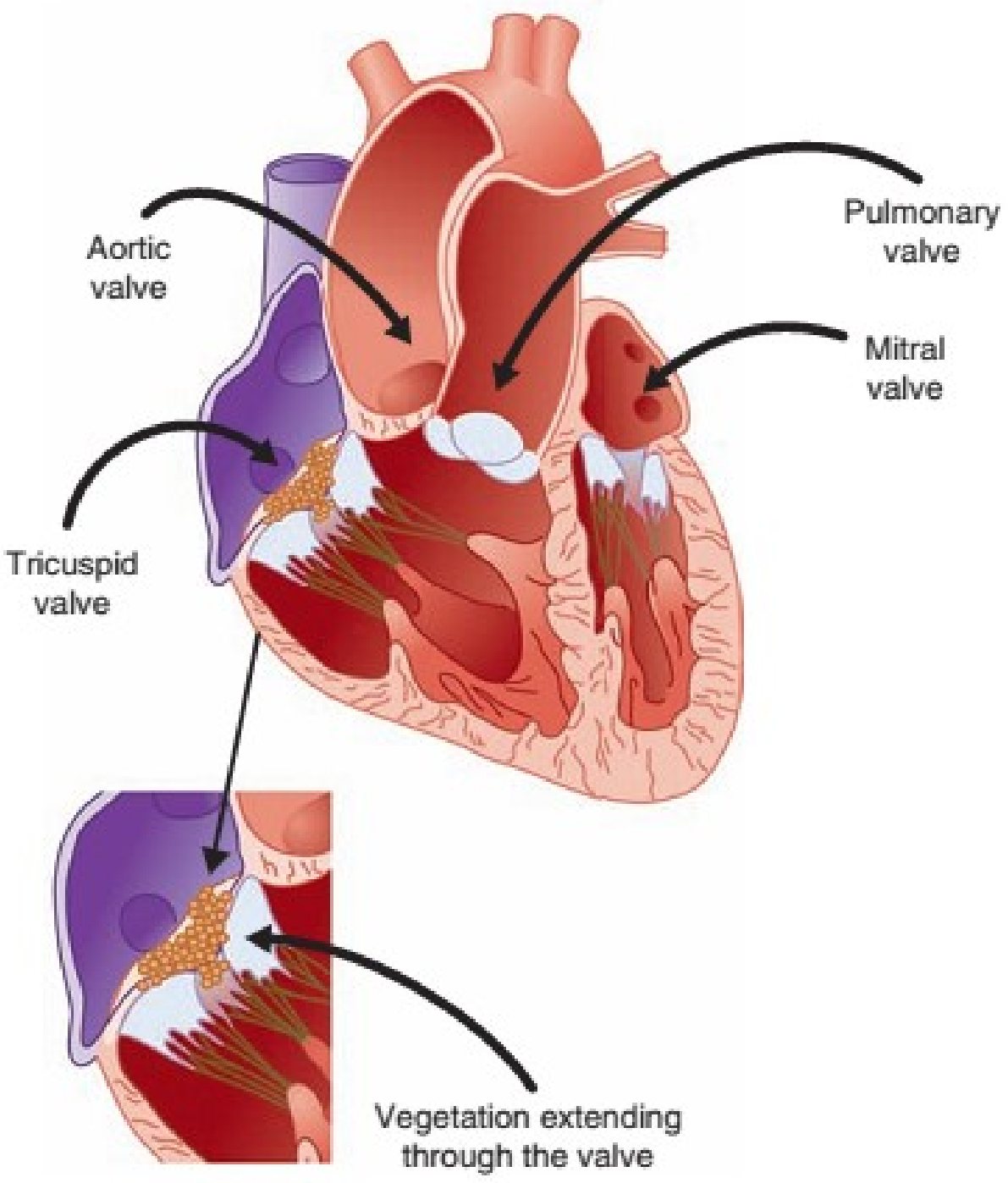
- Common bacteria
  - S. *aureus*
  - Streptococci
  - Enterococci
- Not so common
  - Fungi
  - Pseudomonas
  - HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*)

Pathogenesis

- Alteration of the endothelial surfaces of the heart valves to allow for organism attachment and colonization.
  - Rheumatic heart disease
  - Injury from turbulent blood flow
- Platelets and fibrin now deposit on the damaged valves, forming a **nonbacterial thrombotic endocarditis** (**NBTE**).
- Bacteria through hematogenous spread (i.e., bacteremia) adhere to and colonize the **nidus**, forming a vegetation.

Pathogenesis

- Destruction of underlying tissue
- Embolic events (septic emboli)
  - Septic emboli from right-sided IE (tricuspid and pulmonary valves) → **pulmonary abscess**
  - Left-sided IE (Mitral and aortic valves) → embolus travel to **any organ system**, especially the kidneys, spleen, and brain
    - Skin manifestations

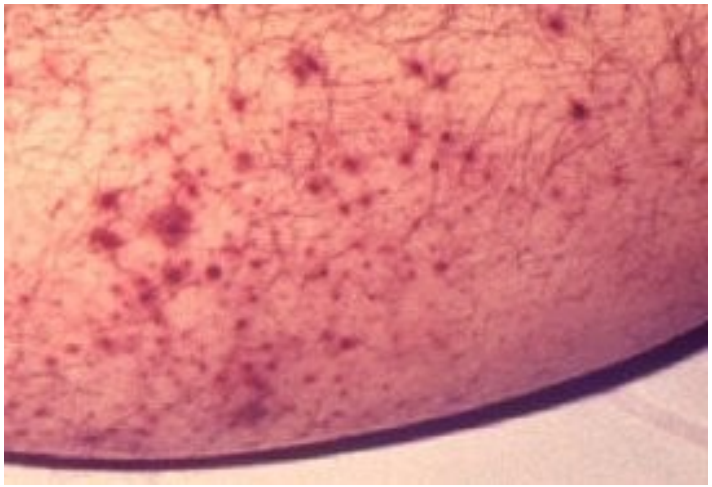

Aortic valve
Pulmonary valve
Mitral valve
Tricuspid valve
Vegetation extending through the valve

Clinical Presentation of IE

- **Symptoms:**
  - Fever, chills, weakness, dyspnea, night sweats, weight loss, and/or malaise.
- Signs
  - Fever is the most common sign of IE.
  - New or changing heart murmur
  - Embolic phenomena (emboli affect the heart, lungs, abdomen, or extremities)
  - Skin manifestations (e.g., **petechiae**, **splinter hemorrhages**, **Osler nodes**, **Janeway lesions**)

Petechiae





1. Nonspecific
2. Often located on extremities or mucous membranes



Splinter Hemorrhages





1. Nonspecific
2. Nonblanching
3. Linear reddish-brown lesions found under the nail bed
4. Usually do NOT extend the entire length of the nail

Osler's Nodes





1. More specific
2. **Painful** and erythematous nodules
3. Located on pulp of fingers and toes
4. More common in **subacute** IE

Janeway Lesions





1. More **specific**
2. Erythematous, **blanching** macules
3. Nonpainful
4. Located on palms and soles

Laboratory Tests

- **Blood cultures**
- Hematologic tests
- Thrombocytopenia
- Electrocardiogram, chest radiograph, and echocardiogram

Modified Duke Criteria

- **Major criteria**
  - **Typical microorganism IE**
    - Viridans streptococci
    - Streptococcus gallolyticus (formerly S. bovis)
    - HACEK group
    - Staphylococcus aureus
    - Enterococci,
  - **Evidence of endocardial involvement**
  - **New valvular regurgitation**

Modified Duke Criteria

- **Minor criteria**
  - Predisposition - predisposing heart condition or intravenous drug use
  - Vascular phenomena - major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janew
  - "Immunologic phenomenon" such as glomerulonephritis, or lesions such as Roth's spots (in the retina of the eyes) or "Osler's nodes (nodules on the fingers or toes)

Diagnostic Criteria

- Any one of the following
  - Direct evidence of endocarditis based upon histological findings (a pathological criterion)
  - Positive Gram stain results or cultures of specimens obtained from surgery or autopsy (a pathological criterion)
  - Two major clinical criteria
  - One major and any three minor clinical criteria, or
  - Five minor clinical criteria

TREATMENT

Desired Outcomes

- Relieve the signs and symptoms of the disease.
- Decrease **morbidity** and **mortality** associated with the infection.
- Eradicate the causative organism with minimal drug exposure.
- Provide cost-effective antimicrobial therapy
- Prevent infective endocarditis from occurring or recurring in high-risk patients with appropriate prophylactic antimicrobials

General Approach to Treatment

- Empirical therapy
  - Should cover MRSA and gram-negative bacilli
    - **Vancomycin plus Gentamicin**
- Then;
  - Isolation of the infecting pathogen and determination of antimicrobial susceptibilities,
  - **High-dose**, **parenteral**, **bactericidal antibiotics** for an **extended period**.

Nonpharmacologic Therapy

Surgery

- Valvectomy and
- Valve replacement
- Echocardiographic features that suggest the need for surgery include:
  - Persistent vegetation or an increase in vegetation size after prolonged antibiotic treatment,
  - Valve dysfunction, or
  - Paravalvular extension (e.g., abscess).

Pharmacologic Therapy

A. Streptococci

1. Penicillin-susceptible streptococci, *S. bovis*

- Penicillin G (2–3 mU IV q4h for 4 weeks)
- Ceftriaxone (2 g/d IV as a single dose for 4 weeks)
- Vancomycin (15 mg/kg IV q12h for 4 weeks)
- Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 2 weeks *plus* gentamicin (3 mg/kg qd IV or IM, as a single dose or divided into equal doses q8h for 2 weeks)

Pharmacologic Therapy

2. Penicillin-resistant streptococci

- **Penicillin** G (4 mU IV q4h) *or* **ceftriaxone** (2 g IV qd) for 4 weeks *plus* **gentamicin** (3 mg/kg qd IV or IM, as a single dose or divided into equal doses q8h for 2 weeks)
- **Vancomycin** as noted above for 4 weeks

Pharmacologic Therapy

B. Enterococci

- **Penicillin** G (4–5 mU IV q4h) plus **gentamicin** (1 mg/kg IV q8h), both for 4–6 weeks
- **Ampicillin** (2 g IV q4h) *plus* **gentamicin** (1 mg/kg IV q8h), both for 4–6 weeks
- **Vancomycin** (15 mg/kg IVq12h) *plus* **gentamicin** (1 mg/kg IV q8h), both for 4–6 weeks

Pharmacologic Therapy

C. Staphylococci

1. Methicillin-susceptible, infecting native valves (no foreign devices)

- **Nafcillin** or **oxacillin** (2 g IV q4h for 4–6 weeks) plus (optional) **gentamicin** (1 mg/kg IM or IV q8h for 3–5 days)
- **Cefazolin** (2 g IV q8h for 4–6 weeks) *plus* (optional) **gentamicin** (1 mg/kg IM or IV q8h for 3–5 days)
- **Vancomycin** (15 mg/kg IV q12h for 4–6 weeks)

Pharmacologic Therapy

2. **Methicillin-resistant**, infecting **native valves** (no foreign devices)
   - **Vancomycin** (15 mg/kg IV q12h for 4–6 weeks)
3. **Methicillin-susceptible**, infecting **prosthetic valves**
   - Nafcillin or oxacillin (2 g IV q4h for 6–8 weeks) plus gentamicin (1 mg/kg IM or IV q8h for 2 weeks) plus rifampin (300 mg PO q8h for 6–8 weeks)

Pharmacologic Therapy

4. Methicillin-resistant, infecting prosthetic valves

- **Vancomycin** (15 mg/kg IV q12h for 6–8 weeks) *plus* **gentamicin** (1 mg/kg IM or IV q8h for 2 weeks) *plus* **rifampin** (300 mg PO q8h for 6–8 weeks)

D. HACEK Organisms

- **Ceftriaxone** (2 g/d IV as a single dose for 4 weeks)
- **Ampicillin/sulbactam** (3 g IV q6h for 4 weeks)

Prevention

- For dental procedures
- But not for:
  - Gastrointestinal or
  - Genitourinary tract procedures

High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis is Advised before Dental Procedures

Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac

Antibiotic Regimens for Prophylaxis of Endocarditis

Standard oral regimen

- Amoxicillin 2.0 g PO 1 h before procedure

Inability to take oral medication

- Ampicillin 2.0 g IV or IM within 1 h before procedure

Penicillin allergy

- Clarithromycin or azithromycin 500 mg PO 1 h before procedure
- Cephalexin 2.0 g PO 1 h before procedure
- Clindamycin 600 mg PO 1 h before procedure

Penicillin allergy, inability to take oral medication

- Cefazolin or ceftriaxone 1.0 g IV or IM 30 min before procedure
- Clindamycin 600 mg IV or IM 1 h before procedure

Outcome Evaluation

- Resolution of signs and symptoms
- Monitor the pt daily for febrile episodes, as well as other vital signs
- Blood cultures
- Evaluate susceptibility reports
- Counsel pt on the necessity of prophylactic antibiotics prior to dental procedures

URINARY TRACT INFECTIONS

Session Objectives

- At the end of this session you will be able to:
  - Define urinary tract infections (UTI)
  - Differentiate the different etiologic agents of UTI
  - Recognize the factors affecting pathogenesis of UTI
  - Identify the clinical presentation of UTIs
  - Establish the treatment approach for UTI

Introduction

- Acute infections of the urinary tract fall into two general anatomic categories:
  - **Lower tract infection** (urethritis and cystitis) and
  - **Upper tract infection** (acute pyelonephritis, prostatitis, and intrarenal and perinephric abscesses).
- Infections of the urethra and bladder are often considered **superficial** (or mucosal) infections, while prostatitis, pyelonephritis, and renal suppuration signify **tissue invasion**.

Introduction

- From a **microbiologic** perspective, UTI exists when pathogenic microorganisms are detected in the urine, urethra, bladder, kidney, or prostate.
- In most instances, growth of $\geq 10^5$ organisms per milliliter from a properly collected midstream "clean-catch" urine sample indicates infection.
- UTIs:
  - Catheter-associated (or **nosocomial**) vs non-catheter-associated (or **community-acquired**)
  - Symptomatic Vs asymptomatic

Epidemiology

- UTIs occur in 1–3% of schoolgirls and then increase markedly in incidence with the onset of sexual activity in adolescence.
- The vast majority of acute symptomatic infections involve young women.
- In the male population, acute symptomatic UTIs occur in **the first year of life** (often in association with urologic abnormalities); thereafter, UTIs are unusual in male patients under the age of 50.
- The development of asymptomatic bacteriuria is rare among men under 50 but common among women between 20 and 50.
- Asymptomatic bacteriuria is more common among elderly men and women, with rates as high as 40–50%.

Etiology

- Gram-negative bacilli.
  - ***Escherichia coli*** causes ~80%
- Other gram-negative rods:
  - *Proteus* and *Klebsiella* spp. and occasionally *Enterobacter* spp., account for a smaller proportion of uncomplicated infections.
- Gram-positive cocci play a lesser role in UTIs:
  - *Staphylococcus saprophyticus* , Enterococci, *Staphylococcus aureus*

Pathogenesis

- Vaginal introitus and distal urethra: normally colonized by **diphtheroids**, **streptococcal species**, **lactobacilli**, and **staphylococcal species** but not by the enteric gram-negative bacilli
- Enteric gram-negative organisms residing in the bowel colonize the introitus, the periurethral skin, and the distal urethra:
  - Alteration of the normal vaginal flora by antibiotics, other genital infections, or contraceptives (especially spermicide).
  - Urethral massage during intercourse.

Pathogenesis

- Under normal circumstances, bacteria placed in the bladder are rapidly cleared through:
  - The **flushing and dilutional effects of voiding**
  - The **antibacterial properties of urine** and **the bladder mucosa.**
- the bladder urine of many healthy persons inhibits or kills bacteria

Conditions Affecting Pathogenesis

- **Gender and Sexual Activity**
  - Female:
    - Prone to colonization
    - Sexual intercourse
    - Voiding after intercourse
    - Use of spermicidal
  - Male
    - **<50 years old**: uncommon
    - Urethral obstruction due to **prostatic hypertrophy**
    - **Insertive rectal intercourse**
    - With **HIV** and who have CD4+ T cell counts of <200/mL

Conditions Affecting Pathogenesis

- **Pregnancy**
  - Decreased ureteral **tone** and **peristalsis**
  - Temporary incompetence of the **vesicoureteral valves**
  - Bladder **catheterization** during or after delivery

Conditions Affecting Pathogenesis

- **Obstruction**
  - Impediment to the free flow of urine: tumor, stricture, stone, or prostatic hypertrophy
- **Vesicoureteral Reflux**
  - Reflux of urine from the bladder into the ureters and sometimes into the renal pelvis
  - Among children with anatomic abnormalities of the urinary tract

Clinical Presentation

- **Cystitis**
  - Dysuria, frequency, urgency, and suprapubic pain
  - Urine often becomes grossly cloudy, malodorous or bloody
  - White cells and bacteria in urine
  - Temperature of >38.3°C (>101°F), nausea, and vomiting, usually indicate concomitant **renal infection**, as does costovertebral angle tenderness.

Clinical Presentation

- **Acute Pyelonephritis**
  - Fever, shaking chills, nausea, vomiting, abdominal pain, and diarrhea.
  - Tachycardia, and generalized muscle tenderness
  - Marked tenderness on deep pressure in one or both costovertebral angles or on deep abdominal palpation.
  - Leukocytosis and bacteria detectable in Gram-stained unspun urine
- **Urethritis**
  - Dysuria, frequency, and pyuria

Diagnostic Testing

- Pyuria
- Culture
- Urologic Evaluation
- Cystoscopy or upon IV pyelography

Treatment

- **Desired Outcome**
  - (a) To eradicate the invading organism(s),
  - (b) To prevent or to treat systemic consequences of infection, and
  - (c) To prevent the recurrence of infection.

General Approach

- Initial selection of an antimicrobial agent for the treatment of UTI is based primarily on:
  - The **severity** of the presenting signs and symptoms,
  - The **site** of infection, and
  - Whether the infection is determined to be **complicated** or **uncomplicated**.
- Other considerations include antibiotic susceptibility, side-effect potential, cost, and the comparative inconvenience of different therapies.

Pharmacologic Therapy

- Ideally, the antimicrobial agent chosen should be well tolerated, well absorbed, achieve **high urinary concentrations,** and have a spectrum of activity limited to the known or suspected pathogen(s).
- The therapeutic management of UTIs is best accomplished by first categorizing the type of infection:
  - Acute uncomplicated cystitis,
  - Symptomatic abacteriuria,
  - Asymptomatic bacteriuria,
  - Complicated UTIs,
  - Recurrent infections, or
  - Prostatitis

Empirical Treatment of UTI and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation
Acute uncomplicated cystitis	E. coli S. saprophyticus	TMP-SMX x 3 days Fluoroquinolone x 3 days Nitrofurantion x 5 days **β**-lactams x 3 days
Pregnancy	As above	Amoxicillin-clavulanate x 7 days, Cephalosporin x 7 days, TMP-SMX x 7 days

Empirical Treatment of UTI and Prostatitis

Acute pyelonephritis		
Uncomplicated	*E. coli*	Quinolone x 14 days, TMP-SMX (if susceptible) x 14 days
	Gram-positive bacteria	Amoxicillin or amoxicillin-clavulanic acid x 14 days
Complicated	*E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *E. faecalis*	Quinolone x 14 days Extended-spectrum penicillin plus aminoglycoside

Empirical Treatment of UTI and Prostatitis

Prostatitis	*E. coli*	TMP-SMX x 4–6 weeks
	K. pneumoniae	
	Proteus spp.	Quinolone x 4–6 weeks
	P. aeruginosa	

ACUTE BACTERIAL MENINGITIS

Definitions

- **Bacterial meningitis** is an acute purulent infection within the subarachnoid space
- **Meningoencephalitis**: involvement of meninges, SAS, and brain parenchyma
- **Aseptic meningitis**: Meningitis + no bacterial pathogen in CSF on Gramstain and routine culture

Anatomy and Physiology (1)

- **MENINGES**
  - Protective covering of the brain and spinal cord
  - Consist of three layers of fibrous tissue: the *pia mater, arachnoid,* and *dura mater*
  - Subarachnoid space contains CSF
  - Pia mater and arachnoid are known collectively as the *leptomeninges*
  - Dura mater is a tough outer membrane that adheres to the periosteum and vertebral column

Anatomy and Physiology (2)

- **CEREBROSPINAL FLUID**
  - Secreted by the choroid plexus in the lateral ventricles
  - Flows unidirectionally
  - About 550 mL/day of CSF is produced
  - Volume of CSF:
    - **Adults**: 150 mL,
    - **Children**: 60 to 100 mL, and
    - **Infants**: 40 to 60 mL
    - To calculate **CSF** concentration of a drug administered intrathecally

Contents of Normal CSF

Type	Normal
WBC (cells/mm^3)	<5
Differential	Monocytes
Protein (mg/dL)	<50
Glucose (mg/dL)	45 – 80
Glucose (CSF/Serum) ratio	0.5 – 0.6
PH	7.3

Epidemiology

- Disease of the very young and very old
- Approximately 1.2 million cases every year around the globe,
  - Resulting in ~170,000 deaths
- 20% of survivors will experience neurologic disabilities.
  - Seizures, sensorineural hearing loss, and hydrocephalus
- Risk Factors
  - Cigarette smoking
  - Cochlear implants
  - Others

Microbiology

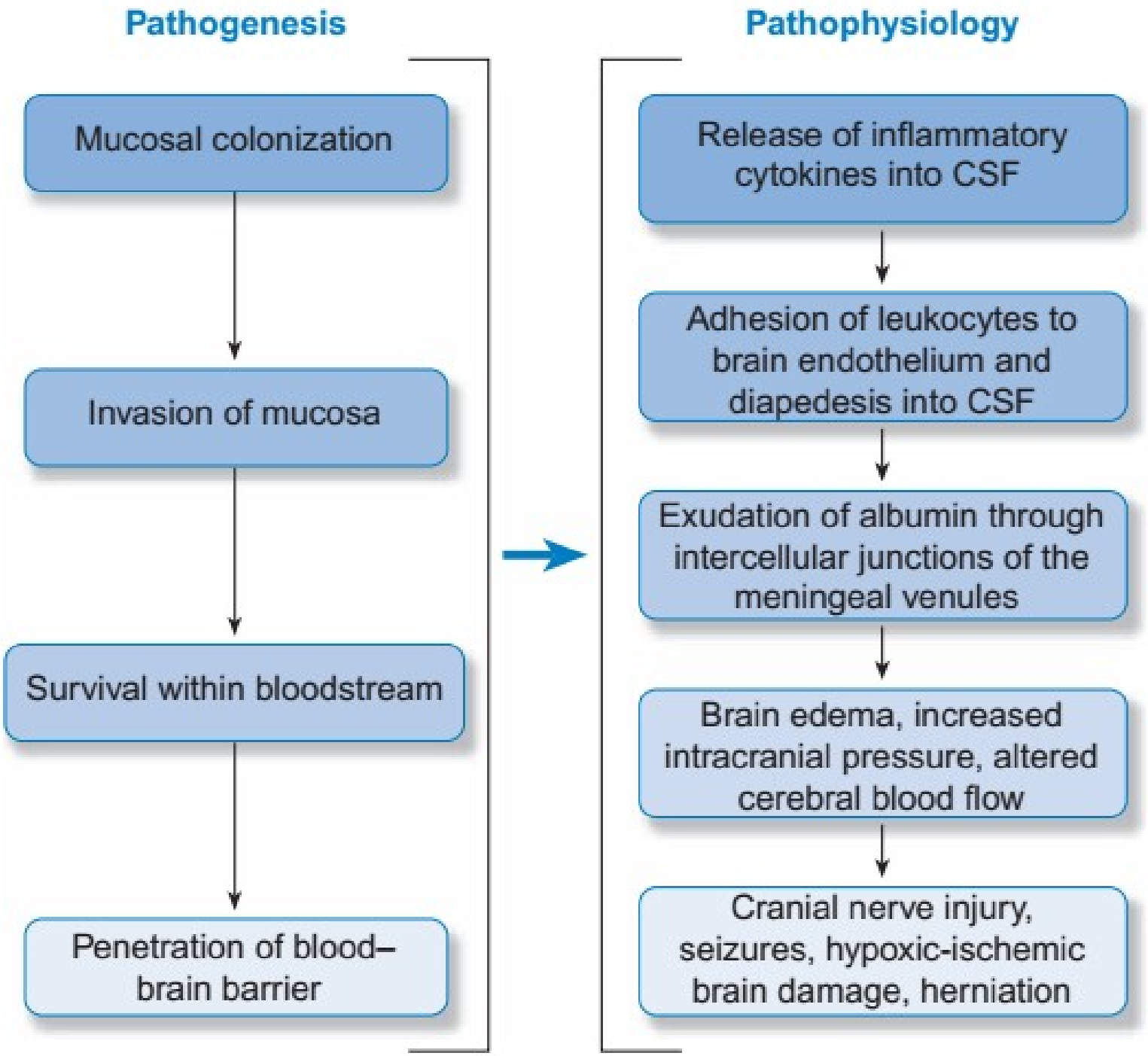
- The bacterial causes of meningitis correlate well with;
  - Age and
  - Underlying conditions,
    - Head trauma
    - Recent neurosurgery
    - Alcoholism
    - Altered immune status

Microbiology

Age Group/Predisposing Condition	Most Likely Organisms
Neonates (<1 mo)	**Group B streptococcus** (S. agalactiae), E. coli, and other gram-negative bacilli (Klebsiella, Serratia species), Listeria monocytogenes
Infants and children (2–23 mons)	S. pneumoniae, N. meningitidis, S. agalactiae, H. influenzae, E. coli
Children and adults (2–50 yrs)	N. meningitidis, S. pneumoniae
Adults (>50 yr)	S. pneumoniae, N. meningitidis, L. monocytogenes, E. coli, Klebsiella species, and other g-vetive bacilli,
Postneurosurgical	S. aureus, gram-negative bacilli (E. coli, Klebsiella species, P. aeuruginosa), S. epidermidis
Closed head trauma	S. pneumoniae, H. influenzae, group A β-hemolytic streptococci

Pathophysiology

- **Meningitis** can develop from;
  - **Hematogenous spread** of organisms (the most common mechanism),
  - **Contiguous spread** from a parameningeal focus (e.g., sinusitis or otitis media), or
  - **Direct bacterial inoculation**, as occurs with head trauma or neurosurgery


Pathogenesis
Mucosal colonization
Invasion of mucosa
Survival within bloodstream
Penetration of blood–brain barrier
Pathophysiology
Release of inflammatory cytokines into CSF
Adhesion of leukocytes to brain endothelium and diapedesis into CSF
Exudation of albumin through intercellular junctions of the meningeal venules
Brain edema, increased intracranial pressure, altered cerebral blood flow
Cranial nerve injury, seizures, hypoxic-ischemic brain damage, herniation

Clinical Features

Signs and Symptoms of Acute Bacterial Meningitis	
✓ **Fever**	✓ Anorexia
✓ **Nuchal rigidity (stiff neck)**	✓ Headache
✓ **Altered mental status**	✓ Photophobia
✓ Seizures	✓ Nausea and vomiting
✓ Brudzinski's sign	✓ Focal neurologic deficits
✓ Kernig's sign	✓ Septic shock
✓ Irritability	

Clinical Features



Kernig's Signs



Brudzinski's signs

CSF Findings

Type	Normal	Bacterial	Viral	Fungal	TB
WBC (cells/mm³)	<5	1,000–5,000	100–1,000	40–400	100–500
Differential	Monocytes	Neutrophils	Lympho	Lympho	Variable
Protein (mg/dL)	<50	100–500	30–150	40–150	≤40–150
Glucose (mg/dL)	45 – 80	Low	Normal	Low	Low
Glucose (CSF/Serum) ratio	0.5–0.6	Decreased	Normal	Decreased	Decreased

Microbiologic Evaluation

- **Examination of**
  - CSF Gram stain
    - ✓Positive in more than 50% of cases
  - CSF culture
    - ✓It is always positive in purulent meningitis
    - ✓Can be negative with antecedent receipt of antibiotic therapy
  - Cultures from other sites (e.g., blood, sputum, urine)

TREATMENT

- **Desired Outcome**
  - Eradication of infection
  - Amelioration of signs and symptoms
  - Prevention of neurologic sequelae, such as seizures, deafness, coma, and death.

Treatment Principles

- Prompt institution of appropriate antimicrobial therapy
  - Delay in antibiotic administration is associated with increased morbidity and mortality
- The antibiotics selected must penetrate adequately
into the CSF.
- The regimen chosen must have potent activity against known or suspected pathogens and
- Exert a **bactericidal** effect.

CSF Penetration Characteristics of Various Antimicrobials

Very Good

- ✓ Chloramphenicol, metronidazole, TMP-SMX, linezolid

Good

- ✓ Penicillins: Penicillin G, ampicillin, nafcillin, piperacillin, ticarcillin
- ✓ Other β-lactams: Aztreonam, clavulanic acid, imipenem, meropenem, sulbactam
- ✓ Cephalosporins: Cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, **cefuroxime**
- ✓ Fluoroquinolones: Ciprofloxacin
- ✓ Vancomycin, daptomycin
- ✓ Other agents: Rifampin

Fair to Poor

- ✓ Aminoglycosides: Amikacin, gentamicin, tobramycin
- ✓ Cephalosporines: 1st and 2nd generation
- ✓ Other agents: Azithromycin, clarithromycin, clindamycin, erythromycin

Empiric Therapy for Bacterial Meningitis

Age Group	Recommended Therapy	Alternative Therapy
Neonates (<1 mo)	Ampicillin + cefotaxime	Ampicillin + gentamicin
Infants and children (1–23 mons)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Older children and adults (2–50 yr)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Elderly (>50 yr)	Ampicillin + cefotaxime, or ceftriaxone + vancomycin	Vancomycin + TMP-SMX + aztreonam

Empiric Therapy

Predisposing Condition	Recommended Therapy	Alternative Therapy
Post-neurosurgical	Vancomycin + ceftazadime	Vancomycin + cefepime or meropenem
Closed head trauma	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Penetrating head trauma	Vancomycin + ceftazadime	Vancomycin + cefepime or meropenem
Presence of risk factor (alcoholism and altered immune	Vancomycin + ceftriaxone or cefotaxime + ampicillin	Vancomycin + TMP-SMX + aztreonam

Antibiotic Dosing Regimens

Antibiotic	Daily Dose (interval in hours)[a]			
	Neonates			
	0–7 days Old	8–28 days Old	Infants and Children	Adults
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	300 mg/kg (6)	12 g (4)
Aztreonam				8 g (6)
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)	12 g (4)
Penicillin G	0.15 million units/kg (8–12)	0.2 million units/kg (6–8)	0.3 million units/kg (4–6)	24 million units (4)
Meropenem			120 mg/kg (8)	6 g (8)
Cephalosporins				
Cefotaxime	100–150 mg/kg (8–12)	150- 200 mg/kg (6–8)	225–300 mg/kg (6–8)	12 g (4)
Ceftriaxone			80–100 mg/kg (12–24)	4 g (12)
Cefazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)	6 g (8)
Cefepime			150 mg/kg (8)	6 g (8)
Aminoglycoside[b,c]				
Gentamicin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (24)
Tobramycin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (24)
Amikacin	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)	15 mg/kg (24)
Linezolid				1,200 mg (12)
Rifampin		10–20 mg/kg (12)	10–20 mg/kg (12–24)	600 mg (24)
TMP-SMX[d]			10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin[c,e]	20–30 mg/kg (8–12)	30–45 mg/kg (6–8)	60 mg/kg (6)	30–45 mg/kg (8–12)

Adjunctive Corticosteroid Therapy

- Corticosteroids can reduce cerebral edema and lower intracranial pressure.
  - Reduce the synthesis and release of the proinflammatory cytokines; TNF-α and IL-1β from monocytes and astrocytes.
  - Initiate the cascade of events that lead to neuronal tissue damage and neurologic sequelae.
  - Significantly reduced hearing loss and neurologic sequelae
  - Dexamethasone 0.15 mg/kg every 6 hours for 2 to 4 days,
    - 20 minutes prior to or concomitant with the first dose of antimicrobials

Definitive Therapy

- ***Haemophilus influenza***
  - β-Lactamase-negative: Ampicillin
    - ✓Alternative: Cefotaxime or ceftriaxone; aztreonam
  - β-Lactamase-positive: Cefotaxime or ceftriaxone
    - ✓Alternative: Aztreonam
- ***Neisseria meningitidis***
  - Cefotaxime or ceftriaxone
  - Alternative: Meropenem
- ***Streptococcus pneumoniae***
  - Cefotaxime or ceftriaxone
  - Alternative: Vancomycin

Definitive Therapy

- ***Pseudomonas aeruginosa***
  - ✓ Cefepime or ceftazidime; meropenem
  - ✓ **Alternative**: Aztreonam
- ***Staphylococcus aureus***
  - Methicillin-susceptible (MSSA): Nafcillin or oxacillin
    - ✓ **Alternative**: Vancomycin ± rifampin; meropenem; linezolid
  - Methicillin-resistant (MRSA): Vancomycin ± rifampin
    - ✓ **Alternative**: TMP-SMX; linezolid
- ***Staphylococcus epidermidis*:**
  - ✓ Vancomycin ± rifampin
  - ✓ **Alternative**: TMP-SMX; linezolid

Definitive Therapy

Streptococcus agalactiae

- ✓ Penicillin G or ampicillin + gentamicin
- ✓ **Alternative**: Cefotaxime or ceftriaxone

Listeria monocytogenes

- ✓ Penicillin G or ampicillin ± gentamicin
- ✓ **Alternative**: TMP-SMX

Enterobacteriaceae

- *E. coli, Klebsiella*: Cefotaxime or ceftriaxone
  - ✓ **Alternative**: Cefepime; aztreonam; meropenem
- *Enterobacter, Serratia*: Cefepime; meropenem

Duration of Therapy

Etiology	Duration
Haemophilus influenzae	7
Neisseria meningitidis	7
Streptococcus pneumoniae	10 – 14
GBS (S. agalactiae)	14 – 21
Listeria monocytogenes	>21
Gram-negative bacilli	21

Follow-up and Monitoring

- **Clinical signs and symptoms (every 4 hours)**
  - Fever, altered mental status, and stiff neck,
- **Laboratory tests**
  - CBC with differential
  - Serum electrolytes (Na, K, Cl, HCO3),
  - Blood glucose, and
  - Renal function tests (e.g., BUN, SCr)
- **Microbiologic Findings**
  - CSF and blood samples for Gram stain, cultures, and sensitivity testing
- **CSF Examination**

INTRA-ABDOMINAL INFECTIONS (IAIs)

Objectives

- Upon completion of this topic you will be able to:
  - Differentiate primary & secondary IAIs.
  - Describe etiologies of primary & secondary IAIs.
  - Describe clinical presentation of IAIs.
  - Recommend the most appropriate drug & non-drug measures to treat IAIs.
  - Recommend an appropriate antimicrobial regimen for treatment of a primary and a secondary IAIs.

Introduction

- IAIs are those contained within the **peritoneal** cavity or **retroperitoneal** space.

- The **peritoneal** cavity extends from the undersurface of the
diaphragm to the floor of the pelvis and contains the stomach, small bowel, large bowel, liver, gallbladder, and spleen.

- The duodenum, pancreas, kidneys, adrenal glands, great vessels (aorta and vena cava), and most mesenteric vascular structures reside in the **retroperitoneum**.

- They may be contained within visceral structures,

Introduction

- **Peritonitis** is defined as the acute inflammatory response of the peritoneal lining to microorganisms, chemicals, irradiation, or foreign-body injury.
- **Primary peritonitis (*spontaneous bacterial peritonitis*)** is an infection of the peritoneal cavity without an evident source of bacteria from the abdomen.
  - Associated with alcoholic cirrhosis, or with ascites caused by postnecrotic cirrhosis, hepatitis, CHF, malignancy, SLE, and nephrotic syndrome.
- **Secondary peritonitis** may involve *perforation of the GI tract* (because of ulceration, ischemia, or obstruction), *postoperative* peritonitis, or *posttraumatic peritonitis* (e.g., blunt or penetrating trauma).
- **Tertiary peritonitis** occurs in critically ill pts, and it is an infection that *persists or recurs* at least 48 hrs after apparently adequate management of primary or secondary peritonitis.

Pathophysiology

- IAI results from bacterial entry into the peritoneal or retroperitoneal spaces or from bacterial collections within intraabdominal organs.
- In primary peritonitis, bacteria may enter the abdomen via the **bloodstream** or the **lymphatic system**
- Hematogenous bacterial spread occurs more frequently with tuberculosis peritonitis or peritonitis associated with cirrhotic ascites.
- When peritonitis results from **PD**, skin-surface flora are introduced via the peritoneal catheter.
- In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of perforation of the GI or female genital tracts caused by diseases or traumatic injuries.

ETIOLOGY

- **Primary** bacterial peritonitis is often caused by a ***single organism.***
  - Children: *S. pneumonia,* GAS, *E. coli*, *Bacteroides* species.
  - If due to cirrhotic ascites: *E. coli* and *Klebsiella*
  - Other pathogens: *H. pneumoniae*, *K. Pseudomonas*, anaerobes
  - May be caused by *Mycobacterium tuberculosis*.
  - Peritonitis in pts undergoing PD: *S. aureus, S. epidermidis*, P. *aeruginosa.*
- Secondary peritonitis is often ***polymicrobial***.

Clinical Presentation

- **Symptoms**
  - Nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.
- **Signs**
  - Temperature may be elevated
  - Bowel sounds are hypoactive
  - Cirrhotic pts may have worsening encephalopathy
  - There may be cloudy dialysate fluid with peritoneal dialysis
- **Laboratory Tests**
  - The WBC may be mildly elevated.
  - Ascitic fluid usually contains more than 250/mm^3 leukocytes
- **Other Diagnostic Tests**
  - Culture of peritoneal dialysate or ascitic fluid should be positive.

Treatment

Goals

- Correction of the intraabdominal disease processes or injuries that have caused infection and drainage of collections of purulent material (abscess).
- Resolve the infection without major organ system complications (pulmonary, hepatic, cardiovascular, or renal failure) or adverse drug effects.

Treatment

General Approach to Treatment

- The treatment of IAI most often requires
  a) Prompt drainage
  b) Support of vital functions
  c) Antimicrobial therapy to treat infection not eradicated by surgery.
- Antimicrobials are an important adjunct to drainage procedures in the treatment of secondary IAIs.
- For most cases of primary peritonitis, *drainage procedures may not* be required, and antimicrobial agents become the mainstay of therapy

Treatment

- With generalized peritonitis, large volumes of IV fluids are required to maintain intravascular volume, to improve cardiovascular function, and to ensure adequate tissue perfusion and oxygenation.
- A common cause of early death is hypovolemic shock caused by inadequate intravascular volume expansion and tissue perfusion.
- An additional important component of therapy is nutrition.
- IAIs often involve the GI tract directly or disrupt its function (paralytic ileus).
- The return of GI motility may take days, weeks, and occasionally, months.
- **Enteral** or **parenteral nutrition** as indicated facilitates improved immune function and wound healing to ensure recovery.

Treatment

Drainage Procedures

- Primary peritonitis is treated with antimicrobials and rarely requires drainage.
- Secondary peritonitis requires surgical removal of the **inflamed** or **gangrenous** tissue to prevent further bacterial contamination.
- If the surgical procedure is suboptimal, attempts are made to provide drainage of the infected or gangrenous structures.
- The drainage of purulent material is the critical component of management of an intra-abdominal **abscess**.
- Without adequate drainage of the abscess, antimicrobial therapy and fluid resuscitation can be expected to fail.

Treatment

Antimicrobial Therapy

- The goals of antimicrobial therapy are as follows:
  - To control bacteremia and prevent the establishment of metastatic foci of infection
  - To reduce suppurative complications after bacterial contamination
  - To prevent local spread of existing infection
- After suppuration has occurred (e.g., an abscess has formed), a cure by antibiotic therapy alone is difficult to achieve; antimicrobials may serve to improve the results with surgery

Treatment

Primary (Spontaneous) Bacterial Peritonitis

- Cirrhosis
  - Ceftriaxone, cefotaxime
  - Alternatives: piperacillin-tazobactam, carbapenems
- Peritoneal dialysis
  - Vancomycin + Ceftriaxone/cefotaxime/ceftazidime/gentamicin

Secondary Bacterial Peritonitis

- Perforated peptic ulcer
  - First-generation cephalosporins
- Other
  - Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam, carbapenem
- Abscess
  - Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam

Treatment

- Acute intra-abdominal contamination, such as after a traumatic injury, may be treated with **a short course (24 hours)** of antimicrobials.
- For established infections (i.e., peritonitis or intra-abdominal abscess), an antimicrobial course limited to **7 days**.
- Therapy for **longer than 7 days** would be justified if the pt remains febrile or is in poor general condition, when relatively **resistant bacteria are isolated,** or when a **focus of infection in the abdomen still may be present.**
- For some abscesses, such as pyogenic liver abscess, antimicrobials may be required for a **month** or longer.

Quiz 2

1. Which antibiotics are not recommended for infective endocarditis?
   A. Bacteriostatic antibiotics
   B. Parenteral antibiotics
   C. High dose antibiotics
   D. None of the above
2. The common cause of UTI is:
   A. E. coli
   B. S. saprophyticus
   C. P. aeruginosa
   D. S. aureus

Quiz 2

3. Describe the indication of prophylaxis of infective endocarditis.
4. How do you re-initiate antiTB drugs after D/C due to hepatotoxicity?
5. What are the indications of pyridoxine prophylaxis to prevent peripheral neuropathy associated with INH?
6. What is the minimum duration in the management of prostatitis?

GASTROINTESTINAL INFECTIONS

INTRODUCTION

- Acute gastrointestinal illnesses rank second only to acute upper respiratory illnesses as the most common diseases worldwide
- In children <5 years old, attack rates range from 2–3 illnesses per child per year in developed countries to as high as 10–18 illnesses per child per year in developing countries.

INTRODUCTION

- **Gastroenteritis** is an illness characterized by diarrhea which may be accompanied by nausea, vomiting, fever, and abdominal pain.
- **Diarrhea** is usually defined as a decrease in consistency of bowel movements (i.e., unformed stool) and an increase of stools to ≥3 per day.
- For best diagnosis and management, it is important to distinguish ***secretory diarrhea*** that produces watery diarrhea from **inflammatory diarrhea**.
- Caused by invasive pathogens, ***inflammatory diarrhea*** often presents as fever, tenesmus, or bloody stool.

Watery vs. Inflammatory

Characteristics	Watery	Inflammatory
Percentage of patients	90	5–10
Stools		
Appearance	Watery	Bloody
Volume	Increased: ++/+++	Increased: +/++
Number per day	<10	>10
pH	5.0–7.5	6.0–7.5
Occult blood	Negative	Positive
Fecal PMN cells	Absent or few	Many

Watery vs. Inflammatory

	Watery	Inflammatory
Mechanisms	Toxins, reduced absorption	Mucosal invasion
Complications		
Dehydration	Could be severe	Mild
Others	Acidosis, shock, electrolyte imbalance	Tenesmus, rectal pro-lapse, seizures

	Watery	Inflammatory
Etiology	*Vibrio cholerae*	*Shigella*
	Enterotoxigenic *E. coli* (ETEC)	*Salmonella*
	Enteropathogenic *E. coli* (EPEC)	*Campylobacter*
	Rotaviruses	*Yersinia*
	Noroviruses	Enterohemorrhagic *E. coli* (EHEC)
		Enteroinvasive *E. coli* (EIEC)

Watery (Cholera-Like) Diarrhea

- Cholera (*Vibrio Cholerae*)
- Escherichia Coli

Cholera (*Vibrio Cholerae*)

- A relatively large inoculum of 10^3 to 10^6 organisms is required for infection if water is the vehicle, and 10^2 to 10^4 if the vehicle is food.

Pathogenesis

- Pathology of cholera results from an **enterotoxin (cholera toxin)** produced by the bacteria.
- Conditions that reduce gastric acidity (antacids, H_2RB, PPIs), or infections with *H. pylori,* increase the risk for clinical disease.
- Cholera toxin stimulates **adenylate cyclase**, which increases intracellular **cyclic adenosine monophosphate (cAMP)** and results in inhibition of sodium and chloride absorption by microvilli and promotes the secretion of chloride and water by crypt cells

Pathogenesis

- The toxin likely acts along the entire intestinal tract, but most fluid loss occurs in the **duodenum**.
- The net effect of the cholera toxin is isotonic fluid secretion (primarily in the small intestine) that exceeds the absorptive capacity of the intestinal tract (primarily the colon).
- This results in the production of watery diarrhea with electrolyte concentrations similar to that of plasma.

Clinical Presentation

- **Diarrhea**:
  - Patients may lose up to **1 L** of isotonic fluid every hour
  - The onset of diarrhea is abrupt
  - Is followed rapidly or sometimes preceded by **vomiting**.
- **Fever**: < 5% of patients
- Abdominal distension and ileus
- Laboratory abnormalities: increased packed RBC volume and total protein, magnesium, and calcium levels

Complications

- Hypoglycemia
- Seizures
- Fever
- Mental alterations
- Metabolic acidosis
- Prerenal azotemia
- Aspiration pneumonia.

Treatment

- Goals of therapy
  - ☞Rapid restoration of fluid losses,
  - ☞Correction of metabolic acidosis, and
  - ☞Replacement of potassium deficiency

Treatment

Rehydration

- Mild cases:
  - ORS; for children: < 2yrs: 50 – 100ml; 2-10yrs: 100 – 200ml after each loose stool.
- For severe cases: **Ringer lactate** IV infusion (alternatively normal saline) 50 - 100 ml/min until shock is reversed; thereafter, according to fluid loss.

Treatment

- Antibiotics are not necessary in most cholera cases
- However, in **severe cases**, antibiotics shorten the duration of diarrhea, decrease fluid loss, and shorten the duration of the carrier state.
  - A single dose of
    - **Doxycycline**
    - **Ciprofloxacin**
    - Erythromycin/azithromycin
    - Cotrimoxazole

Escherichia Coli

- Diarrheagenic *E. coli* is differentiated into several distinct categories based on pathogenic features of diarrheal disease:
  1. Enterotoxigenic *E. coli* (**ETEC**)
  2. Enteroinvasive *E. coli* (**EIEC**)
  3. Enteropathogenic *E. coli* (**EPEC**)
  4. Enteroaggregative *E. coli* (**EAEC**)
  5. Enterohemorrhagic *E. coli* (**EHEC**)

Escherichia Coli

- The most common diarrheagenic *E. coli* infection is caused by **ETEC** manifested by **watery** (enterotoxigenic) diarrhea.
- **Dysentery** is caused by **EHEC**.
- Infections with **EIEC** and **EPEC** are primarily a disease of **children** in developing countries.
- **EAEC** strains are implicated in persistent diarrhea (≥14 days) in HIV-infected patients.

Pathogenesis

- **Enterotoxigenic *E. coli*** are capable of producing enterotoxins
- Luminal accumulation of electrolytes that draws water into the intestine, and production of a cholera-like secretory diarrhea
- EHEC is able to produce shiga-like toxins
- The cytotoxic effect of shiga-like toxins disrupts the mucosal integrity of the large intestine, causing diarrhea

Clinical Presentation

- **ETEC**
  - Nausea and watery stools
    - There is no blood or pus in the stool
    - Abrupt in onset and resolves within 24 to 48 hours without complication
- **EPEC**
  - Acute onset of profuse watery diarrhea, vomiting, and low-grade fever.
- **EAEC**
  - Persistent, watery, mucoid, secretory diarrhea with low-grade fever
- **EIEC**
  - Presents most commonly as watery diarrhea

Clinical Presentation

- EHEC:
  - As many as 12 bloody stools per day
  - Cramping abdominal pain, abdominal distension
  - Nausea occurs in about two-thirds of patients, and vomiting occurs in less than half.
  - The white blood cell count is elevated and accompanied by a left shift

Treatment

- Prevent dehydration by correcting fluid and electrolyte imbalances.
- ORT is often lifesaving in infants and children
- Loperamide and to a lesser extent, bismuth subsalicylate, are effective in decreasing the severity of ETEC diarrhea; empirical antibiotics shorten the duration of the disease.
- **Fluoroquinolones** (e.g., ciprofloxacin, norfloxacin, and levofloxacin) are the most commonly recommended agents owing to increasing antimicrobial resistance among other drug classes

Inflammatory (Dysentery-Like) Diarrhea

- Bacillary Dysentery (Shigellosis)
- Salmonellosis

Bacillary Dysentery (Shigellosis)

- The shigellae are gram-negative bacilli belonging to the family *Enterobacteriaceae*.
- Ingestion of as few as 10 to 200 viable organisms of the *Shigella* species causes disease in healthy adults, explaining the ease with which the disease is transmitted from person to person
- The bacteria multiply and spread within the submucosa of the small bowel

Bacillary Dysentery (Shigellosis)

- Penetration of the mucosa is conferred genetically by large "invasion plasmids" and results in:
  - Distortion of the crypts,
  - Death to intestinal epithelium,
  - Causing focal ulceration,
  - Sloughing of mucosal cells,
  - Bloody mucoid exudate into the gut lumen, and
  - Submucosal accumulation of inflammatory cells with microabscess formation.

Clinical Presentation

- Initial signs and symptoms include abdominal pain, cramping, and fever followed by frequent watery stools.
- Within a few days, patients experience a decrease in fever, severe abdominal pain, and tenderness prior to the development of bloody diarrhea and other signs of dysentery.

Treatment

- Shigellosis is usually a self-limiting disease.
- Most patients recover in 4 to 7 days, although 10% may experience a recurrence.
- ORT is the foundation of treatment (dysentery is not generally associated with significant fluid loss).
- However, intravenous fluid replacement therapy may be necessary, especially in children and the elderly.

Treatment

- Antibiotics:
  - Preferred agents of choice are ***fluoroquinolones***
  - A single dose is reasonable for mild to moderate illness, but for complicated bacillary dysentery
  - In children and pregnant women, ***azithromycin*** can be used

Salmonellosis

- *Salmonella enterica* are gram-negative bacilli belonging to the family Enterobacteriaceae.
- The most prevalent *Salmonella enterica* serotypes are Typhi or Paratyphi, which cause enteric fever.

Pathogenesis

- The inoculum necessary for clinical illness is estimated to be **10^6 organisms**, and this infectious dose is lowered in patients with achlorhydria (gastric pH >4.0).
- Once ingested and successfully beyond host defense mechanisms such as low gastric pH and bile salts, organisms can attach and invade the distal ileum and proximal colon.
- Gastroenteritis often is characterized by massive neutrophil infiltration followed by lymphocytes and macrophages.

Pathogenesis

- Degranulation and release of toxic substances by neutrophils may contribute to inflammation and result in:
  - Tissue damage,
  - Fluid secretion, or
  - Leakage across the intestinal mucosa.

Clinical Presentation

- Most patients experience symptoms within 72 hours of ingestion of contaminated food or water.
- Patients often complain of nausea and vomiting followed by abdominal cramps, headache, fever, and diarrhea

Clinical Presentation

- Bacteremia is the most common complication of gastroenteritis.
- High-risk patients include
  - Infants,
  - Elderly, and
  - Patients with severe underlying illness or immunosuppression, including those with AIDS.

Treatment

- Gastroenteritis is usually self-limiting,
  - fluid and electrolyte replacement is the primary mode of treatment.
  - Most patients respond well to ORT.
- Antimotility drugs
- Antibiotic therapy
  - Used in high-risk patients
    - neonates or infants
    - persons older than age 50 years
    - immunodeficiency
  - Ciprofloxacin for 5–7 days is recommended.
  - Alternatives: azitromycin, cotrimoxazole

SEXUALLY TRANSMITTED INFECTIONS

Learning Objectives

- Describe the association between STIs and HIV
- Identify the etiologies and mode of transmission of some of the most common STIs
- Understand the major symptoms of commonly encountered STIs
- Determine the most effective treatment approaches for commonly encountered STIs

STI versus STD

- **STI** – Infections acquired through sexual intercourse (may be symptomatic or asymptomatic)
- **STD** – Symptomatic disease acquired through sexual intercourse
- STI is most commonly used because it applies to both symptomatic and asymptomatic infections

Introduction

- Most STIs are treatable
  - However, resistance to many of the older antibiotics is a challenge
- Other have no cure, such as herpes, genital warts, HIV
- Many STIs can lead to related conditions such as:
  - Pelvic inflammatory disease
  - Cervical cancer
  - Complications in pregnancy
- STIs can have socio-economic consequences
- Education about these diseases and

Commonly Encountered STIs

- Syphilis
- Gonorrhea
- Chlamydia
- Chancroid
- Genital Herpes
- Genital warts
- Trichomoniasis
- Lymphogranularoma Venereal

Management approach for STI

- There are two basic approaches in the management of STIs:
  - **Etiologic Management:** etiologic diagnosis using laboratory tests to identify the causative agent
    - Benefits: focused, specific therapy, avoiding the cost and toxicity of unnecessary medications.
  - **Syndromic Management approach**
    - Considers the likely causative agent(s) for a given clinical syndrome and treats accordingly, without regard for identifying the specific infection.

STI Syndromes

1. Urethral discharge or burning on urination in men
2. Vaginal discharge
3. Genital ulcer
4. Lower abdominal pain in women
5. Scrotal swelling
6. Inguinal bubo
7. Neonatal Conjunctivitis

1. Urethral Discharge Syndrome

- Possible etiologies:
  - Gonococcal infection (81%)
  - Chlamydia Trachomatis (36.8%)

Urethral discharge





Recommended Treatment for Urethral Discharge and Burning on Urination

- **Ceftriaxone 250mg IM stat**/Spectinomycin 2 gm IM stat

Plus

- **Azithromycin 1gm po stat**/Doxycycline 100 mg po bid for 7 days/Tetracycline 500 mg po qid for 7 days/Erythromycin 500 mg po qid for 7 days in cases of contraindications for Tetracycline (children and pregnancy)

- Note: The preferred regimen is Ceftriaxone 250mg IM stat plus *Azithromycin 1gm po stat*

Persistent/Recurrent Urethral Discharge

- Complain of persistent or recurrent burning sensation on urination, with or without discharge, due to various reasons:
  - Inadequate treatment or poor compliance
  - Re-infection (partner/s not managed)
  - T. vaginals is also known to cause urethritis in men
  - Infection by drug-resistant organisms (N. gonorrhea)

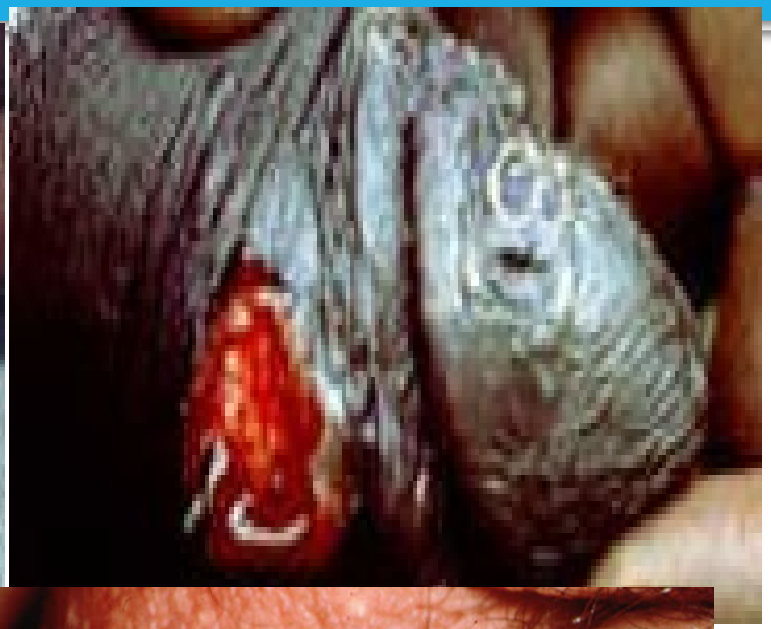
- **Metronidazole** 2 gm p.o. stat or **Tinidazole** 1gm po once for 3 days (Avoid Alcohol)

2. Genital Ulcer Diseases (GUD)

- Clinical manifestation and patterns of GUD may vary with presence of HIV infection.
  - The causes of genital ulcer are Trreponema Pallidum (**syphilis**), **HSV2** infection, Haemophilus ducreyi (**chancroid**), C. trachomatis serovar L1, L2 & L3 (**LGV**), Claymmatobacterium granulomatis (Donovanosis)
- **Syphilis**
  - Clinically has three stages (primary, secondary, teritiary)
  - The ulcer starts during the primary stage of the disease as papules & rapidly ulcerative
  - The ulcer is typically painless, clean base and raised boarder

Genital Ulcer Disease









Genital Ulcer Disease Treatment

Recommended treatment for non-vesicular genital ulcer

- **Benzathin penicillin** 2.4 million units IM stat/Doxycycline (in penicillin allergy) 100mg bid for 14 days

Plus

- **Ciprofloxacin** 500mg bid orally for 3 days /Erythromycin 500mg tab qid for 7 days

Plus

- **Acyclovir** 400mg tid orally for 10 days (or 200mg five

Recommended treatment for vesicular multiple first episode genital ulcer

- **Acyclovir 400mg tid for 10 days**

or

- **Acyclovir 200 mg 5 times per day for 10 day**

3. Vaginal Discharge

- Abnormal Vaginal discharge in terms of quantity, colour or odor could be most commonly as a result of vaginal infections
- The most common causes of vaginal discharge are
  - **Neisseria gonorrhoeae**, **Chlamydia trachomatis**, T. vaginalis, Gardnerella vaginalis , C. albicans.
- One or more of the following are risk factors for STIs related cervicitis in Ethiopia:
  - Multiple sexual partners in the last 3 months
  - New sexual partner in the last 3 months
  - Ever traded sex
  - Age below 25 year

Vaginal Discharge





Recommended Treatment for Vaginal Discharge

Risk Assessment Positive	Risk assessment Negative
Ceftriaxone 250mg IM stat/Spectinomycin 2 gm IM stat **plus** **Azithromycin** 1gm po stat/Doxycycline 100mg po bid for 7 days **Plus** **Metronidazole** 500mg bid for 7 days **If discharge is white or curd-like add Clotrimazole vaginal pessary 200 mg at bed time for 3 days** **Note: The preferred regimen is Ceftriaxone 250mg IM stat plus Azithromycin 1gm po stat plus Metronidazole 500 mg bid for 7 days**	Metronidazole 500mg bid for 7 days If discharge is white or curd-like: add Clotrimazole vaginal pessary 200 mg at bed time for 3 days

4. Lower Abdominal Pain Due to PID

- PID is ascending infection of the upper genital tract (uterus, tubes, etc) from the cervix and/or vagina
- Common etiologies:
  - Sexually transmitted:
    - Neisseria gonorrhea,
    - Chlamydia trachomatis,
    - Mycoplasma hominis
  - Others (non-STI): streptococci, E. coli, etc
- Vaginal discharge is often present

Recommended Treatment for PID

Recommended treatment for PID	
Out patient	**Inpatient**
Ceftriaxone 250mg IM stat/ **Spectinomycin** 2 gm IM stat **plus** **Azithromycin** 1gm po **stat** **/Doxycycline** 100mg po bid for 14 days **plus** **Metronidazole** 500mg bid for 7 days Admit if there is no improvement within 72 hours Note: The preferred regimen is Ceftriaxone 250mg IM stat plus Azithromycin 1gm po stat plus Metronidazole 500 mg bid for 7	**Ceftriaxone** 250mg IV/IM daily /**Spectinomycin** 2gm IM bid **Plus** Azithromycin 1gm po daily / Doxycycline tablet 100 mg bid for **14 days** **Plus** Metronidazole 500mg IV bid for **14 days**

5. Scrotal Swelling

- Common STI causes of scrotal swelling are similar to those of urethral discharge
  - Neisseria gonorrhea
  - Chlamydia trachomatis
- Exclude non-STI causes of scrotal swelling:
  - TB
  - Inguinal hernia
  - Testicular torsion, etc

Scrotal Swelling: Recommended Therapy

- Non-Pharmacologic: scrotal support
- Pharmacologic

Recommend treatment for Scrotal Swelling

Ceftriaxone 250mg IM stat/ Spectinomycin 2gm IM stat

plus

Azithromycin 1gm po stat/Doxycycline 100mg bid PO for 7 days

Note :The preferred regimen is Ceftriaxone

6. Inguinal Bubo

- This is a painful, fluctuant, swelling of the lymph nodes in the inguinal region (groin)
- Swelling of inguinal lymph nodes as a result of STIs (or other causes)
- Common causes:
  - Chlamydia trachomatis (LGV)
  - Hemophylus ducreyi (chancroid)
  - Calymatobacterium granulomatis (granuloma inguinale)
  - Treponema pallidum (syphilis)

Inguinal Bubo





Inguinal Bubo

Recommended treatment for Inguinal bubo

Ciprofloxacin 500mg bid for 3 days

plus

Doxycycline 100mg bid orally for 7 days/ Erythromycin 500mg qid orally for 14 days

7. Neonatal Conjunctivitis

- Infection of the eyes of the neonate as a result of genital infection of the mother, transmitted during birth
- Causes:
  - Neisseria gonorrhea
  - Chlamydia trachomatis



Neonatal Conjunctivitis: Treatment

Ceftriaxone 125mg IM stat maximum dose / **Spectinomycin** 25 mg/kg IM stat maximum dose 75mg

plus

Erythromycin 50mg/kg orally in four divided doses for 14 days

HIV/AIDS

Objectives

- Upon completion of this topic you will be able to
  - Explain the routes of transmission for HIV, and its natural disease progression
  - Explain the WHO staging of HIV/AIDS
  - Understand criteria to initiate antiretroviral therapy
  - Recommend appropriate first and second-line antiretroviral regimen for pts with HIV infection
  - Describe the components of a monitoring plan to assess effectiveness and adverse effects of antiretroviral regimen

INTRODUCTION

- Acquired immunodeficiency syndrome (AIDS) is the most severe manifestation of a clinical spectrum of illness caused by infection with HIV.
- HIV primarily affects the CD4 lymphocyte.
- When CD4 cells are destroyed, a person’s immunity is impaired.
- As immune function decreases, OIs increase.
- HIV progresses over time to death if no treatment is given.

Epidemiology

- HIV/AIDS is a **global** pandemic, with cases reported from virtually every country.
- There were an estimated 38.0 million people living with HIV at the end of 2019
  - Over two thirds of all people living with HIV live in the WHO African Region (25.7 million).
    - Even though SSA accounts 10% of the world's population.
  - 690,000 people died from HIV-related causes in 2019 and 1.7 million people were newly infected

Transmission

Main modes of transmission are:

- Sexual
  - Heterosexual
  - Homosexual
- Blood transfusion
- Needle prick; sharing of sharp materials; IDU
- Mother to child [MTCT]
- Mucosal exposure to infected blood & some body fluids

Risk factors

- Having unprotected anal or vaginal sex;
- Having another sexually transmitted infection (STI)

- Sharing contaminated needles, syringes and other injecting equipment and drug solutions when injecting drugs;
- Receiving unsafe injections, blood transfusions and tissue transplantation, and medical procedures that involve unsterile cutting or piercing; and
- Experiencing accidental needle stick injuries, including among health workers

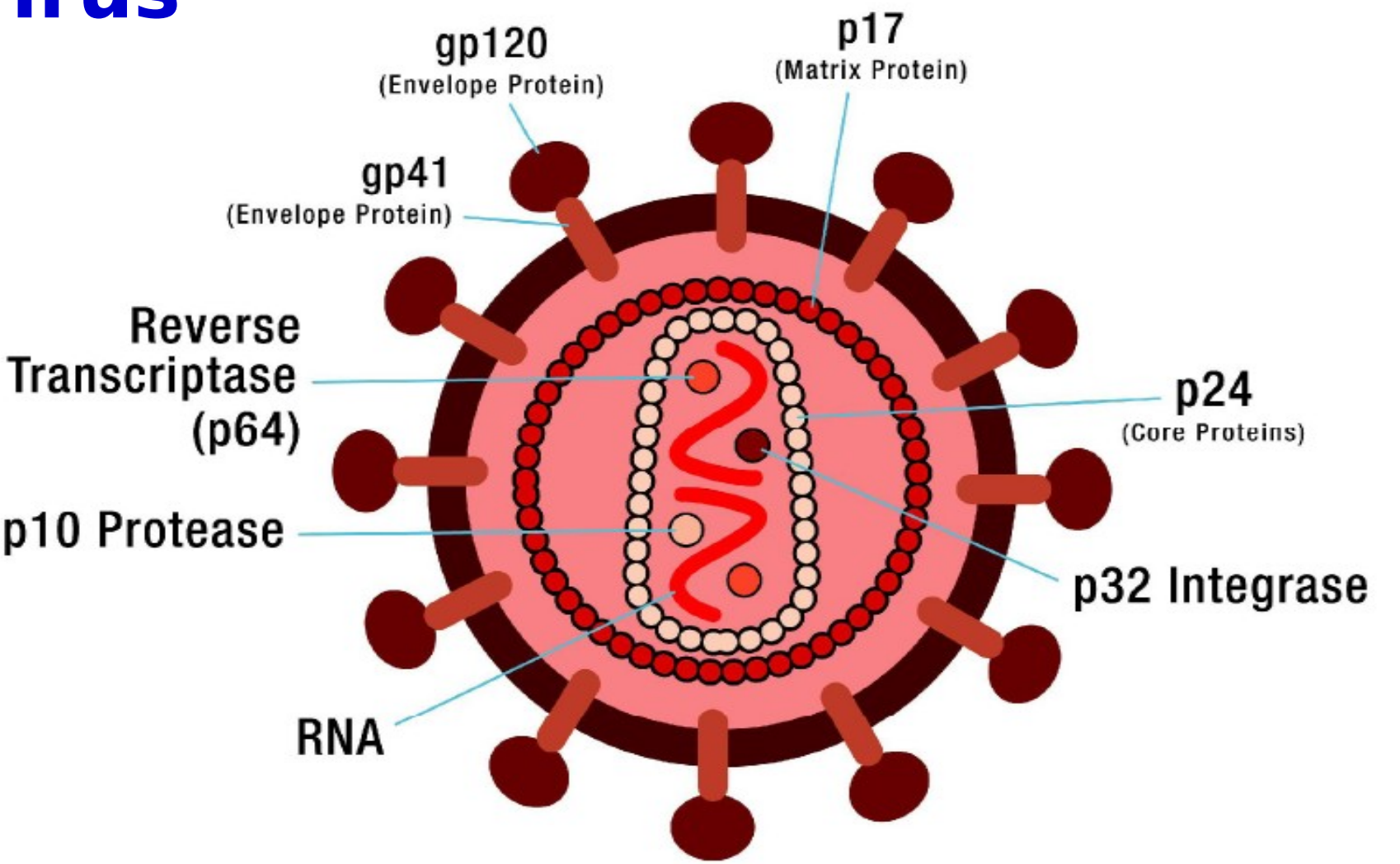
Etiology and Virology

- HIV has two major types & several subtypes/strains:
- HIV 1- Pandemic:
  - HIV M (A, B, C, D, E, F, ... J) > 95% Global burden
  - HIV O
  - HIV N
- HIV 2 – mainly in West Africa
- In sub-Saharan Africa, the majority of infections are caused by subtype C.
- Subtype B viruses are predominant in Americas, Western Europe & Australia accounting for 12–13% of global infections.

Etiology and Virology

- HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme **reverse transcriptase.**
- The greatest variability in strains of HIV occurs in the viral envelope.
- HIV-2 has same genetic organization as HIV-1, but with significant differences in the envelope glycoproteins.
- HIV-2 variant may be less pathogenic or have a longer period of latency preceding disease.

HIV Virology: Structure of the Virus



Replication Cycle of HIV

- The CD4 molecule is found predominantly on T-helper **lymphocytes**.
- It is also expressed on the surface of monocytes / macrophages and dendritic/ Langerhans cells.
- The replication cycle of HIV begins with the high-affinity binding of the **gp120** protein to its receptor on the CD4 molecule.
- Once gp120 binds to CD4, the gp120 undergoes a conformational change that facilitates binding to one of two **major co-receptors** of HIV- 1 [**CCR5** & **CXCR4**].

Replication Cycle of HIV

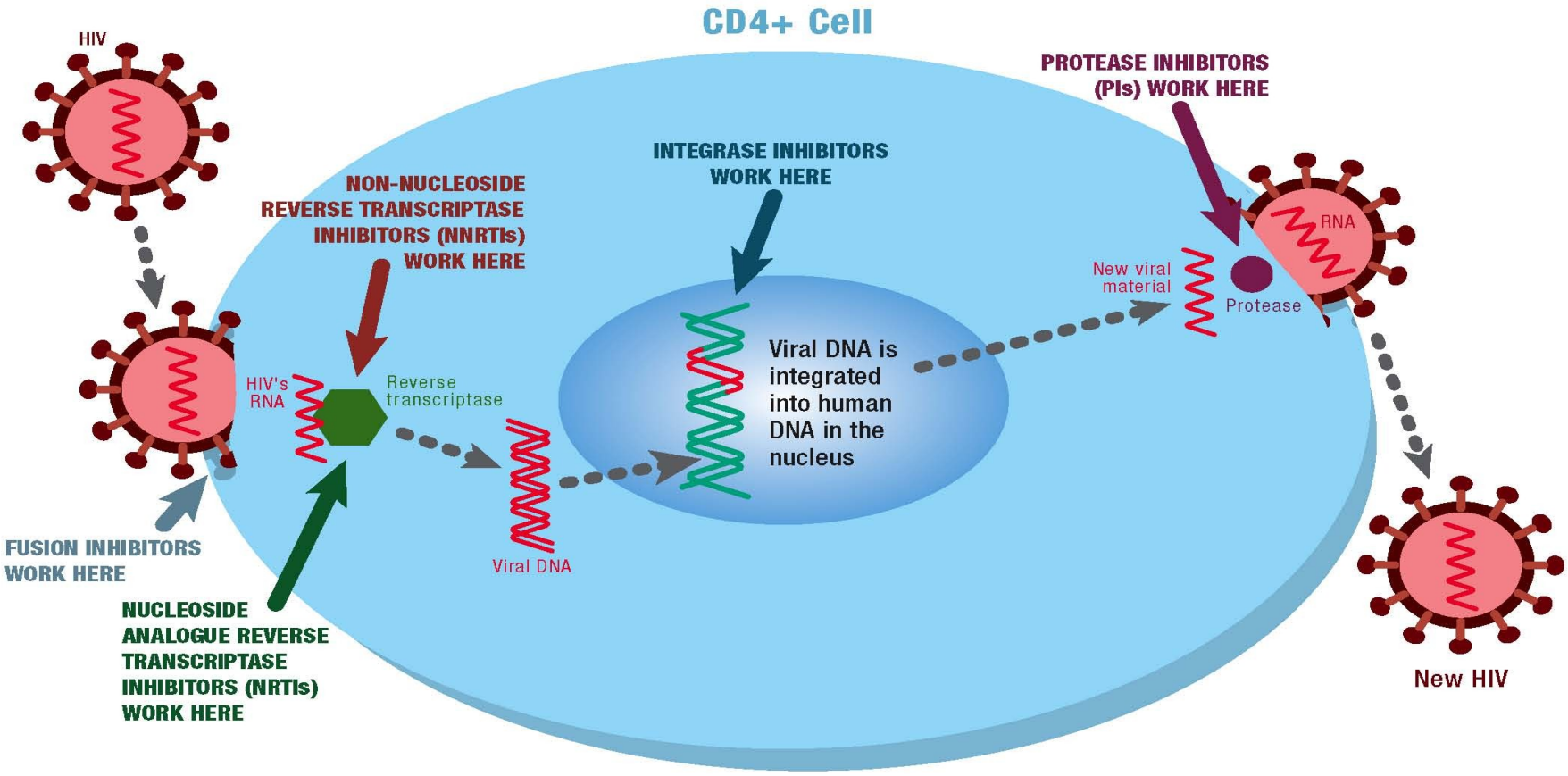
- The virus then firmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule.
- This facilitates fusion of the virion by penetrating the plasma membrane of the target cell.
- Following fusion the preintegration complex is released into the cytoplasm of the target cell.
- The complex enters the nucleus, the reverse transcription of the genomic RNA into DNA occurs; and
- The protein coat opens to release the resulting double-strand pro-viral HIV-DNA.
- With activation of the cell, i**ntegrase** catalyzes the integration of viral DNA into the host cell chromosomes.

Replication Cycle of HIV

- **Protease** catalyzes cleavage and assembly of long HIV proteins, enzymes, and genomic DNA to form a mature virion.
- Budding of the progeny virion occurs through the host cell membrane, where the core acquires its external envelope.
- Finally a mature virus is released to the circulation to infect another cell.
-

What is the importance of knowing the life cycle?

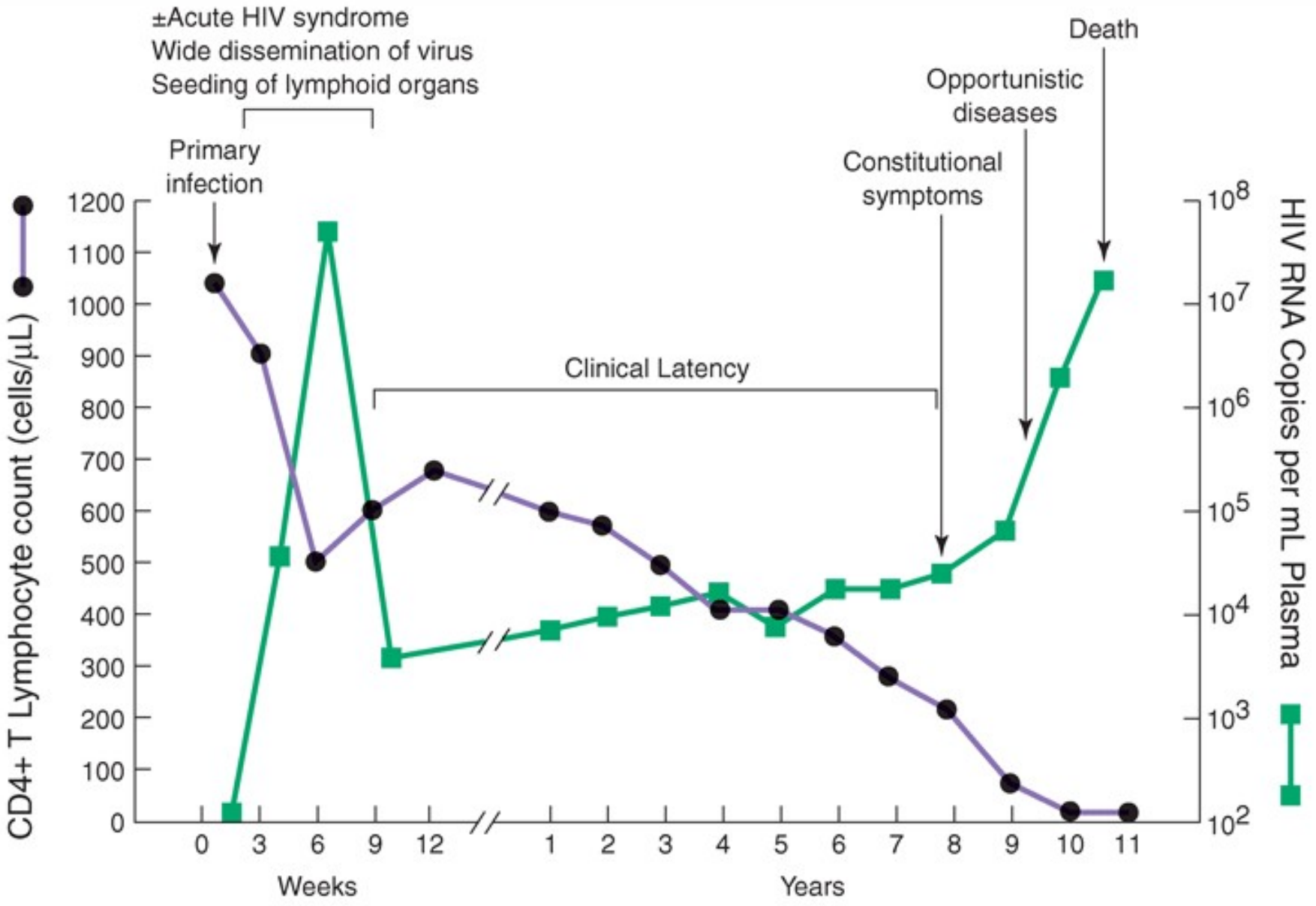
HIV Life Cycle:
Sites for Therapeutic Intervention.



Summary: Six steps in life cycle of HIV in the body

1. **Attachment/Binding**: HIV attaches to the CD4 cell.
2. **Fusion:** the virion penetrates the plasma membrane of the CD4+ cells.
3. **Reverse Transcription**: the enzyme reverse transcriptase makes DNA copy of the viral RNA.
4. **Integration**: new viral DNA is then integrated into CD4 cell nucleus using the enzyme **integrase**.
5. **Assembly**: the newly formed viral components are assembled together using the enzyme **protease**.
6. **Budding and release**: the new mature virus gets its envelop proteins and is released in to the circulation through budding to continue the cycle.

Typical course of an untreated HIV-infected individual



HIV Disease Staging

Disease Staging: Why Staging?

- To assess disease severity & to monitor disease progression

T-staging:

- Staging while on ART to asses progress or response.
- Up and down staging is possible.
- Guides when to change treatment.

WHO Staging of HIV/AIDS

- Primary HIV Infection /Acute retroviral syndrome
- Stage I - asymptomatic
- Stage II - mild disease
- Stage III - moderate disease
- Stage IV - advanced immunosuppresion

WHO Clinical Stage I

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- Asymptomatic

  or

- Persistent generalized lymphadenopathy (PGL):
  - Bilaterally swollen lymph nodes in the cervical area, under the arm, or groin.
  - Usually not painful (“Rule of 1,2,3” >1cm,>2 sites, >3 months)
- **Performance scale 1: able to carry on normal activity**

WHO Clinical Stage II

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent upper respiratory tract infections
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal fingernail infections

And/or performance scale 2(normal activity with effort,but unable to do active work)

Papular pruritic Eruption





Herpes Zoster



Seborrheic Dermatitis
(Dandruff)

WHO Stage III

- Severe wt loss (>10% of presumed or measured body wt)
- Unexplained chronic diarrhea for > one month
- Unexplained persistent fever (intermittent or constant for > one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis

WHO Stage III

- Conditions where confirmatory **diagnostic testing is necessary:**
  - Unexplained anemia (<8 g/dl), and or
  - neutropenia (<500/mm3) and or
  - thrombocytopenia (<50 000/ mm3) for more than one month
- **Performance Scale 3 (bedridden <50% of the day for the past month)**

Oral Candidiasis



Courtesy of Samuel Anderson, MD



Courtesy of Dr. R. Ojon

WHO Stage IV

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy, or

- **Performance Scale 4 (bedridden >50% of the day for the past month)**

HIV Wasting Syndrome

- Wt loss >10% body wt

plus

- Unexplained chronic diarrhea (>1 mo) or
- Unexplained fever (>1 mo) plus chronic weakness



Management

- Management of HIV/AIDS can be divided into four categories:
  - Universal precaution for IP
  - Prevention and therapy for OIs and malignancies
  - Antiretroviral treatment
  - Hematopoietic stimulating factors, and
  - Overall care and support

Management

1. Prevention:

A. Primary Prevention:

- Vaccine development is on trial;
- Effective prevention of transmission through universal precautions of IP is vital.
- PMTCT

B. Secondary Prevention:

- HAART and prophylactic regimens can prevent OIs and improve survival.
- Prophylaxis for common OIs should be given to pts per the national guideline.
- Secondary prophylaxis includes **PEP.**

Management

2. HAART:

- HAART is one component of the comprehensive care and treatment of PLWHA.
- Treatment regimens for HIV infection are constantly changing.
- People are still doing well over 30 years with good adherence to HAART.

Goals of ART

- **Clinical goal**: Prolong & improve quality of life
- **Virologic goal**: Reduce viral load
  - HIV RNA < 50 copies/mL or “undetectable” within 4-6 months of ART initiation is good achievement.
- **Immunologic goal**: Immune reconstitution
- **Therapeutic goals:** Maintain future treatment options, minimizes toxicity & maximizes benefit.
- **Preventive goals**: Reduce HIV transmission:

Classes of Antiretrovirals

1. Reverse transcriptase (RT) inhibitors
   - ✓ Nucleoside RT inhibitors (NRTI)
   - ✓ Nucleotide RT inhibitors (NtNRI)
   - ✓ Non-nucleoside RT inhibitors (NNRTI)
2. Protease inhibitors (PI)
3. Fusion inhibitor
4. Integrase inhibitors
5. CCR5 Inhibitor

Classes of Antiretrovirals

- Combination of at least 3 drugs:
  - 2 NRTIs
  - 1 INTRIs or 1 NNRTI or 1-2 PI; OR
  - Rarely Triple NRTIs
- Therapy with only one or two agents allows HIV to overcome therapy through resistance mutations.
- Regular follow up is mandatory with clinical and laboratory evaluation.
- CD4 counts every 3-6 months
- Viral load tests every 3-6 months and 1 month following a change in therapy; and
- Other tests should be done regularly based on national guideline.

Preferred and alternative first-line ART regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC + DTG	TDF + 3TC + EFV 400 mg	TDF + 3TC + EFV 600 mg AZT + 3TC + EFV 600 mg TDF + 3TC + PI/r TDF + 3TC + RAL TAF + 3TC + DTG ABC + 3TC + DTG
Children	ABC + 3TC + DTG	ABC + 3TC + LPV/r ABC + 3TC + RAL	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL	AZT + 3TC + NVP	AZT + 3TC + LPV/r

Preferred and alternative second-line ART regimens

Population	Failing first line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents	TDF + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r
	TDF + 3TC + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r or DRV/r)
	AZT + 3TC + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC + ATV/r (or LPV/r or DRV/r)
Children and infants	ABC + 3TC + DTG	AZT+ 3TC + LPV/r (or ATV/r)	AZT + 3TC + DRV/r
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG	AZT (or ABC) + 3TC + LPV/r (or ATV/r)
	AZT + 3TC + NVP	ABC + 3TC + DTG	ABC + 3TC + LPV/r (or ATV/rf or DRV/r)

Dosages of antiretroviral drugs for adults & adolescents

ARV drug	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine	300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleotide reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 g twice daily

Dosages of antiretroviral drugs for adults & adolescents

ARV drug	Dose
Protease inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	400/100 mg twice daily
For individuals receiving TB therapy: adjust dose of LPV/r (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily) with monitoring	
Integrase strand transfer inhibitors (INSTIs)	
Raltegravir (RAL)	400 mg twice daily
Dolutegravir (DTG)	50 mg once daily

PEP

- **Indications for PEP**
  - **Occupational exposure** (healthcare workers, police)
    - **Exposure to other people's blood**
  - **Non occupational**
    - **Discordant couples** following **barrier protection breakage**,
    - **Rape**
- **PEP regimens**
  - **AZT/3TC**: 1 tab bid for 28 days
  - **TDF/3TC**: 1 tab qd for 28 days
  - **Add DTG or LPV/r or EFV**: 2 tabs bid for 28 days in case of high risk
  - Given at earliest possible opportunity, **within 72 hrs** of exposure

PrEP

- Oral PrEP is the daily **use of ARV drugs by HIV-uninfected people** to block the acquisition of HIV
- *Serodiscordant couples-* daily **TDF or TDF + FTC** for the uninfected partner.
- *If same sex:* **TDF + FTC** daily (male to male)
- *Men and transgender women who have sex with men-* **TDF + FTC**

ARV drug toxicities

AZT

- **Anemia**, neutropaenia, myopathy, lipodystrophy
- **Lactic acidosis** or severe hepatomegaly with steatosis

Mgt:

- Substitute **AZT with TDF** or **ABC** if used in 1st -line ART

TDF

- Tubular renal dysfunction, **Fanconi syndrome**
- Decreases in **bone mineral density**
- **Lactic acidosis** or **severe hepatomegaly** with steatosis

Mgt :

- Substitute **TDF with AZT or ABC** if being used in 1st -line ART
- Substitute **TDF with ABC**, if being used in 2nd -line ART

ARV drug toxicities

ABC

- Hypersensitivity reaction
- Electrocardiographic abnormalities (PR interval prolongation)

Mgt :

- Substitute **ABC with TDF or AZT** if is being used in first-line ART
- Substitute **ABC with TDF if ABC** is being used in second-line ART

EFV

- Persistent **CNS toxicity** (such as abnormal dreams, depression or mental confusion)
- Hepatotoxicity
- Hypersensitivity reaction, Stevens-Johnson syndrome
- Male gynaecomastia

Mgt :

- Substitute with DTG
- If the person cannot tolerate either NNRTI, use **boosted Pis or DTG**

ARV drug toxicities

NVP (not an option currently)

- **Hepatotoxicity**
- Severe **skin rash** and hypersensitivity reaction (Stevens-Johnson syndrome)

Mgt:

- substitute with EFV
- If the person cannot tolerate either NNRTI, use boosted PIs

ARV drug toxicities

LPV/r

- ECG abnormality (PR and QT interval prolongation)
- Hepatotoxicity
- Pancreatitis
- Lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea

Mgt:

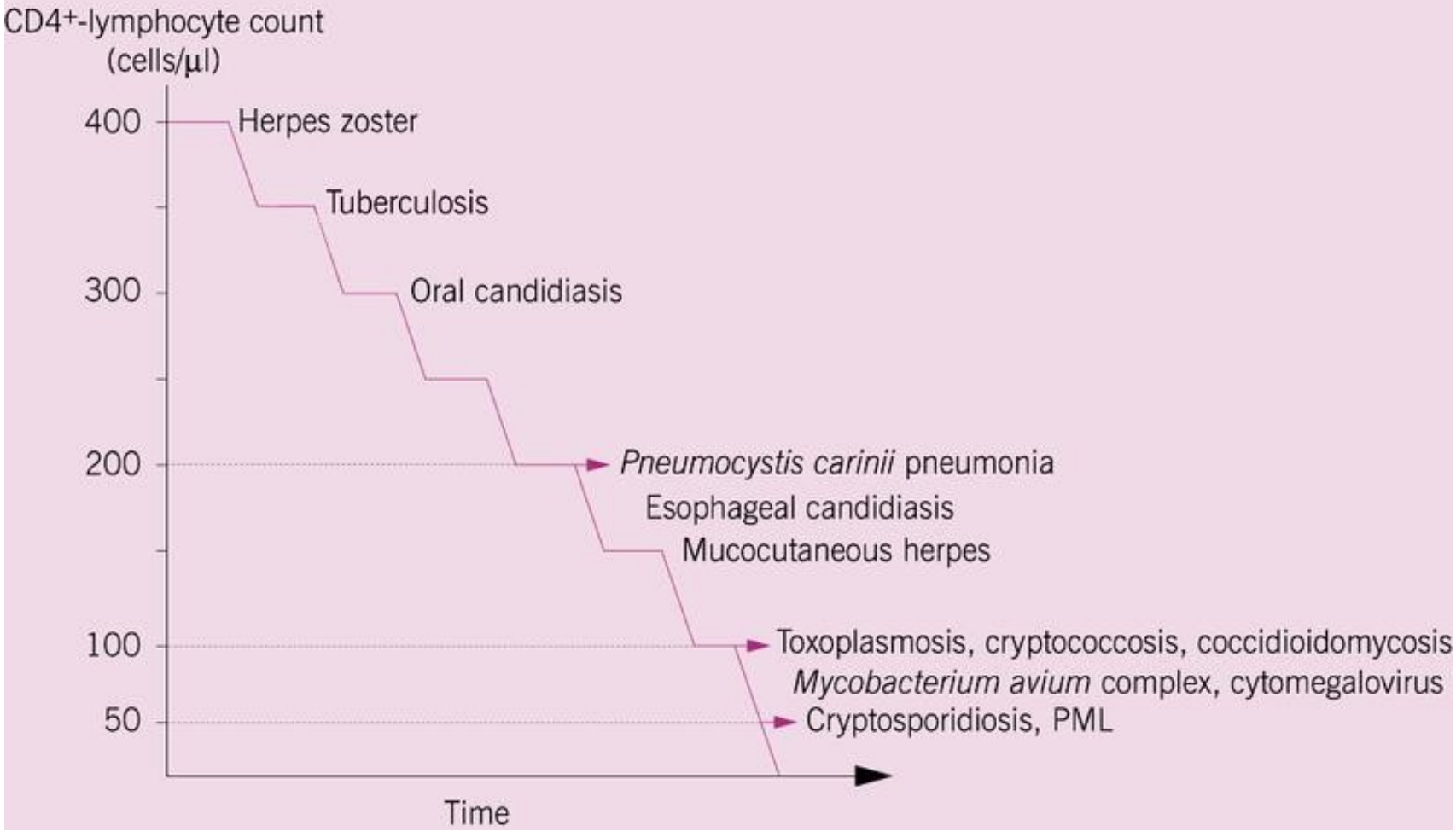
- If LPV/r is used in 1st - line ART for children, use an age-appropriate NNRTI
  - (**NVP** for <3 years age and **EFV** for children 3 years and older). ATV can be used for children older than 6 years
- If LPV/r is used in 2nd - line ART for adults, use **ATV/r or DRV/r.**

MANAGEMENT OF OIs

Definition of OIs

- Infections that develop as a result of damage to the immune system.
- OIs take advantage of the opportunity provided by a weakened immune system.
- Predominant causes of morbidity and mortality among HIV-infected pts.
- The level of immunity determines the occurrence and type of OIs.

ASSOCIATION BETWEEN OPPORTUNISTIC INFECTIONS AND CD4⁺-LYMPHOCYTE COUNT



PCP

- The cause of pneumocystosis is a fungal agent, *P. jiroveci,* formerly named *P. carinii*
- The name change was made to distinguish the organism that infects humans (*P. jiroveci*) from the strain that infects rodents (*P. carinii*).
- Frequently PCP occurs when the CD4 count drops below **200 cells/µL**

PCP: Clinical Presentation

- Typical clinical presentations
  - ✓ **Insidious onset of low grade fever(79-100%)**
  - ✓ **Dry cough (95%)**
  - ✓ **Dyspnea exacerbated by exertion (95%)**
  - ✓ Extra pulmonary manifestations: *hepatosplenomegaly, skin lesions, and pleural effusions*
- P/E often reveals
  - ✓ **Fever**
  - ✓ **Tachypnea**
  - ✓ **Tachycardia**
  - ✓ **Scattered rales in the lungs**

PCP: Dx

- **Diagnosis**: presumptive diagnosis of PCP is based on clinical judgment and CXR
- CXR typically shows bilateral, diffuse, interstitial pulmonary infiltrates at the lower lobe
- Note that the chest X-ray can be normal in 20% of pts.
- Definitive diagnosis of PCP is based on demonstration of the organism from an induced sputum sample using special stains like Giemsa or methylamine silver stains.
- But these tests are not routinely done in Ethiopia.

PCP: Treatment

Treatment:

- Cotrimoxazole (15-20 mg/kg trimethoprim plus 75-100 mg/kg sulfamethoxazole) in three or four divided doses for 21 days.
- Alternative regimens for mild to moderate PCP:
  - Primaquine 15-30 mg/day PO once daily plus Clindamycin 600 mg IV TID **OR** 300-450 mg PO QID **OR**
  - TMP 5 mg/kg PO TID plus Dapsone 100 mg PO QD **OR**
  - Atovaquone 750 mg PO BID **OR**
  - Pentamidine 4 mg/kg/day IV once daily

PCP: Treatment

- **Secondary prophylaxis** after completion of the course of treatment with cotrimoxazole should be started
- Adjuvant corticosteroid
  - Indicated for severely ill pts with marked respiratory distress and extensive CXR findings ($PaO_2 \leq 70$ mm Hg)
  - Reduces mortality by 50%
  - Regimen
    - Prednisone 40 mg po bid x 5 days
    - 40 mg po qd x 5 days
    - 20 mg qd x 11 days
  - No benefit for mild episodes

PCP: Prophylaxis

- **Indications**
  - Primary prophylaxis (to prevent disease)
    - CD4 < 350/mm^3
    - WHO Stage II, III, IV
    - HIV-associated oral candidiasis
    - Unexplained fever
  - Secondary prophylaxis (after PCP, to prevent recurrence)
    - Prior episode of PCP

PCP: Prophylaxis

- **Standard regimen**
  - Cotrimoxazole (TMP/SMX) 160/800 mg tab QD
- **Alternate regimens**
  - Dapsone 100mg QD
- May safely discontinue if immune system restored from ART
  - Must have CD4 > 350 for 3 months

Cryptococcus Meningitis

- HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*.
- Patients with CD4 counts of **<100 cells/µL**.

Clinical Manifestations:

- Sub acute meningitis or meningoencephalitis with fever, malaise, and headache.
- Classic meningeal S/S (e.g., neck stiffness or photophobia) occur in approximately one fourth to one third of pts.
- Certain pts might present with encephalopathic symptoms e.g. altered mentation, personality changes and memory loss.

Cryptococcus Meningitis

- The CSF usually indicates a mildly elevated protein, normal or slightly low glucose, and a few lymphocytes and numerous organisms.
- The opening pressure in the CSF is elevated (with pressures >200 mm of water) in the majority of pts.
- Disseminated disease is a common manifestation, with or without concurrent meningitis.
- Skin lesions might be observed.

Cryptococcus Meningitis

Diagnosis

- Clinical
- LP with CSF analysis including India ink staining
- Serum and CSF cryptococcal AG detection
- Fungal culture

Cryptococcus Meningitis

Treatment

- Option A:
  - Induction (2 weeks):
    - High dose of fluconazole 1200 mg/day alone (In children 12mg/kg/day) and
  - Consolidation phase (8 weeks):
    - Fluconazole 800 mg/day, in children 12mg/kg/day).
  - Maintenance treatment (or secondary prophylaxis):
    - Fluconazole 200 mg daily (in children 6mg/kg/day)

Cryptococcus Meningitis

- Option B
  - Induction phase (2 weeks):
    - Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day.
  - Consolidation phase (8 weeks):
    - Fluconazole 400-800 mg/day.
  - Maintenance treatment (or secondary prophylaxis):
    - Fluconazole 200 mg daily (in children 6mg/kg/day).
- D/C
  - Anti-fungal maintenance treatment for at least one year and have a CD4 cell count of greater than or equal to 200 cells/mm3

Toxoplasmosis

- CNS toxoplasmosis is caused by the intracellular protozoan parasite, **Toxoplasma gondii**.
- Immunocompetent persons with primary infection are usually asymptomatic, but latent infection can persist for life.
- In immunosuppressed pts, especially HIV/AIDS pts, the parasite can reactivate and cause disease
- Seroprevalence varies substantially in different communities; in Ethiopia, general prevalence is about 80% in the adult population.
- The greatest risk is among pts with a CD4+ T lymphocyte count **<100 cells/µL**.

Toxoplasmosis

Clinical manifestations:

- The most common clinical manifestations are: headache, confusion, and/or motor weakness & fever.
- P/E might demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma.
- CT scan or brain MRI will typically show multiple ring enhancing lesions, often with associated edema.

Toxoplasmosis

Diagnosis:

- HIV infected pts with CNS toxoplasmosis are mostly seropositive for anti-toxoplasma IgG antibodies.
- A positive result does **not** support the diagnosis.
- However, absence of the IgG antibody makes a diagnosis of toxoplasmosis unlikely.
- Definitive diagnosis requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, and detection of the organism in a clinical sample.
- In the absence of imaging support, empirical treatment is justified when pts present with focal neurological findings and the **CD4 count is < 200 cells µL**.

Toxoplasmosis

Treatment:

- Trimethoprim/sulfamethoxazole 160/800, oral, 2 tablets 12 hourly for 28 days, followed by 1 tablet 12 hourly for 3 months in adults.
- Preferred regimen:
  - Pyrimethamine (200 mg loading dose followed by 50 mg PO daily among patients <60 kg or 75 mg daily among patients >60 kg)

    PLUS
  - Sulfadiazine (1000 mg four times PO daily among patients <60 kg to 1500 mg four times PO daily among patients >60 kg)

    PLUS
  - Leucovorin 10 to 25 mg PO daily

FUNGAL INFECTIONS

Classification

- Fungal infections are best classified by the area of the body infected
- **Superficial mycoses** involve only the outermost keratinized layers of the skin (stratum corneum) and hair.
- The **cutaneous mycoses** extend deeper into the epidermis and may also infect the nails.
- The **subcutaneous mycoses** infect the dermis and subcutaneous tissues; entry into these sites is by inoculation or implantation of dirt or vegetative matter.
- **Systemic mycoses** cause disease of the internal organs of the body

Classification	Site Infected	Example
Superficial	Outermost skin and hair	Malasseziasis (Tinea versicolor)
Cutaneous	Deep epidermis and nails	Dermatophytosis
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis
Systemic	Disease of more than one internal organ	
	Opportunistic	Candidiasis Cryptococcosis Aspergillosis Mucormycosis
	Nonopportunistic	Histoplasmosis Blastomycosis Coccidioidomycosis

Classification

- Superficial mycotic infections of the skin are referred to as **dermatophytoses**
- They are common infections that usually are caused by dermatophytes classified by genera:
  - Trichophyton,
  - Epidermophyton, and
  - Microsporum

Tineas

- Tinea Pedis
- Tinea Capitis
- Tinea Corporis
- Tinea Cruris
- Tinea Faciei
- Tinea Versicolor

Tinea Pedis

- Tinea pedis is the most common dermatophytoses (affecting 70% of adults).
- It is better known as "athlete's foot" and occurs in hot weather, with exposure to surface reservoirs (locker room floors), and with use of occlusive footwear.

Tinea Pedis

- Interdigital, vesiculobullar
  - *T. rubrum*
  - *T. mentagrophytes*
- Severely pruitic, demarcated lesions, raised erythematous margin and thin, dry scaling
- Can be obtained from group showers or other public facilities





Tinea Pedis

- Treatment with topical therapy for 2 to 4 weeks often is adequate for mild infections; however, **severe infections** or involvement of **the nails requires oral therapy.**
- Recurrence of infection occurs in up to 70% of individuals.
- Prolonged treatment with either topical or systemic therapy may be required

Tinea Capitis

- Tinea capitis is a mycotic infection involving the scalp, hair follicles, and adjacent skin that primarily affects children.
- Head Ringworm
  - *T. tonsurans*
- Most common in school age children 3-10

Tinea Capitis

- Treatment should consist of oral therapy, as well as the cleaning of combs and brushes, which can be contaminated.
- Daily shampooing is recommended for removal of scales.
- Family members who culture positive for Trichophyton tonsurans should be treated with an antifungal shampoo (e.g., ketoconazole, selenium sulfide, or povidone-iodine).

Tinea Corporis

- Body Ringworm
- Tinea corporis is an infection of the **glabrous skin of the trunk and extremities**.
- One or more well-demarcatd, erthematous, scaly discrete patches, raised borders and central healing
- *T. rubrum, T tonsurus, T. mentagrophytes*
- Therapy is similar to that for tinea pedis, tinea manuum, and tinea cruris



Tinea Manuum

- Tinea manuum usually involves the palmar surface of the hands, is unilateral, and can involve the feet.
- Treatment of this infection is similar to tinea pedis.
- Emollients that contain lactic acid also can be useful.

Tinea Cruris

- Tinea cruris is an infection of the proximal thighs and buttocks.
  - **Jock Itch**
- Severely pruritic, sharply demarcated lesions with raised erythematous margin, thin, scaling.
- Passed from one person to the other
- *T. rubrum, T mentagrophytes, E. floccosum*
- Often recurrent



Tinea Cruris

- Treatment with topical therapy is recommended and should continue for 1 to 2 weeks after symptom resolution.
- Severe infections can require oral therapy.
- Relief of pruritus and burning can be facilitated by the use of short-term (2 or 3 days) topical steroids (2.5% hydrocortisone)

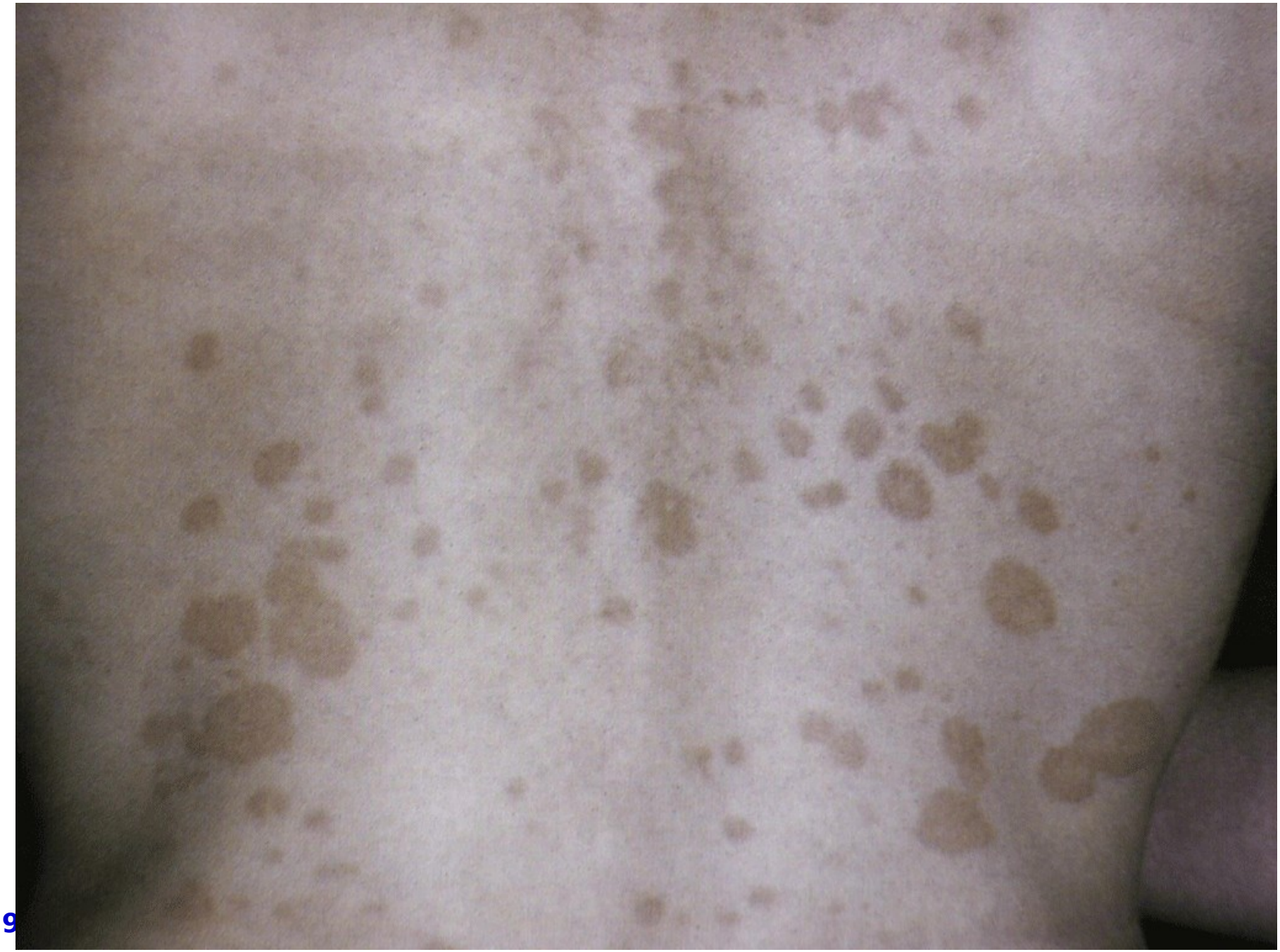
Tinea Faciei

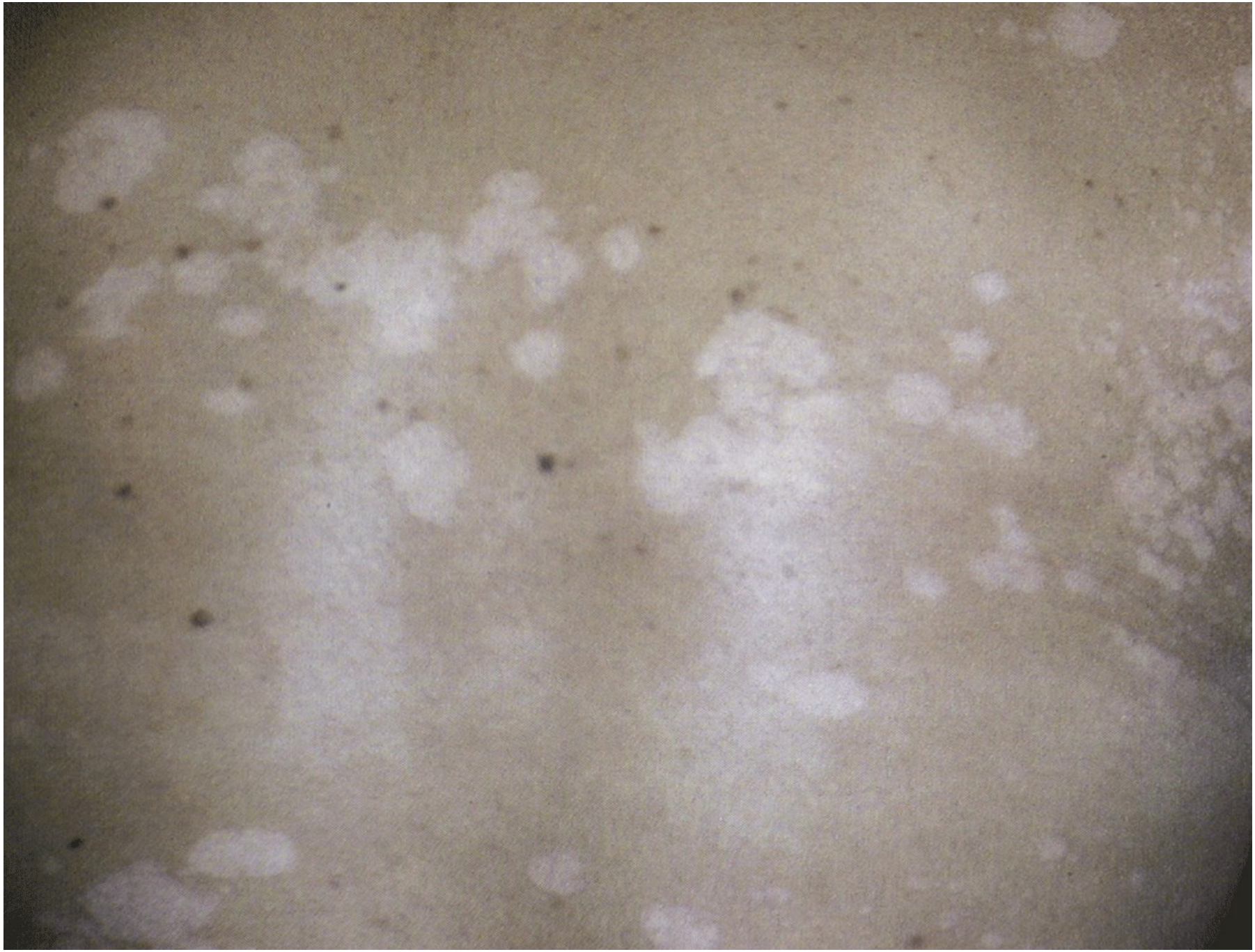
- Ringworm like
- On the face
- Lesions often difficult to recognize; pruritis and erythematous, subtle margins
- *T. rubrum*
- More frequently reported in pts with AIDS



Tinea Versicolor

- Pityriasis versicolor
- Hyper- and hypopigmented scaly patches
- Thin pale lesions that are hard to see unless person is tan or dark skinned
- ***Malassezia* sp** normally commensal on skin surface
- Confined to trunk or proximal aspects of limbs
- Topical treatment usually is adequate unless there is extensive involvement, recurrent infections, or failure of topical therapy





Tinea Barbae

- Tinea barbae affects the hairs and follicles of beards and mustaches.
- Treatment is similar to that for tinea capitis.
- **Removal of the beard or mustache** is recommended

Topical Antifungals

Agent	Tinea pedis dosing	Tinea corporis dosing	Tinea cruris dosing
Clotrimazole 1%	BID x 4 weeks	BID x 4 weeks	BID x 2 weeks
Miconazole 2%	BID x 4 weeks	BID x 4 weeks	BID x 2 weeks
Terbinafine 1%	BID x 1 wk if between toes or 2 wks if > area	Daily x 1 week	Daily x 1 week
Butenafine 1%	BID x 1 wk or Daily x 4 wks	Daily x 2 weeks	Daily x 2 weeks
Tolnaftate 1%	BID x 4 weeks	BID x 4 weeks	BID x 2 weeks

Tinea Unguium (Onychomycosis)

- Onychomycosis is a fungal infection of the nail apparatus
- Toenails > fingernails
- Dermatophytes : *Trichophyton rubrum* (71%) and *Trichophyton mentagrophytes*
- *C. albicans*





Treatment

- Topical vs systemic
  - Oral antifungal therapy is considered to be more effective than topical for treating onychomycosis

Systemic Agents

Agent	Comments
Griseofulvin, 500 mg/day Ultramicrosize better F	6 mo-1 yr tx
Terbinafine, 250 mg/day	6wks (finger)-12 wks (toe)
Itraconazole, 200 mg	Toe: qd x 12 wks; Pulse (toe, finger) bid x 1wk, 3 wks off;

Seborrheic Dermatitis

- Dandruff of scalp
- *Malasseria* sp
- Range of different clinical appearances, Erythema, scaling central part of chest, upper back, face, ears
- Commonly seen in patients with AIDS, may be more severe
- Treatment: topical azoles, 1% hydrocortisone cream

Vulvovaginal Candidiasis

- VVC refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species.
- Classification:
  - Sporadic or Recurrent
  - Uncomplicated vs complicated

Treatment:

- **Uncomplicated Vulvovaginal Candidiasis**

Clotrimazole	1, 2, 10% cream	One applicator x 1 day
	100 mg tablet	One 100 mg tablet x 7 days
	200 mg tablet	One 200 mg tablet x 3 days
	500 mg tablet	One 500 mg tablet x 1 day
Miconazole	2% cream	One applicator x 1 day
	100 mg suppository	One 100 mg suppository x 7 days
	200 mg suppository	One 200 mg suppository x 3 days
Nystatin	100,000-unit tablet	One tablet x 14 days
Fluconazole	150 mg	One tablet x 1 day

Complicated VVC

- Immunocompromised
- Uncontrolled diabetes mellitus
  - lengthen therapy to 10 to 14 days
- Pregnancy
  - Topical agents are safe
  - Oral agents are contraindicated in pregnancy

Recurrent VVC

- RVVC is defined as having more than four episodes of VVC within a 12-month period.
- RVVC is best treated in two stages:
- an initial intensive stage followed by prolonged antifungal therapy to achieve mycologic remission.
  - 10 to 14 days of induction therapy with a topical or oral azole, followed by 150 mg of fluconazole once weekly for 6 months

Oropharyngeal and Esophageal Candidiasis

- ***Oropharyngeal candidiasis* (OPC),** or ***thrush,*** refers to an infection of the oral mucosa.

Local factors	Potential mechanisms
Use of steroids and antibiotics	Suppression of cellular immunity and inhibition of phagocytosis by steroids, including chronic use of inhaled and topical steroids Alteration of endogenous oral flora by broad-spectrum antibiotics, especially when used with steroids, creates a milieu for proliferation of *Candida* species because of reduced environmental and nutritional competition
Dentures	Enhanced adherence of *Candida* species to the acrylic material of dentures, reduced saliva flow under surfaces of denture fittings, improperly fitted dentures, and poor oral hygiene provide a milieu conducive to the survival of

Xerostomia caused by drugs (e.g., tricyclic antidepressants and phenothiazine), chemotherapy, radiotherapy to the head/neck, and various diseases	Reduced dilutional and cleansing effect caused by low secretion rate and low pH in saliva: saliva and mucosa secretions have defense factors,
Smoking	
Disruption of oral mucosa caused by chemotherapy and radiotherapy, ulcers, endotracheal intubation trauma, and burns	Oral mucositis induced by radiation and breaks in the physical barrier of the oral epithelium, which is protective against invasion by microorganisms; altered rate of mucosa regeneration by cancer chemotherapy, which increases

Systemic factors	Potential mechanisms
Drugs (e.g., cytotoxic agents, corticosteroids, and immunosuppressants, omeprazole, and environmental chemicals (e.g., benzene and pesticides)	Reduced immunity ; potent inhibition of gastric acid by PPIs can facilitate the growth of Candida species; PPIs also can inhibit the cytotoxic effect of lymphocytes and reduce salivary secretion
Neonates or the elderly	Immature immune system of neonates

HIV infection/AIDS	Depletion of CD4 T lymphocytes
Diabetes	altered neutrophil function,
Malignancies (e.g., leukemia and head/neck cancer)	Use of intensive radiotherapy and chemotherapy
Nutritional deficiencies (e.g., iron, folate, and vitamins B_1, B_2, B_6, B_{12}, and C)	alter host defense mechanisms, or change epithelial barrier integrity

Treatment

- **Initial episodes of OPC: Treat for 7–14 days**
  - **Nystatin 100,000 units/mL suspension: 5 mL swish and swallow 4 times daily**
  - **Fluconazole100 mg tablets: 100–200 mg daily**
  - **Itraconazole 10 mg/mL solution: 200 mg daily**
- **Fluconazole-refractory OPC: Treat for > 14 days**
  - **Itraconazole 10 mg/mL solution: 200 mg daily**
  - **Amphotericin B deoxycholate 50 mg injection**

- **Esophageal candidiasis: Treat for 14–21 days**
  - **Fluconazole 100 mg tablets: 200–400 mg**
  - **Itraconazole 10 mg/mL solution: 200 mg daily**
- **Fluconazole-refractory EC: Treat for 21–28 days**
  - **Itraconazole 10 mg/mL solution: 200 mg daily**
  - **Amphotericin B deoxycholate: 0.3–0.7 mg/kg/day IV**

SEPSIS AND SEPTIC SHOCK

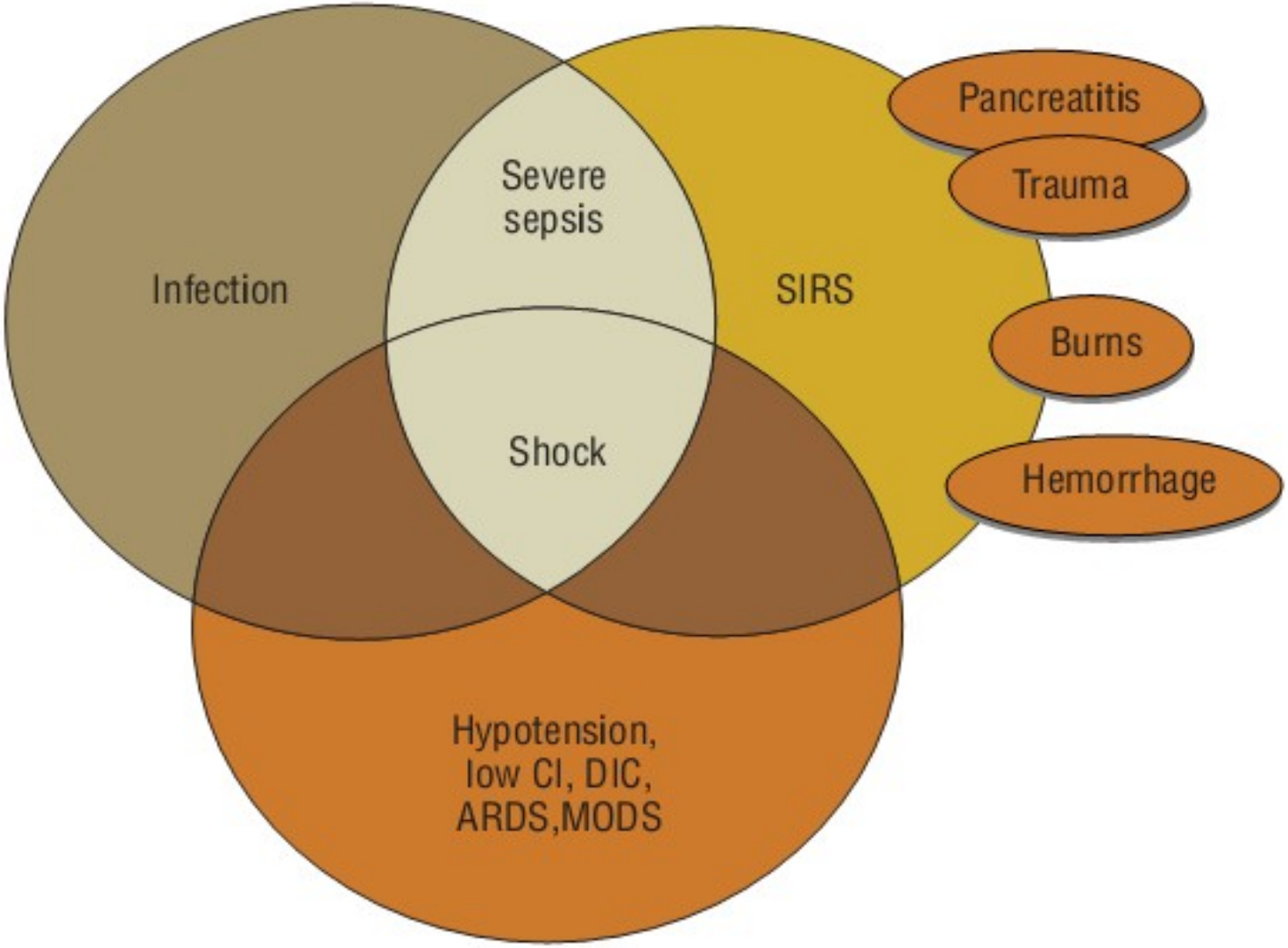
Definitions Related to Sepsis

- **Bacteremia (fungemia):** Presence of viable bacteria (fungi) in the bloodstream
- **Infection:** Inflammatory response to invasion of normally sterile host tissue by the microorganisms
- **Systemic inflammatory response syndrome (SIRS):** Systemic inflammatory response to a variety of clinical insults that can be infectious or noninfectious etiology
  - The response is manifested by two or more of the following conditions:
    - T >38°C (100.4°F) or <36°C (96.8°F);
    - HR > 90 beats/min;
    - RR > 20 breaths/min
    - WBC >12,000 cells/mm3, <4,000 cells/mm3, or >10% immature (band) forms
    - Hyperglycemia

Definitions Related to Sepsis

- **Sepsis**: The SIRS secondary to infection
- **Severe sepsis**: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities can include, but are not limited to, lactic acidosis, **oliguria**, or acute alteration in mental status
- **Septic shock**: Sepsis with persistent hypotension despite fluid resuscitation, along with the presence of perfusion abnormalities.
- **Multiple-organ dysfunction syndrome (MODS)**: Dysfunction of more than one organ, requiring intervention to maintain homeostasis

Relationship of infection, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock.



Infection Sites & Pathogens

- The leading primary sites of microbiologically documented infections that led to sepsis are:
  - The respiratory tract (21%–68%),
  - Intra-abdominal space (14%–22%), and
  - Urinary tract (14%–18%)
- Although almost any microorganism can be associated with sepsis and septic shock, the most common etiologic pathogens are:
  - Gram-positive bacteria (40% of patients),
  - Gram-negative bacteria (38%) and
  - Fungi (17%)
- Certain viruses and rickettsiae can produce a similar syndrome.

Pathogens

- **Gram-Positive Bacterial Sepsis:**
  - Staphylococcus aureus,
  - Streptococcus pneumoniae,
  - Coagulase-negative staphylococci,and
  - Enterococcus species.
  - Streptococcus pyogenes and viridans streptococci are less commonly involved
- **Gram-Negative Bacterial Sepsis**
  - Escherichia coli
  - Pseudomonas aeruginosa
  - Klebsiella species,
  - Serratia species,
  - Enterobacter species, and
  - Proteus species
  - More likely to produce septic shock, clinical sepsis and mortality than G+ organisms (50% versus 25%)

Pathogens

- **Anaerobic and Miscellaneous Bacterial Sepsis**
  - Anaerobes are usually considered low-risk organisms for the development of sepsis.
  - If present, anaerobes are often found together with other pathogenic bacteria that are commonly found in sepsis
- Other less common pathogens include meningococcus, gonococcus, rickettsia, chlamydia, and spirochetes.
- **Fungal Sepsis**
  - **Candida albicans** remains the most dominant species,
  - Mortality ranges from 41% to 71% in patients with fungemia

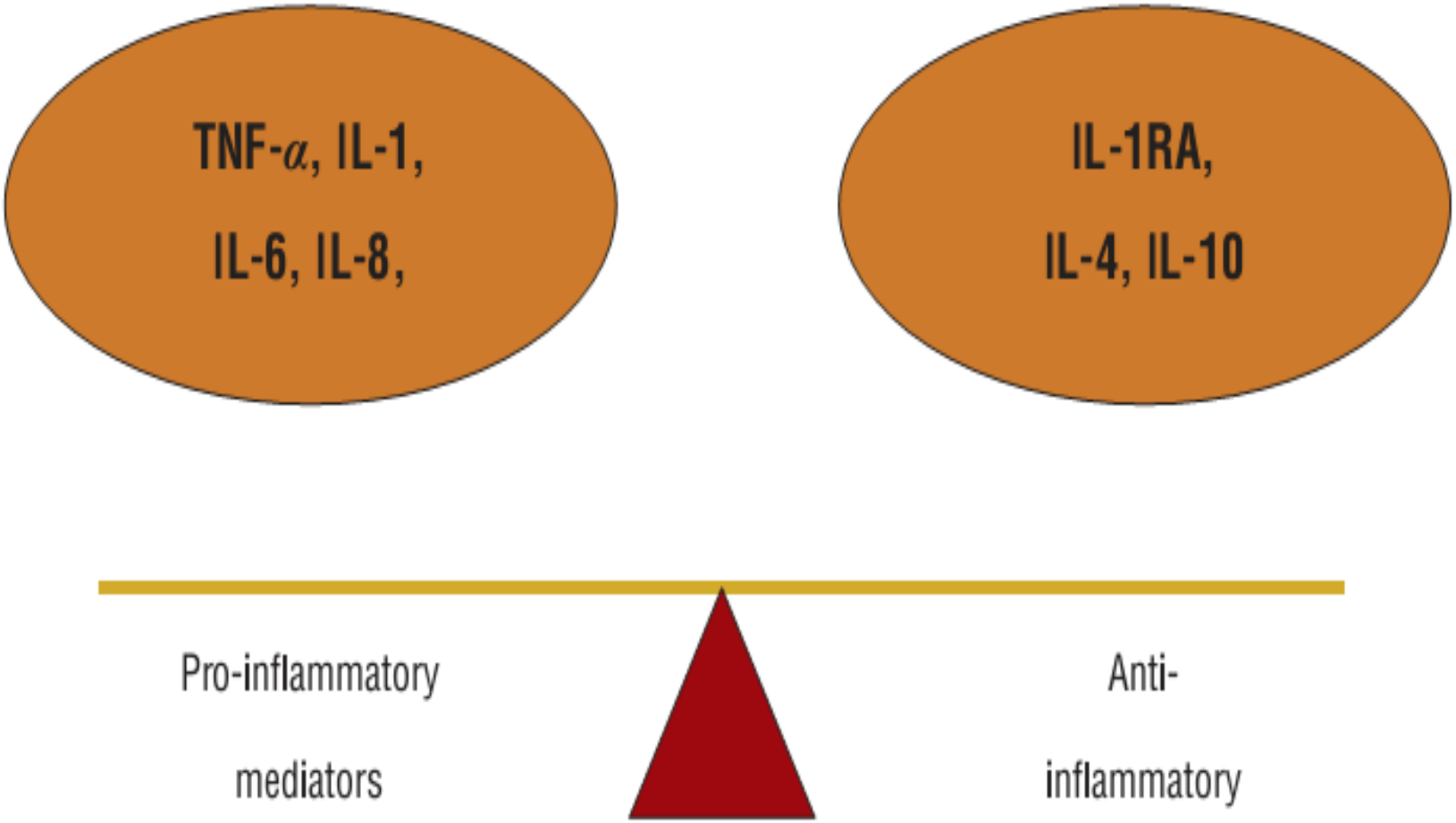
Pathophysiology

- The normal host response to infection is designed to localize and control bacterial invasion and initiate repair of injured tissue through phagocytic cells and inflammatory mediators
- Sepsis results when the inflammatory response becomes **systemic** and **extends** to normal tissue distant from the initial tissue site.

Pathophysiology

- Infection or injury is controlled through pro- and anti-inflammatory mediators.
- **Pro-inflammatory mediators** facilitate clearance of the injuring stimulus, promote resolution of injury, and are involved in processing of damaged tissue.
- In order to control the intensity and duration of the inflammatory response, **anti-inflammatory mediators** are released that act to regulate pro-inflammatory mediators
- The balance between pro- and anti-inflammatory mediators localizes infection/injury of host tissue.
- However, systemic responses ensue when equilibrium in the inflammatory process is lost

Pathophysiology



Clinical Presentation of Sepsis

- Early sepsis: **fever**, **chills**, and **change in mental status**
  - Others:
    - Tachycardia
    - Tachypnea
    - Nausea and vomiting
    - Hyperglycemia
    - Myalgia
    - Lethargy and malaise
    - Proteinuria
    - Leukocytosis
    - Hypoxia
    - Hyperbilirubinemia

Clinical Presentation of Sepsis

- Late sepsis: slow process
  - Lactic acidosis
  - Oliguria
  - Leukopenia
  - Thrombocytopenia
  - Myocardial depression
  - Pulmonary edema
  - Hypotension
  - Hypoglycemia
  - Gastrointestinal hemorrhage

Diagnostic and Laboratory Tests

- Cultures
- Complete blood count with differential
- Coagulation parameters

Treatment

Desired Outcomes

- To prevent morbidity and mortality by:
  - Reducing or eliminating organ failures;
  - Treating and eliminating the source of infection;
  - Avoiding adverse reactions of treatment; and
  - Providing cost-effective therapy

General Approach to Treatment

- The speed and appropriateness of therapy administered in the initial hours after sepsis develops influences outcome, as is the case for acute **myocardial infarction** and **cerebrovascular accidents**
- Early goal-directed resuscitation of septic patients during the **first 6 hours** after recognition.
- Early administration of broad-spectrum anti-infective therapy.

Pharmacologic Therapy

Initial Resuscitation

- Crystalloid or colloid fluids
- A patient in septic shock typically requires up to **10 L** of crystalloid solution during the first 24-hour period.

Anti-Infective Therapy

- Empiric anti-infective therapy should include one, two, or three drugs, depending on the site of infection and causative pathogens
- Factors that determine selection are:
  - Site of infection
  - Causative pathogens
  - Community- or nosocomial-acquired infection
  - Immune status of patient
  - Antibiotic susceptibility and resistance profile for the institution
  - Patient history (underlying disease, previous cultures or infections, and drug intolerance)
  - Adverse reactions

Anti-Infective Therapy

Infection (Site or Type)	Community-Acquired	Hospital-Acquired
Urinary tract	Ceftriaxone or Ciprofloxacin or levofloxacin	Ciprofloxacin, levofloxacin or ceftazidime, ceftriaxone (± gentamicin)
Respiratory tract	(Levofloxacin, moxifloxacin, gemifloxacin or ceftriaxone) + (clarithromycin or azithromycin)	(Piperacillin, ceftazidime, or cefepime) + (gentamicin or Ciprofloxacin)
Intra-abdominal	(Ampicillin-sulbactam or Ciprofloxacin) + (metronidazole)	(Piperacillin-tazobactam or Cefepime) + metronidazole (Ciprofloxacin or levofloxacin) +

Anti-Infective Therapy

Skin and soft tissue	Vancomycin	vancomycin + (ampicillin/ sulbactam or piperacillin/tazobactam)
Catheter-related		Vancomycin
Unknown		piperacillin/tazobactam or ceftazidime/cefipime or imipenem/meropenem

Vasopressor and Inotropic Therapy

- When fluid resuscitation alone provides inadequate arterial pressure and organ perfusion, vasopressors and inotropic agents should be initiated.
- Inotropic agents such as dopamine and dobutamine have been effective in improving cardiac output by increasing cardiac contractility.
- Vasopressors such as norepinephrine should be considered when a systolic blood pressure is less than 90 mm Hg

Vasopressor and Inotropic Therapy

- Agents commonly considered for vasopressor or inotropic support include **dopamine**, **dobutamine**, **norepinephrine**, **phenylephrine**, and **epinephrine**

- Norepinephrine should generally be considered to be the first-choice vasopressor in septic shock after failure to restore adequate blood pressure and organ perfusion with appropriate fluid resuscitation.

- Norepinephrine is a potent α-adrenergic agent with less pronounced β-adrenergic activity.

Vasopressor and Inotropic Therapy

- **Dopamine** is an α- and β -adrenergic agent with dopaminergic activity.
- Doses of >5 mcg/kg/min increase MAP and cardiac output, primarily because of the increase in heart rate and cardiac contractility through stimulation of ß-adrenergic receptors
- At higher doses,α-adrenergic effects predominate, resulting in arterial vasoconstriction.

Neonatal sepsis

- **Early-onset sepsis**
  - Birth to 7 days
  - Is multiorgan system disease frequently manifested as respiratory failure, shock, meningitis (in 30% of cases), DIC, acute tubular necrosis, and symmetrical peripheral gangrene.
  - Usually is a result of infection caused by the bacteria in the **mother's genitourinary tract**.
  - Organisms related to this sepsis include group B streptococci, *E. coli*, *Klebsiella*, *L. monocytogenes*, and *H. influenzae.*
  - Most infected infants are **premature** and show nonspecific cardiorespiratory signs, such as grunting, tachypnea, and cyanosis at birth.

Neonatal sepsis

- **Early-onset sepsis**
  - Risk factors for early-onset sepsis include
    - vaginal colonization with group B streptococci,
    - prolonged rupture of the membranes (>24 hours),
    - amnionitis,
    - maternal fever or leukocytosis,
    - fetal tachycardia, and
    - preterm birth.
    - African American race and
    - male sex

Neonatal sepsis

- **Early-onset sepsis**
  - Early manifestations—grunting, poor feeding, pallor, apnea, lethargy, hypothermia, or and abnormal cry—may be nonspecific.
  - Profound neutropenia, hypoxia, and hypotension may be refractory to treatment with broad-spectrum antibiotics, mechanical ventilation, and vasopressors such as dopamine and dobutamine.
  - In the initial stages of early-onset septicemia in a preterm infant, it is often difficult to differentiate sepsis from respiratory distress syndrome.
  - Early-onset sepsis should be evaluated by blood and CSF cultures, CSF Gram stain, cell count, and protein and glucose levels.

Neonatal sepsis

- **Early-onset sepsis**
  - Normal newborns generally have an elevated CSF protein content (100 to 150 mg/dL) and may have 25 to 30/mm^3 white blood cells, which are 75% lymphocytes in the absence of infection.
  - Some infants with neonatal meningitis caused by group B streptococci do not have an elevated CSF leukocyte count but are seen to have microorganisms in the CSF on Gram stain.

Neonatal sepsis

- **Early-onset sepsis**
  - **Empiric management**
    - Ampicillin + gentamicin;10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.
    - Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis.
    - Tailor therapy to pathogen.
    - Consider discontinuation of therapy if pathogen not isolated.

Neonatal sepsis

- **Late-onset sepsis** (8 to 28 days)
  - Usually occurs in a healthy full-term infant who was discharged in good health from the normal newborn nursery.
  - Clinical manifestations may include lethargy, poor feeding, hypotonia, apathy, seizures, bulging fontanelle, fever, and direct-reacting hyperbilirubinemia.
  - Late-onset sepsis may be caused by the same pathogens as early-onset sepsis,
  - Late in the neonatal period also may have infections caused by the pathogens usually found in older infants (H. *influenzae*, S. *pneumoniae*, and N. *meningitidis*).
  - In addition, viral agents (HSV, cytomegalovirus, or enteroviruses) may manifest with a late-onset, sepsis-like picture.

Neonatal sepsis

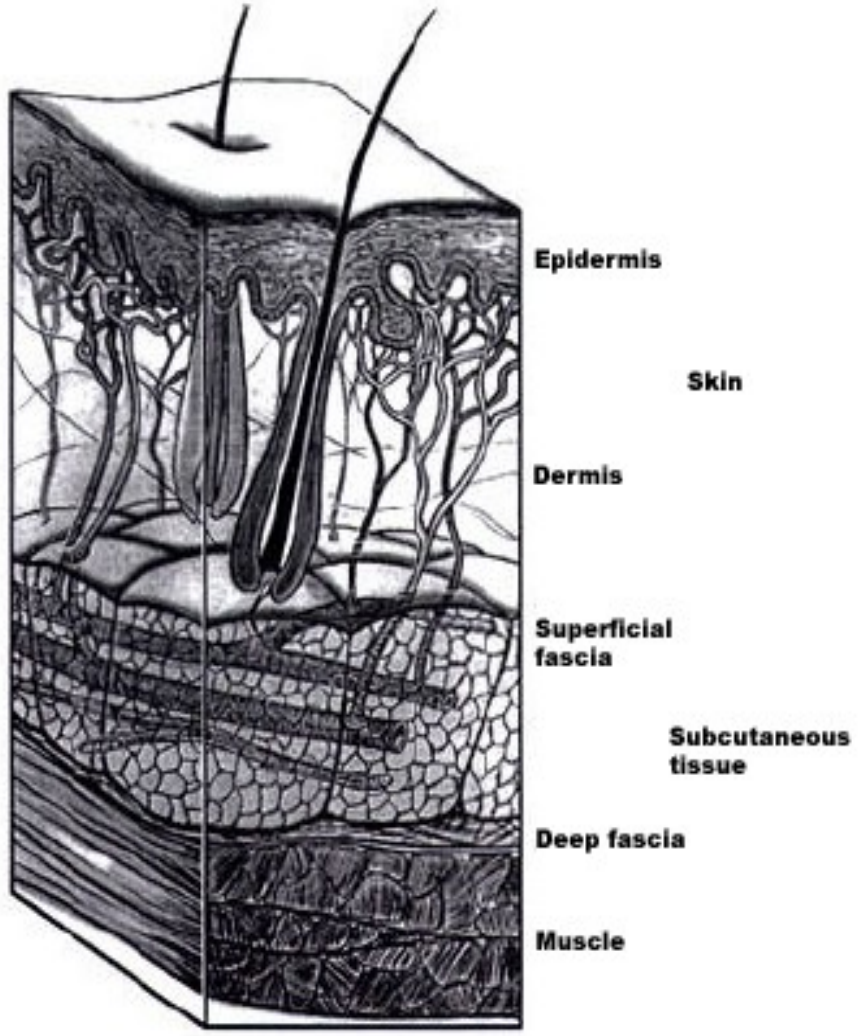
- **Late-onset sepsis**
  - **Empiric management**
    - Vancomycin + aminoglycoside. Duration dependent on pathogen and site.
    - Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance.
    - Consider cephalosporin if meningitis suspected.
    - Consider a carbapenem if third-generation cephalosporin recently received.

SKIN AND SOFT TISSUE INFECTION

Skin and Soft-Tissue Infections

Introduction

- Skin
  - Epidermis
    - Outermost, protective la
  - Dermis
    - Blood vessels, nerves
  - Subcutaneous tissue
    - Fascia (adipose cells)



Skin and soft tissue infections

- Skin/soft tissue infections are common and vary widely in severity
  - Can involve any or all layers of skin, fascia and muscle
- Many classification systems, based on:
  - Infection local or diffuse
  - Systemic signs
  - Necrotizing
  - Infecting organism
- Important to have an idea of what the infecting organism is, and determine appropriate empiric antibiotic therapy where necessary

Skin composition & host defenses to infection

- Multilayered construction of skin
  - Stratum corneum, epidermis, dermis, subcutaneous fat, superficial fascia
- Skin is dry, continuously renewed
- Limited epithelial cell adherence by pathogens
- Intact stratum corneum (acts as a barrier)
- Low skin pH (normally about 5.5)
- Host immune system (IgA and IgG production in sweat)
- Resident skin flora (competitive inhibition)

Factors that could predispose to SSTI

- Damage to corneal layer allowing bacterial penetration
- High conc. of bacteria ($>10^5$)
- Excessive skin moisture
- Occlusion of blood supply to skin
- Obesity
- Blood dyscrasias
- Corticosteroid use
- Neutrophil function defects
- Bedsore
- Diabetes
- Alcohol abuse

Impetigo

- Impetigo is a superficial skin infection
- Seen most commonly in children (2 – 5 yrs)
- Pathogenesis
  - Bacteria invades normal skin via minor wounds (e.g., insect bites, abrasions), develops in approximately 10 days
  - More common in hot, humid, summer weather
  - Can be communicable
  - Spread facilitated by crowding, poor hygiene
- Causes
  - Usually group A streptococci
  - Occasionally S. *aureus*

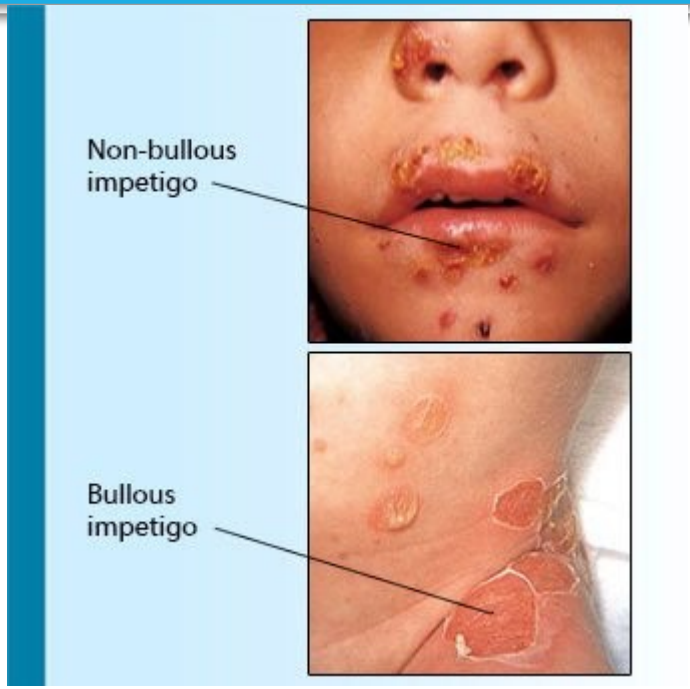
Impetigo

Clinical presentation

- Exposed skin, especially the **face**, is the most common site for impetigo.
- **Pruritus** is common, and **scratching** of the lesions may further spread infection through excoriation of the skin.
- **Nonbullous** impetigo manifests initially as small, fluid-filled vesicles.
- These lesions rapidly develop into pus-filled blisters that readily rupture.
- Purulent discharge from the lesions dries to form **golden yellow crusts** that are characteristic of impetigo.
- In **bullous-impetigo**, the lesions begin as vesicles and turn into bullae containing clear yellow fluid.
- Bullae soon rupture, forming thin, light brown crusts

Impetigo

- **Antimicrobial therapy (7-10 days duration)**
  - β-lactams
    - ✓ Dicloxacillin
    - ✓ Cephalexin
  - PCN allergy
    - ✓ Erythromycin
    - ✓ Clindamycin
    - ✓ Mupirocin ointment



Cellulitis

- Description
  - Acute spreading skin infection that involves primarily the ***deep dermis*** and ***subcutaneous fat***
  - Non-elevated, poorly defined margins
  - Warmth, pain, erythema and edema, and tender lymphadenopathy
  - Malaise, fever, and chills
  - Usually, patient has had previous minor trauma, abrasions, ulcers, or surgery (could be tinea infections, psoriasis, or eczema).
  - Often, patients have impaired lymphatic drainage.
- Microorganism:
  - Usually *Streptococcus pyogenes* and occasionally *S. aureus* (rarely other organisms)

Cellulitis

- Treatment: 5–10 days (may extend therapy if infection has not improved)



1) Penicillin G if definitively streptococcal
2) First-generation cephalosporin (cefazolin, cephalexin)
3) Ceftriaxone
4) Clindamycin

Cellulitis

- Treat empirically for MRSA if associated with *penetrating trauma*, *injection drug use*, *purulent drainage*, *nasal colonization with MRSA*, *concurrent evidence of MRSA infection* elsewhere or systemic inflammatory response syndrome (SIRS) criteria (severe non-purulent).

  i)* *Outpatient: Clindamycin, trimethoprim/sulfamethoxazole (add β-lactam for *Streptococcus*), doxycycline (add β-lactam for *Streptococcus*)

  ii)Inpatient: Vancomycin, linezolid, daptomycin, or

Carbuncle & Furuncle

- **Furuncle** is acute inflammation of subcutaneous layers of skin, gland, or hair follicles
- **Carbuncle** is more **extensive extending** into SC fat and developing into **multiple abscesses**





Carbuncle


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Carbuncle & Furuncle

- **Clinical findings**
  - **Furuncles**: occur in skin areas subject to friction and perspiration containing hair follicles (neck, face, buttocks)
  - **Carbuncle**
    - ✓ Larger, deeper, indurated lesion typically at nape of neck, on back, or on thighs
    - ✓ Often occur along the course of multiple hair follicles and may be associated with fever and malaise.
- **Etiology:** S. *aureus*

Carbuncle & Furuncle

- Non-pharmacologic therapy
  - Furuncle: Most treated with moist heat, promoting localization and drainage of the process
  - Carbuncle/furuncle with surrounding cellulitis
    - ✓ Require antistaphylococcal antibiotic
    - ✓ Surgical drainage for large and fluctuant lesions

Carbuncle & Furuncle

- Antimicrobial therapy
  - ✓ Oral
    - Cephalexin 500 mg QID x 10d
    - Oxacillin 750 mg QID x10d
    - Cloxacillin 500 mg QID x10d
  - ✓ IV
    - Cefazolin 1-2 g q8h
    - Nafcillin 1-1.5 g q4h
  - ✓ PCN allergy:
    - Clindamycin 150-300 mg PO QID x10d
    - Erythromycin 250-500 mg PO QID x10d

Necrotizing soft tissue infections

- NSTIs consist of a group of highly *lethal infections* that require early and aggressive **surgical debridement** in addition to appropriate antibiotics and intensive supportive care.
- These infections are characterized clinically by *fulminant destruction of tissue*, *systemic signs of toxicity* and a *high rate of mortality*.
- The major clinical entities of necrotizing infections are **necrotizing fasciitis** and **clostridial myonecrosis** (gas gangrene)

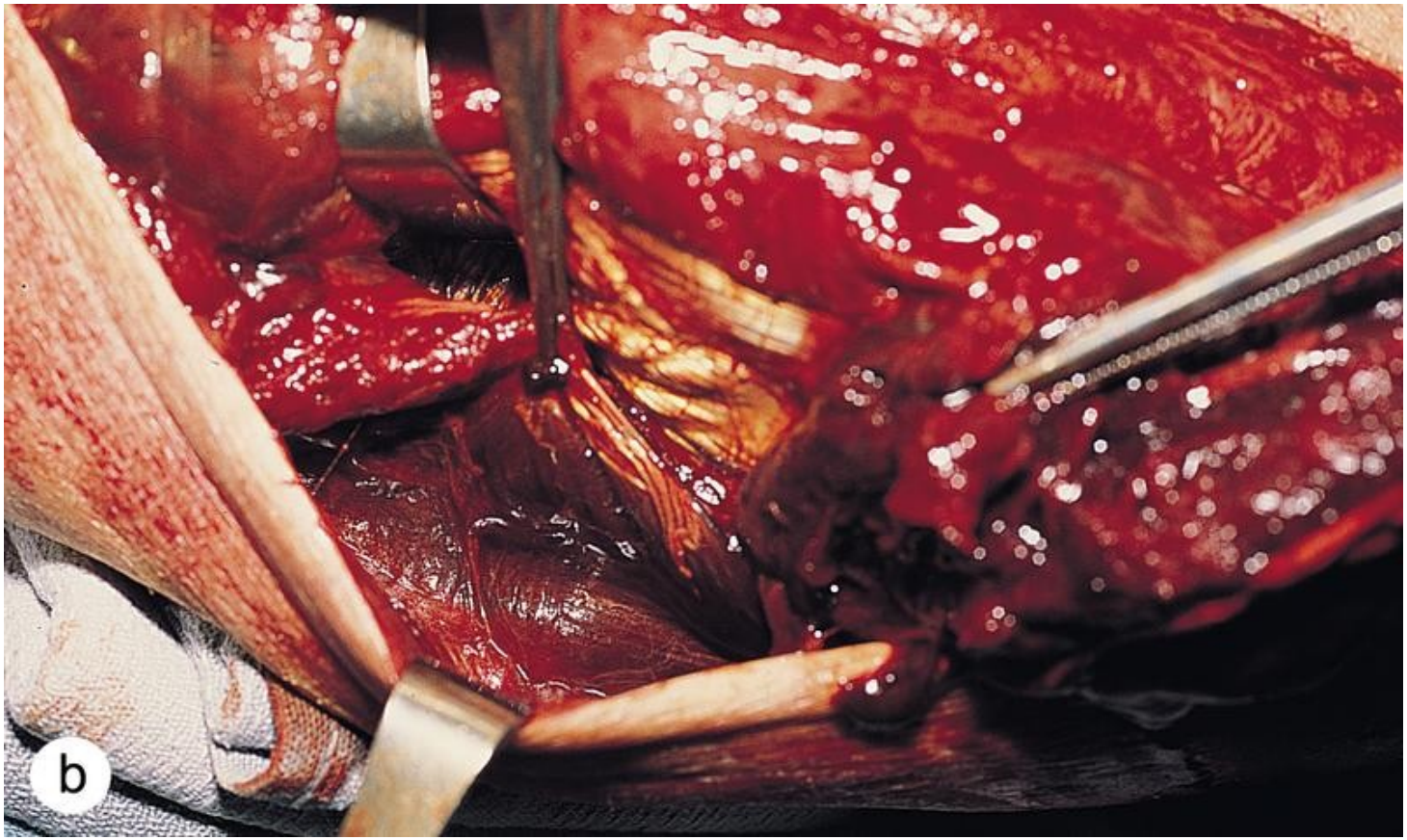
Necrotizing Fasciitis

- Necrotizing fasciitis is a serious, life-threatening infection of the fascia (the thin connective tissue overlying the muscle and under the skin and subcutaneous tissue).
- It is also known as "flesh-eating" bacterial disease, killer bug disease, synergistic necrotizing cellulitis and fasciitis necrotans.
- It causes extensive undermining of surrounding tissues and subcutaneous layers and necrosis is typically more advanced than the appearance suggests.
- By far, it is the fastest-spreading disease known to man, with progression rate of up to **3 cm per hour**.

Necrotizing Fasciitis



Necrotizing Fasciitis



Necrotizing Fasciitis





Necrotizing Fasciitis





Necrotizing Fasciitis

Pathophysiology

- Necrotizing fasciitis is caused by multiple bacteria, however the bacteria do not actually eat the tissue. So “flesh-eating bacteria” is a misnomer.
- The bacteria produce pyogenic exotoxins and other virulence factors capable of activating T cells nonspecifically which cause over-production of cytokines that over stimulate macrophages.
- The macrophages cause the actual tissue damage by releasing oxygen free radicals that are normally intended to destroy bacteria but are capable of damaging nearly any macromolecule they contact in the body.

Necrotizing Fasciitis

- Bacterial factors including surface proteins M-1 and M-3 increase the adherence of bacteria to the tissues, and further protect the bacteria against phagocytosis by neutrophils.
- Deep infection causes vascular occlusion, ischemia, and tissue necrosis.
- Nerve damage produces characteristic localized anesthesia.
- Septicemia and systemic toxicity.
- If untreated, it is invariably fatal with mortality rate of 25 – 83%
- Predisposing factors are DM, malignancy, alcohol or drug abuse and poor nutrition.

Necrotizing Fasciitis

- **Classification and etiology**
  - There are 3 types of necrotizing fasciitis based on causing organism:
    - Type I: polymicrobial infection
    - Type II: group A streptococcal infection
    - Type III: gas gangrene or clostridial myonecrosis

Necrotizing Fasciitis

- **Type I NF** is a mixed infection caused by aerobic and anaerobic organisms that act synergistically to cause destruction of fat and fascia.
- Most commonly occurs after **surgical procedures** and in patients with **peripheral vascular disease** and DM.
- It is also more common among **injection-drug users**.
- Commonly affects feet, head and neck, and perineum.
- NF affecting the male genitalia has been termed Fournier's gangrene.
- Predominant isolates : *S. aureus, E. coli, GAS,*

Necrotizing Fasciitis

- **Type II NF** is caused by virulent strains of S. pyogenes and is more commonly referred to as streptococcal gangrene.
- Occurs in any age group and among pts who **do not** have complicated medical illnesses.
- Predisposing factors include blunt trauma, varicella infection, IVDA, penetrating injury, surgical procedures, childbirth
- Rapidly extending necrosis of subcutaneous tissues and skin, gangrene, severe local pain and systemic toxicity.
- Highly associated with an early onset of shock (Streptococcal toxic shock syndrome) and organ failure.

Necrotizing Fasciitis

- **Type III NF/clostridial myonecrosis** is a necrotizing infection that involves the skeletal muscle.
- Gas production and muscle necrosis are prominent features of this infection, which explains why this infection is commonly referred to as gas gangrene.
- The infection advances rapidly, often over a matter of a few hours.
- Most infections occur after surgery or trauma, with Clostridium perfringens identified as the most common etiologic agent.

Clinical Presentation

Symptoms

- Systemic symptoms generally are marked (e.g., fever, chills and leukocytosis) and may include shock and organ failure, especially in pts with type II infections.
- In general, pain in the affected area and systemic toxicity are more pronounced than would be expected with cellulitis.

Clinical Presentation

Signs

- At the beginning of an infection, it may be difficult to differentiate b/n NF and cellulitis.
- Like cellulitis, the affected area is initially hot, swollen, and erythematous without sharp margins.
- The affected area is often shiny, tender, and painful.
- Diffuse swelling of the area is followed by the appearance of bullae filled with clear fluid.
- The infectious process progresses rapidly, with the skin taking on a maroon or violaceous color after several days.
- Without appropriate intervention, the infection will evolve rapidly into a frank cutaneous gangrene, sometimes with myonecrosis (involvement of skin and muscle).

Management of Necrotizing SSTI

- Surgery
- Antibiotic treatment
  - Acceptable empiric antibiotic regimens include:
    - A carbapenem or beta-lactam-beta-lactamase inhibitor **plus**
    - An agent with activity against methicillin-resistant *S. aureus* (MRSA; such as vancomycin or linezolid) **plus**
    - Clindamycin, for its antitoxin effects against toxin-elaborating strains of streptococci and staphylococci

Necrotizing SSTI

- **Carbanems**:
  - Imipenem
  - Meropenem (20 mg/kg per dose every eight hour)
  - Ertapenem
- **Beta-lactam–beta-lactamase** inhibitors:
  - Piperacillin-tazobactam,
  - Ampicillin-sulbactam, or
  - Ticarcillin-clavulanate.

Bite Wounds

- Pathogenesis
- Estimated 4 million people bitten by dogs annually
  - Majority in extremities; facial bites more common in children <10 years of age
- 40-50% of cat bites become infected
- Human Bites
  - Higher complication rate and infection rate (50%) than animal bites
  - Wounds to hand are more serious and more frequently become infected than bites to other areas
  - Clenched fist wounds required surgical exploration by experienced surgeon and antimicrobial therapy

Bite Wounds

- Clinical findings
  - Two distinct groups
    - Those presenting at 8-12 hours post bite
      - Might only need general wound care, tetanus, rabies if necessary
    - Those presenting >12 hours after injury
      - Usually have an established infection, manifested by localized cellulitis, pain at injury site, and purulent discharge (often gray and malodorous in case of P. multocida).

Bite Wounds

Dog/cat bite wounds	*Human Bite wounds*
α hemolytic streptococci	Streptococci spp.
S. aureus	*S. aureus, S. epidermidis*
Pasturella multocida	*H. parainfluenzae*
β hemolytic streptococci	*K. pneumoniae*
anaerobes-- *Bacteroides* spp.	*Eikenella corrodens*
Fusobacterium spp.	*Peptostreptococcus* spp.
Various gram negative rods	*Bacteroides* spp.
	Fusobacterium spp.

Bite Wounds

- Non-pharmacologic therapy
  - Tear and puncture wounds require copious irrigation, should be done ASAP
  - Surgical debridement and exploration considered on basis of examination
  - Immobilization and elevation of injured area essential
- Tetanus toxoid to those requiring a booster (>5-7 yrs since last i00mmunization)
- Rabies should be considered with stray/wild animals (10 day observation period)

Bite Wounds

- Antimicrobial therapy
- Prophylaxis of non-infected animal wound not usually recommended, but, indications include:
  - Established infection
  - Wound to hand or near joints
  - Deep puncture wounds
  - Wound difficult to irrigate
  - Immunocompromised patient
  - Wound not well perfused
  - Age >50
  - (May not be needed for all dog bites--if wound well irrigated, and on lower extremity)
- Topical
  - Triple antibiotic ointment (polymixin B/neomycin/bacitracin) only for minor, clean abrasions due to bite

Bite Wounds

- **Antimicrobial therapy**
  - Oral
    - Amoxicillin/clavulanic acid 875/125 mg BID
    - Dicloxacillin 500 mg QID
    - Dicloxacillin 500 mg QID + PCN 500 mg QID
  - IV
    - Ampicillin/sulbactam 1.5 g q6h, then switch to oral
  - PCN allergy
    - Cefuroxime 500 mg PO BID
    - Clindamycin 300 mg PO QID
    - Doxycycline 200 mg PO BID
    - Levofloxacin 500 mg PO QD
  - Prophylaxis: 5d, Treatment: 7-14d.

Rabies prophylaxis

- **Pre-exposure prophylaxis**
  - **Who should receive pre-exposure prophylaxis**
    - Veterinarians, veterinary students, and veterinary technicians
    - Laboratory workers working with rabies virus or material and specimens that might contain infectious rabies virus
    - Other persons whose vocation or avocation bring them in contact with animal species at risk for rabies (eg, animal control officials and cavers)

Rabies prophylaxis

Post-exposure prophylaxis

- Post-exposure prophylaxis includes rabies vaccine with or without rabies immune globulin.
- **Indications** — To prevent rabies infection, post-exposure prophylaxis should be administered to all patients who have had a known or likely exposure to rabies
- Consider an exposure to be:
  - A bite or scratch from an animal with rabies
  - An open wound or mucous membrane exposure to saliva, cerebrospinal fluid, or central nervous system (CNS) tissue from an animal with rabies

Rabies prophylaxis

- **Timing of immunization** — Once it has been determined that a patient should receive rabies post-exposure prophylaxis, prophylaxis should begin as soon as possible after the exposure
- Post-exposure prophylaxis should be administered following a rabies exposure, even if there is a delay;
  - Post-exposure prophylaxis is only too late when signs of clinical rabies develop.
  - The average incubation period is 45 days, although latency periods between exposure and onset of disease as long as one to eight years have been reported

Rabies prophylaxis

Vaccination category	Biologic	Schedule
Not previously vaccinated	RIG	Total dose is 20 units/kg body weight. As much of the full dose as feasible should be infiltrated around the wound(s) and any remaining given IM.
	Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1 mL, IM (deltoid area), 1 each on days 0, 3, 7 and 14
Previously vaccinated	RIG	Not indicated
	Vaccine	HDCV or PCECV 1 mL, IM (deltoid area), 1 each on days 0 and 3

BURN

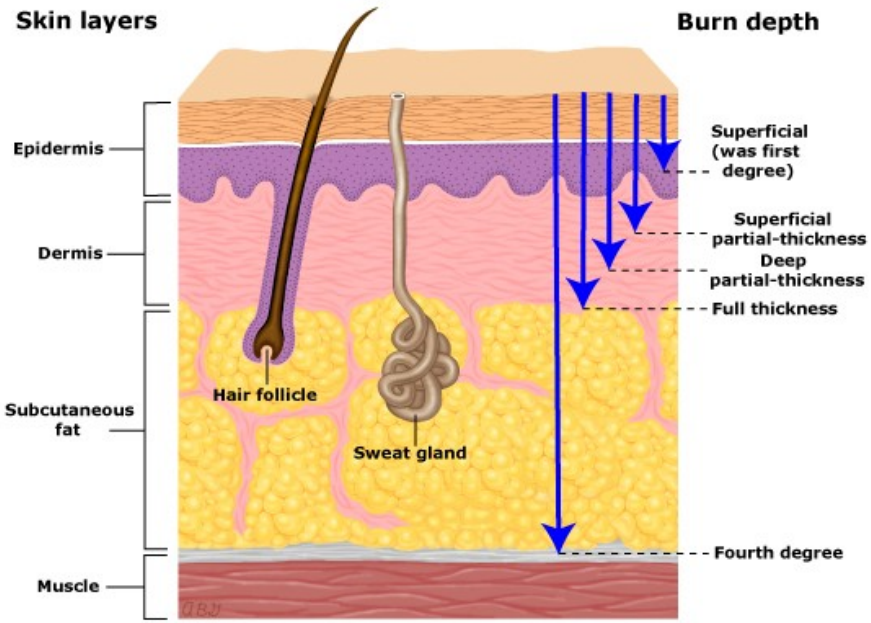
Classification

- **Burn Mechanisms**
  - **Heat:** flames, hot liquids, hot solid objects, and steam
  - **Electrical discharg**e: Electrical energy is transformed into heat as the current passes through poorly conducting body tissues
  - **Friction:** mechanical disruption of tissues as well as heat generated by friction
  - **Chemicals:** alteration of pH, disruption of cellular membranes, and direct toxic effects on metabolic processes
  - **Radiation**: Radio frequency energy or ionizing radiation
    - E.g., sunburn

Classification

Classification by Depth

- The traditional classification of burns as first, second, third, or fourth degree
- Current classification of burn depth are
  - Superficial,
  - Superficial partial-thickne
  - Deep partial-thickness, a
  - Full-thickness



Classification

- **Superficial**
  - Involve only the epidermal layer of skin
  - They do not blister but are painful, dry, red, and blanch with pressure
  - Commonly seen with sunburns



Classification

- **Partial-thickness**
  - Involve the epidermis and portions of the dermis
  - **Superficial partial thickness**
    - Form blisters within 24 hours b/n the epidermis and dermis
    - Painful, red, and weeping and
    - Heal in 7 to 21 days
    - Scarring is unusual



Classification

- **Deep partial thickness**
  - extend into the deeper dermis
  - painful to pressure only
  - almost always blister (easily unroofed),
  - are wet or waxy dry,
  - cause hypertrophic scarrin



Classification

- **Full-thickness**
  - extend through and destroy all layers of the dermis and often injure the underlying subcutaneous tissue
  - Burn eschar, the dead and denatured dermis, is usually intact
  - Skin appearance can vary leathery gray to charred a



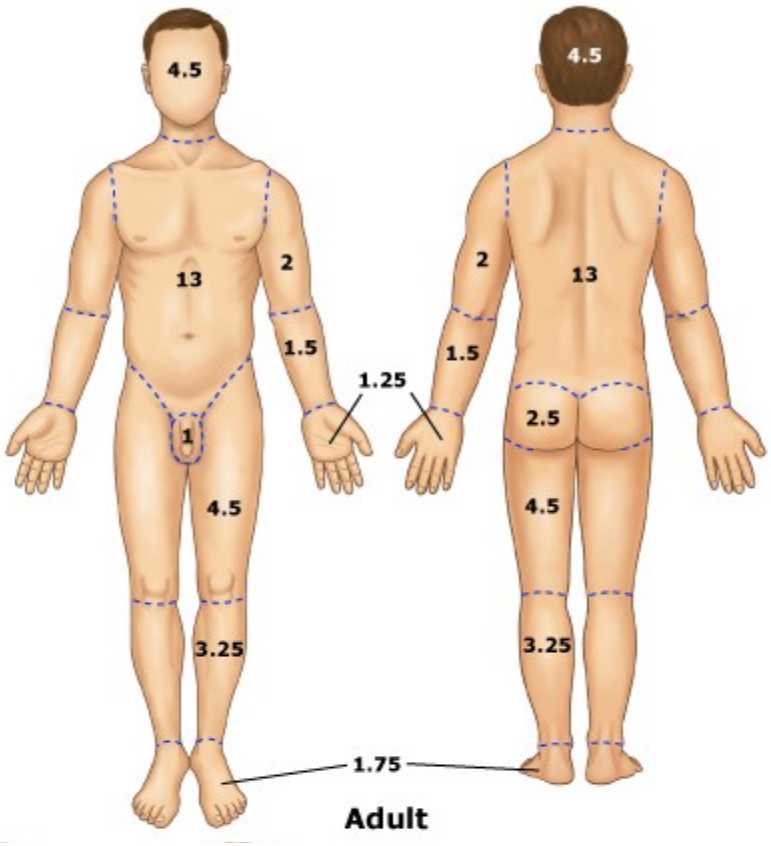
Extent of Burn Injury

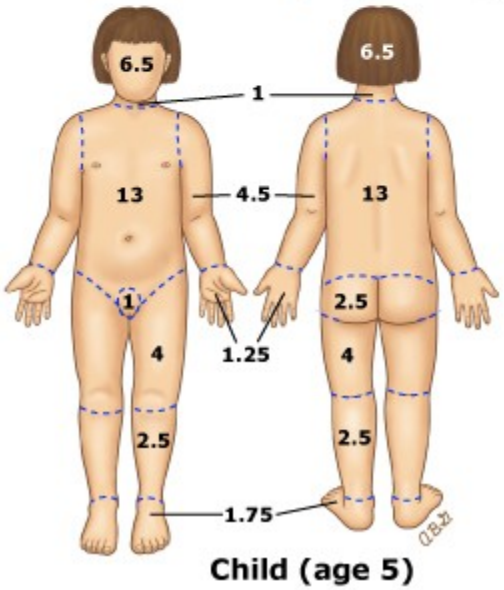
- Estimation of burn size is essential to guide therapy and to determine when to transfer a patient to a burn center.
- Expressed as the total percentage of body surface area (ie, TBSA)
- Superficial (first-degree) burns are **not** included in percentage TBSA
- **Methods of estimation**
  - Lund-Browder chart and "Rule of Nines

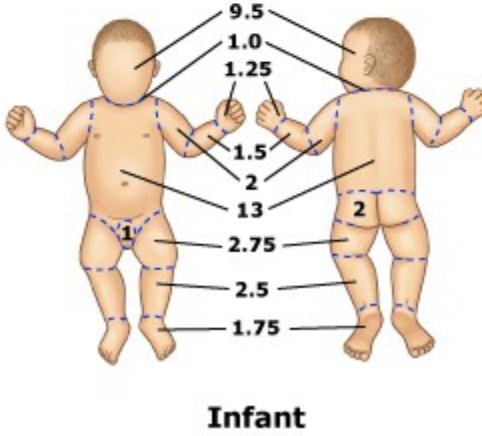
Extent of Burn Injury

- Lund-Browder
  - most accurate method for estimating TBSA for both adults and children
  - Children have proportionally larger heads and smaller lower extremities

Modified Lund-Browder chart







Extent of Burn Injury

- **Rule of Nines –**
  - the most expeditious method to estimate TBSA in adults
    - The head represents 9 percent TBSA
    - Each arm represents 9 percent TBSA
    - Each leg represents 18 percent TBSA
    - The anterior and posterior trunk each represent 18 percent TBSA

Extent of Burn Injury

- **Palm method**
  - Small or patchy burns can be approximated by using the surface area of the patient's palm.
  - The palm of the *patient's* hand, excluding the fingers, is approximately 0.5 percent of total body surface area,
  - The entire palmar surface including fingers is 1 percent in children and adults

Anatomic Location of Burn Injury

- The location of a burn often directs treatment.
- Burns on the face, hands, feet, and genitalia as well as large burns in other areas of the body and those associated with inhalational injury are often referred to burn centers for specialized expertise

Treatment

- Admit all children with burns covering > 10% of their body surface; those involving the face, hands, feet, perineum and joints; those that are circumferential and those that cannot be managed in an outpatient ward.
- Fluid resuscitation is required for burns covering > 10% total body surface.
- Use Ringer's lactate or normal saline with 5% glucose;
- First 24 h: Calculate fluid requirements by adding maintenance fluid requirements to the additional emergency fluid requirements
  - Volume equal to 4 ml/kg for every 1% of surface burnt.
- Administer half of total fluid in first 8 h, and remaining fluid in next 16 h.

Treatment

- Second 24 h: give half to three quarters of fluid required during the first day.
- Blood may be given to correct anemia or for deep burns to replace blood loss.
- In all cases, administer tetanus prophylaxis.
- Prevent infection:
  - If skin is intact, clean with antiseptic solution, gently, without breaking the skin.
  - If skin is not intact, carefully debride the burn.
  - Give topical antibiotics or antiseptics (the options depend on resources; they include: silver nitrate, silver sulfadiazine, gentian violet, betadine and even mashed papaya).

Treatment

- Treat secondary infection if present.
  - If there is evidence of local infection (pus, foul odor or presence of cellulitis), treat with amoxicillin (15 mg/kg orally three times a day) plus cloxacillin (25 mg/kg orally four times a day).
  - If septicemia is suspected, use gentamicin (7.5 mg/kg IM or IV once a day) plus cloxacillin (25–50 mg/kg IM or IV four times a day).
  - If infection is suspected beneath an eschar, remove the eschar.

Treatment

- Pain control
  - Make sure that pain control is adequate, including before procedures such as changing dressings.
    - Give paracetamol (10–15 mg/kg every 6 h) by mouth, or give IV narcotic analgesics (IM injections are painful), such as morphine sulfate (0.05–0.1 mg/kg IV every 4 h) if pain is severe.
  - Check tetanus vaccination status.
    - – If not immunized, give tetanus immune globulin.
    - – If immunized, give tetanus toxoid booster, if this is due.

Treatment

- Nutrition
  - Children should receive a high-calorie diet containing adequate protein, and vitamin and iron supplements.
    - (Omit the iron initially in severe malnutrition.)
  - Children with extensive burns require about 1.5 times the normal calorie
  - and two to three times the normal protein requirements.

OSTEOMYELITIS AND SEPTIC ARTHRITIS

General Principles

- Osteomyelitis is an inflammation of the bone marrow and surrounding bone associated with infection.
- Any bone can be involved, and it can affect all age groups.
- Bone may be infected by three routes: **hematogenous spread**, **direct infection** of bone from an adjacent or contiguous source, and infection secondary to **vascular insufficiency**.
- Patients with recurrent osteomyelitis are considered to have **chronic osteomyelitis.**
- Septic arthritis (infectious arthritis) is usually acquired hematologically.
  - It can occur from spread of osteomyelitis into the joint.

Etiology and Pathogenesis

- **Hematogenous osteomyelitis** usually involves a single pathogen;
- Polymicrobial infection is common in contiguous-spread osteomyelitis and vascular insufficiency.
- Osteomyelitis secondary to vascular insufficiency is most common in patients with DM.
  - Patients with impaired blood flow may develop osteomyelitis in the toes or small bones of the feet.
  - Infection often first presents as cellulitis, progressing to deep ulcers, and finally to underlying bone.

Etiology and Pathogenesis

- Predisposing factors for septic arthritis include trauma or underlying systemic disorders (diabetes mellitus, rheumatoid arthritis, osteoarthritis, chronic granulomatous disease, cancer, or chronic liver disease).
- **Nongonococcal arthritis** is associated with monoarticular joint pain and swelling, and reduced range of motion and fever.
- **Gonococcal arthritis** typically affects multiple joints and is associated with fever, dermatitis, and tenosynovitis.

Clinical Presentation

- **Signs and symptoms**: fever and chills, localized pain, tenderness, and swelling, neurologic symptoms if spinal cord compression
- **Laboratory tests**: elevated WBC, elevated ESR, elevated CRP
- **Diagnostic tests**
  - Radiographic tests: Positive results lag behind infectious process.
  - CT and MRI
  - Radionuclide imaging: Positive as soon as 24–48 hours after infectious process beg

Features of Osteomyelitis

Feature	Hematogenous	Contiguous spread	Vascular insufficiency
Definition	Spread of bacteria through the bloodstream from a distant site	Spread of bacteria from an adjacent tissue infection or by direct inoculation	Infection results from insufficient blood supply to fight the bacteria
Patient population	Children (< 16 yr): femur, tibia, humerus Adult: vertebrae	Adults (25–50 yr): femur, tibia, skull	Adults (> 50 yr)
Predisposing factors	Bacteremia (e.g., IV catheters, IVDU, skin infections, URI) Sickle cell anemia	Open reduction of fractures, gunshot wound, dental or sinus infections, soft tissue infections	Diabetes PVD Post-CABG (sternum)

Features of Osteomyelitis

Feature	Hematogenous	Contiguous spread	Vascular insufficiency
Common pathogens	Usually monomicrobial Children: S. *aureus* (60–90%), S. *epidermidis*, S. *pyogenes*, S. *pneumoniae*, H. *influenzae*, P. *aeruginosa*, Enterobacter, E. *coli* (all < 5%) Adults: S. *aureus* and gram-negative bacilli Sickle cell anemia: Salmonella (67%), S. *aureus*, S.	Usually mixed infection: S. *aureus* (60%), S. *epidermidis*, Streptococcus Gram-negative bacilli: P. *aeruginosa* (foot punctures), Proteus, Klebsiella, E. *coli* Anaerobic (human bites, decubitus ulcers)	Usually polymicrobial: S. *aureus*, S. *epidermidis*, Streptococcus Gram-negative bacilli Anaerobic (Bacteroides fragilis group) Infected prosthesis: S. *aureus*, S. *epidermidis*

Empiric Therapy

- **Pediatric:** Cefazolin, nafcillin, oxacillin, clindamycin (if prevalence of MRSA in community is ≥10%), or vancomycin (if prevalence of MRSA and clindamycin-resistant S. *aureus* is ≥10%)
- **Adults:** Nafcillin, oxacillin, cefazolin, ceftriaxone, clindamycin, or vancomycin (alternatives linezolid or daptomycin)
- Patients with **sickle cell anemia**: Ceftriaxone/cefotaxime or ciprofloxacin/levofloxacin

Therapy Length

- **Acute osteomyelitis:** 4–6 weeks
- **Chronic osteomyelitis:** 6–8 weeks of parenteral therapy and 3–12 months of oral therapy

SURGICAL ANTIBIOTIC PROPHYLAXIS

Introduction

- Surgical site infections (SSI) are a significant cause morbidity and mortality.
- Approximately **2% to 5%** of patients undergoing clean extra-abdominal operations and **20**% undergoing intra-abdominal operations will develop an SSI.
- SSIs have become the second most common cause of nosocomial infection, and these data are likely underestimated due to a large number of surgical procedures being performed on an outpatient basis

Introduction

- SSIs are classified as either
  - ✓ **Incisional**: *superficial incisional* SSI (skin or subcutaneous tissue) and *deep incisional* SSI (deeper soft tissues of the incision).
  - ✓ **Organ/space**: involve any anatomic site other than the incised areas (eg, meningitis after brain tumor removal).
- An infection is considered an SSI if the infection occurs within *30 days of the operation*.
- If a *prosthetic* is implanted during the operation, the timeline extends out to *1 year*.

Risk Factors

- Risk factors for SSIs can be divided into two categories:
  1. Patient risk factors for SSI include
     - ✓ age
     - ✓ comorbid disease states (especially chronic lung disease and diabetes)
     - ✓ malnutrition
     - ✓ immunosuppression
     - ✓ nicotine or steroid use, and
     - ✓ colonization with S. *aureus*.

Risk Factors

2. **Operative characteristics**
   - **Shaving** of the surgical site prior to operating can produce microscopic lacerations and increase the chance of SSI
   - Maintaining aseptic technique and proper sterilization of medical equipment is effective in preventing SSI.
     - Surgical staff should wash their hands thoroughly.
     - In clean operations, most bacterial inoculums introduced postoperatively are generally small.

Pathophysiology

- Surgical operations are classified at the time of operation as
  - clean,
  - clean-contaminated,
  - contaminated, or
  - dirty.

Wound Classification

Classification	Criteria	SSI Risk	Antimicrobial Prophylaxis
Clean	No acute inflammation or transection of GI, oropharyngeal, GU, biliary, or respiratory tracts; elective case, no technique break	Low	Indicated
Clean-contaminated	Controlled opening of GI, oropharyngeal, GU, biliary, or respiratory tracts with minimal spillage or minor technique break; clean procedures performed emergently or with major technique breaks	Medium	Indicated
Contaminated	Acute, non-purulent inflammation present; major spillage or technique break during clean-	High	Indicated

Pathophysiology

- Antimicrobial prophylaxis is appropriate for clean, clean-contaminated, and contaminated operations.
- Dirty operations take place in situations of existing infection and antimicrobials are used for treatment, not prophylaxis
- Appropriate prophylactic antimicrobial selection relies on anticipating which organisms will be encountered during the operation.

Pathophysiology

- SSIs associated with extra-abdominal operations are the result of skin flora organisms in nearly all cases.
  - These organisms include gram-positive cocci, with S. *aureus* and S. *epidermidis* being among the most frequently isolated SSI pathogens
- Intra-abdominal operations involve a diverse flora with the potential for polymicrobial SSIs.
  - E. coli make up a large portion of bowel flora and are frequently isolated as pathogens.
  - Other enteric gram-negative bacteria, as well as anaerobes (especially *Bacteroides* spp.), may be encountered during intra-abdominal operations.

Antimicrobial Prophylaxis

- **Route of Administration**
  - IV antimicrobial administration is the most common delivery method for surgical prophylaxis.
  - IV administration ensures complete bioavailability while minimizing the impact of patient specific variables

Antimicrobial Prophylaxis

- **Timing of first dose**
  - ✓ For prevention of SSIs, correct timing of antimicrobial administration is imperative so as to allow the persistence of therapeutic concentrations in the blood and wound tissues during the entire course of the operation.
    - Infusing antimicrobials for surgical prophylaxis within 60 minutes of the first incision is recommended
    - Exceptions are fluoroquinolones and vancomycin, which can be infused 120 minutes prior to avoid infusion-related reactions.

Antimicrobial Prophylaxis

- If an operation exceeds two half-lives of the selected antimicrobial, then another dose should be administered.
- Repeat dosing reduces rates of SSI. For example, cefazolin has a half-life of about 2 hours, thus another dose should be given if the operation exceeds 4 hours.

Antimicrobial Prophylaxis

- **Duration:** the duration of antimicrobial prophylaxis should not exceed 24 hours (48 hours for cardiac surgery); additional doses of antimicrobial past this time point do not demonstrate added benefits

1) GI surgery

i) Gastroduodenal

- Likely pathogens: Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes
- Prophylaxis regimen: Cefazolin 1 g × 1

ii) Cholecystectomy

- Likely pathogens: Enteric gram-negative bacilli, anaerobes
- Prophylaxis regimen: Cefazolin 1 g × 1 for high-risk patients; Laparoscopic: none

iii) Transjugular intrahepatic portosystemic shunt (TIPS)

- Likely pathogens: Enteric gram-negative bacilli, anaerobes
- Prophylaxis regimen: Cefoxitin or cefotetan 1 g × 1 or cefazolin 1 g plus metronidazole 1 g × 1

iv) Colorectal

- Likely Pathogens: Enteric gram-negative bacilli, anaerobes

1) GI surgery

iv) Colorectal

- Likely pathogens: Enteric gram-negative bacilli, anaerobes
- Prophylaxis regimen: Orally: neomycin 1g + erythromycin base 1g at 1, 2, and 11 PM 1 day preoperatively plus mechanical bowel preparation; IV: cefoxitin or cefotetan 1g × 1

v) GI endoscopy

- Likely pathogens: Variable, depending on procedure, but typically enteric gram-negative bacilli, gram-positive cocci, oral anaerobes
- Prophylaxis regimen: Orally: amoxicillin 2g×1; IV: ampicillin 2g×1 or cefazolin 1g×1

2) Urologic surgery

i) Prostate resection, shock-wave lithotripsy, ureteroscopy

- ✓ Likely pathogens: Escherichia coli
- ✓ Prophylaxis regimen: Ciprofloxacin 500 mg orally or Trimethoprim–sulfamethoxazole 1 DS tablet

ii) Removal of external urinary catheters, cystography, urodynamic studies, simple cystourethroscopy

- ✓ Likely pathogens: Escherichia coli
- ✓ Prophylaxis regimen: Ciprofloxacin 500 mg orally or Trimethoprim–sulfamethoxazole 1 DS tablet

3) Gynecological surgery

i) Cesarean section

- ✓ Likely pathogens: Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci
- ✓ Prophylaxis regimen: Cefazolin 2 g × 1

ii) Hysterectomy

- ✓ Likely pathogens: Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci
- ✓ Prophylaxis regimen: Vaginal: cefazolin 1 g × 1; Abdominal: cefotetan 1 g × 1 or cefazolin 1 g × 1

4) Head and neck surgery

i) Maxillofacial surgery

- ✓ Likely pathogens: S. aureus, streptococci oral anaerobes
- ✓ Prophylaxis regimen: Cefazolin 2 g or clindamycin 600 mg

ii) Head and neck cancer resection

- ✓ Likely pathogens: S. aureus, streptococci oral anaerobes
- ✓ Prophylaxis regimen: Clindamycin 600 mg at induction and every 8 hours × 2 more doses

5) Cardiothoracic surgery

i) Cardiac surgery

- ✓ Likely pathogens: S. aureus, S. epidermidis, Corynebacterium
- ✓ Prophylaxis regimen: Cefazolin 1 g every 8 hours × 48 hours, Intranasal mupirocin twice daily for 5 days preoperatively for patients colonized with S. aureus

ii) Thoracic surgery

- ✓ Likely pathogens: S. aureus, S. epidermidis, Corynebacterium, enteric gram-negative bacilli
- ✓ Prophylaxis regimen: Cefuroxime 750 mg IV every 8 hours × 48 hours

6) Vascular surgery

- **Abdominal aorta and lower extremity vascular surgery**
  - ✓ Likely pathogens: S. aureus, S. epidermidis, enteric gram-negative bacilli
  - ✓ Prophylaxis regimen: Cefazolin 1 g at induction and every 8 hours × 2 more doses

7) Orthopedic surgery

i) Joint replacement

- Likely pathogens: S. *aureus*, S. *epidermidis*
- Prophylaxis regimen: Cefazolin 1 g × 1 preoperatively, then every 8 hours × 2 more doses. Intranasal mupirocin twice daily for 5 days preoperatively for patients colonized with S. aureus

ii) Hip fracture repair

- Likely pathogens: S. *aureus*, S. *epidermidis*
- Prophylaxis regimen: Cefazolin 1 g × 1 preoperatively, then every 8 hours for 48 hours

iii) Open/compound fractures

- Likely pathogens: S. *aureus*, S. *epidermidis*, gram-negative bacilli, polymicrobial
- Prophylaxis regimen: Cefazolin 1 g × 1 preoperatively, then every 8 hours for a course of presumed infection

8) Neurosurgery

i) CSF shunt procedures

- ✓ Likely pathogens: S. *aureus*, S. *epidermidis*
- ✓ Prophylaxis regimen: Cefazolin 1 g every 8 hours × 3 doses or ceftriaxone 2 g × 1

ii) Spinal surgery

- ✓ Likely pathogens: S. *aureus*, S. *epidermidis*
- ✓ Prophylaxis regimen: Cefazolin 1 g × 1

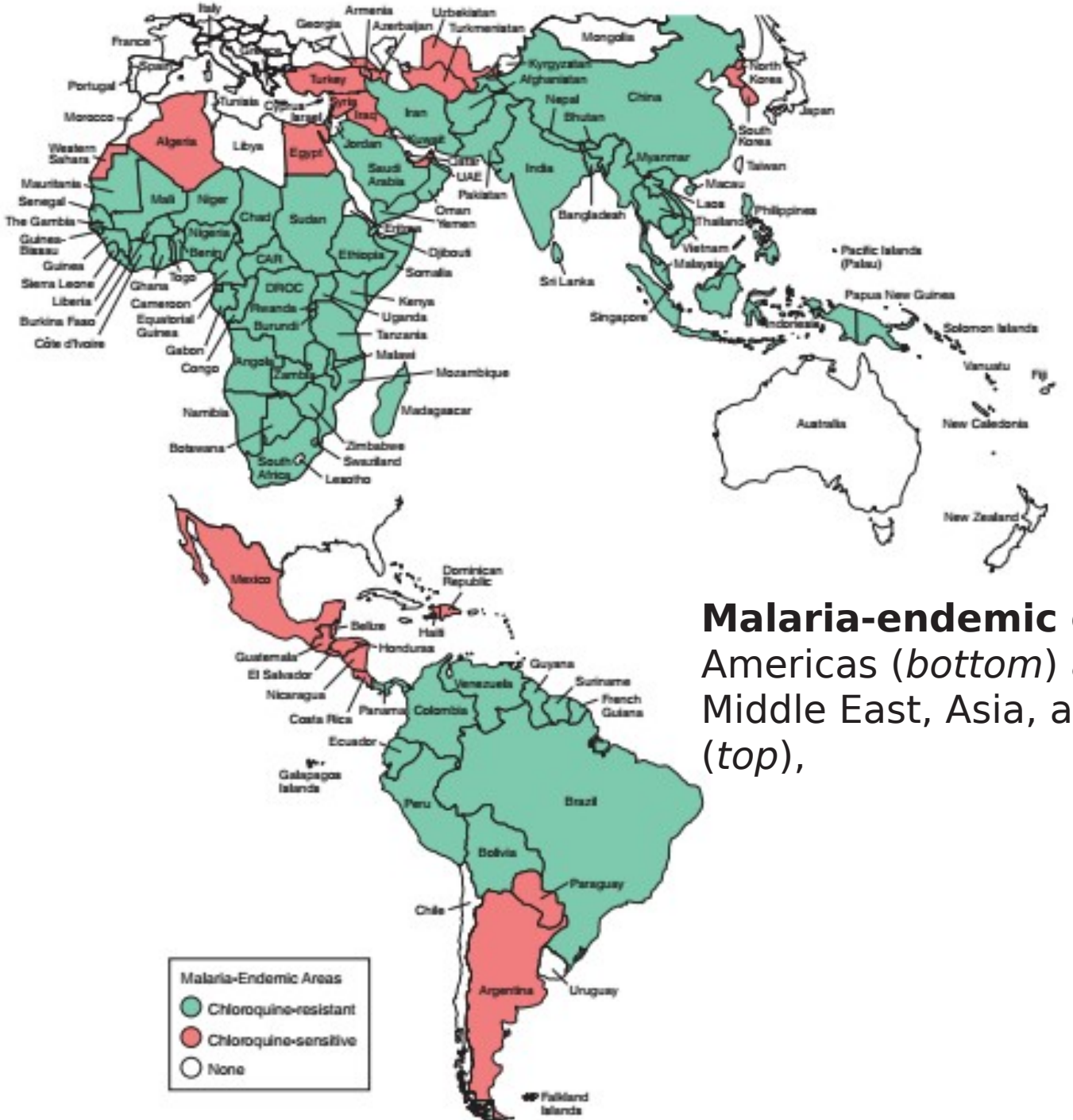
iii) Craniotomy

- ✓ Likely pathogens: S. *aureus*, S. *epidermidis*
- ✓ Prophylaxis regimen: Cefazolin 1 g × 1 or cefotaxime 1 g × 1

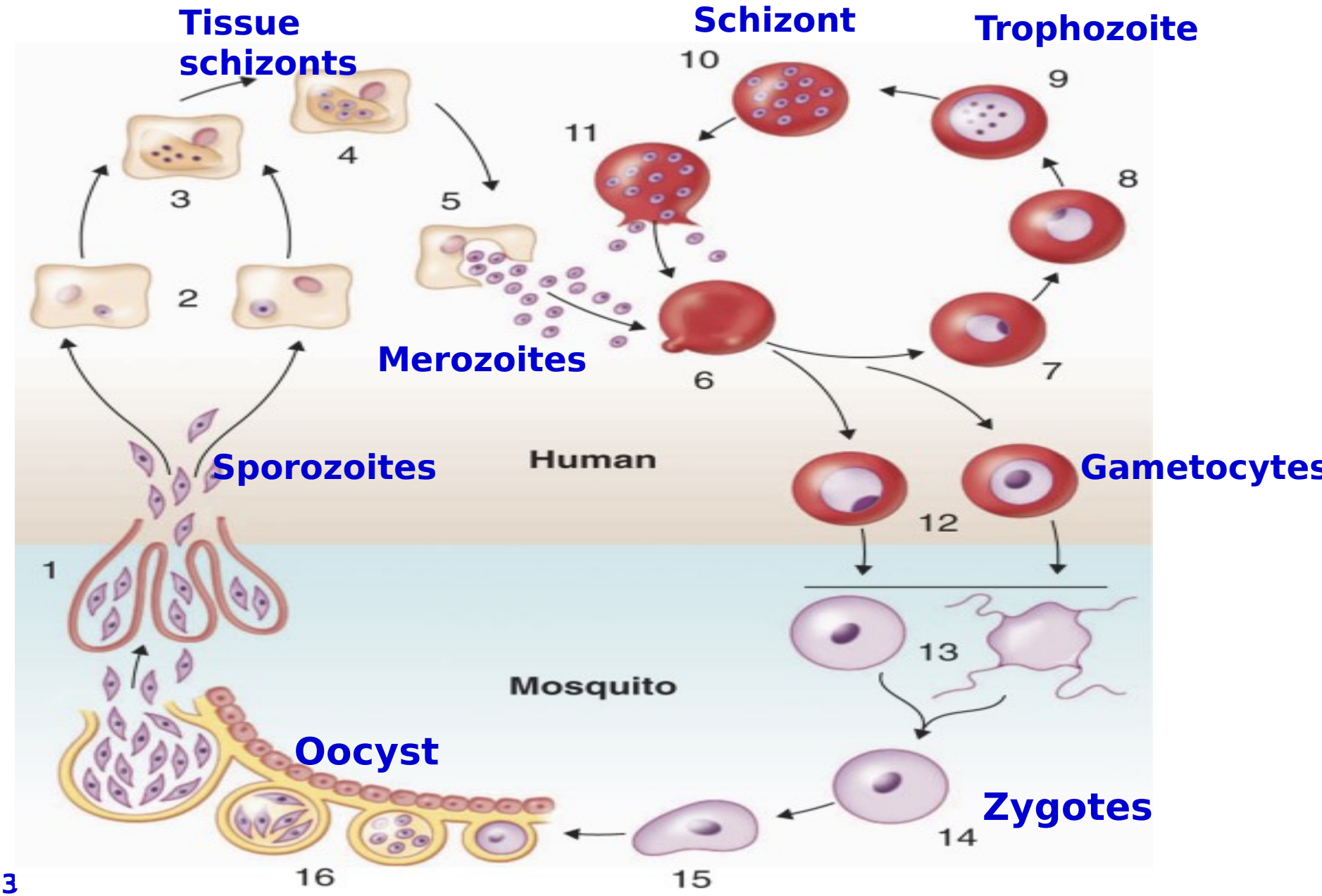
MALARIA

Introduction

- About 52 million people (68%) live in malaria risk areas in Ethiopia,
  - Primarily at altitudes below 2,000 meters
- Historically, there have been an estimated 10 million clinical malaria cases annually.
  - Since 2006, however, cases have reduced substantially
- 60%-70% of malaria cases have been due to *P. falciparum*, with the remainder caused by *P. vivax*.
- *Anopheles arabiensis* is the main malaria vector



Malaria-endemic countries in the Americas (*bottom*) and in Africa, the Middle East, Asia, and the South Pacific (*top*),


Tissue schizonts
Schizont
Trophozoite
Merozoites
Sporozoites
Human
Gametocytes
Mosquito
Oocyst
Zygotes
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

Diagnosis of malaria

- Clinical
- Laboratory
  - Identify species of malaria

Clinical Malaria

- Nonspecific symptoms
  - Lack of a sense of well-being,
  - Headache,
  - Fatigue, abdominal discomfort, and muscle aches
- Physical findings
  - Fever
  - Mild anemia
    - Commona mong young children living in areas with stable transmission
  - Palpable spleen. (in some cases)

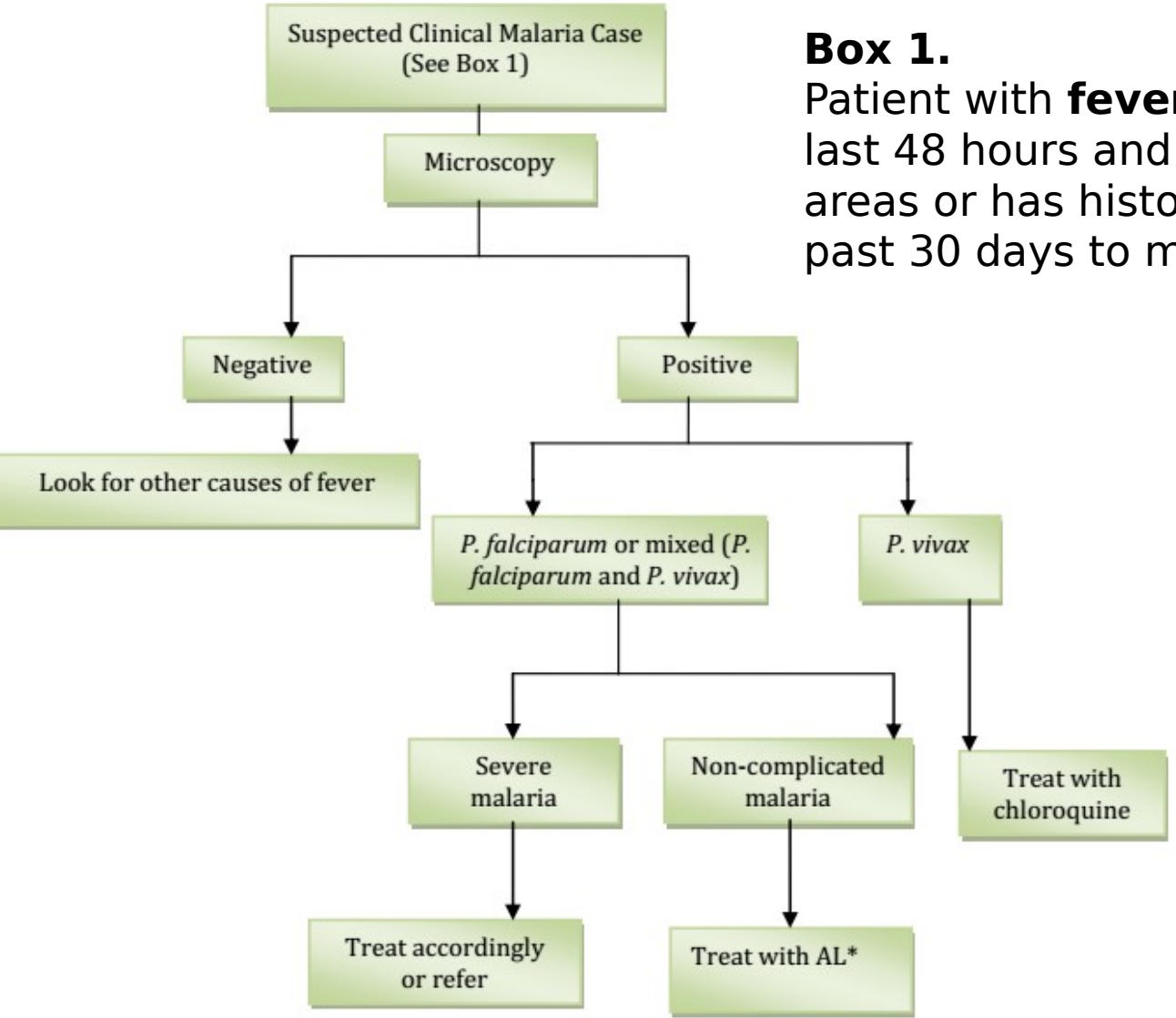
Lab Diagnosis

- Microscopic diagnosis of malaria
  - Golden standard
  - Initial diagnosis level of parasitemia
  - Evaluation of rate of clearance of parasitaemia.
- Rapid diagnostic tests (RDTs)

Management

- **Desired Outcome**
  - To eradicate the infection within 48 to 72 hours
  - To avoid complications such as hypoglycemia, pulmonary edema, and renal failure that are responsible for increased mortality in malaria

Flow Chart for the Dx and Rx of Malaria



Box 1.
Patient with **fever** or history of fever in the last 48 hours and lives in malaria endemic areas or has history of travel within the past 30 days to malaria endemic areas

Treatment of Uncomplicated Malaria

- **Uncomplicated malaria** is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Treatment of Uncomplicated Malaria

1. *P. falciparum* positive

- **First-line**:
  - Artemether plus lumefantrine (**20/120 mg**),
    - **6-dose regimen over a 3-day period**
- **Alternatives:**
  - Quinine HCl 600mg PO TID for 7 days
  - Artesunate plus amodiaquine,
  - Artesunate plus mefloquine,
  - Artesunate plus sulfadoxine-pyrimethamine,
  - Dihydroartemisinin plus piperaquine.

Treatment of Uncomplicated Malaria

Tablet containing artemether-lumefantrine (20/120mg) in a fixed dose.

Weight (KG)	Age	Day 1		Day 2		Day 3	
		Morning	Evening	Morning	Evening	Morning	evening
5 – 14	4 – 2 Yrs	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab
15 – 24	3 – 7 Yrs	2 tab	2 tab	2 tab	2 tab	2 tab	2 tab
25 – 34	8 – 10 Yrs	3 tab	3 tab	3 tab	3 tab	3 tab	3 tab

Treatment of Uncomplicated Malaria

2. P. *vivax*

- First-line: Chloroquine 150 mg base table (250mg chloroquine phosphate (salt))
  - Dose:
    - 10 mg base/kg po immediately (Day 1),
    - 10 mg base/kg po at 24 hours (Day 2), and
    - 5mg base/kg po at 48 hours (Day 3) for a total dose of 25mg chloroquine base/kg over three days
    - PLUS premaquine 0.25mg/kg for 14 days
- 0.25 – 0.5mg/kg/day **primaquine** once a day for 14 days to eradicate liver phase in *P. vivax* and *P. ovale* infections

3. Mixed infection:

- Artemether plus lumefantrine (**20/120 mg**) plus premaquine

Treatment of Sever Malaria

- Presence of one or more signs and symptoms of sever illness and/or
- Demonstrable asexual *P. falciparum* parasitaemia in peripheral blood sample

Treatment of Severe Malaria

Signs	Manifestations
Major	
Unarousable coma/ cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Acidemia/acidosis	Arterial pH of <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as labored deep breathing, often termed “respiratory distress”
Severe normochromic, normocytic anemia	Hematocrit of <15% or hemoglobin level of <5 g/dL with parasitemia <10,000/μL
Renal failure	Scr >3 mg/dL; urine output (24 h) of < 400 mL in adults or <12 mL/kg in children; no improvement with rehydration
Pulmonary edema/adult respiratory distress	Noncardiogenic pulmonary edema, often aggravated by overhydration

Treatment of Severe Malaria

Signs	Manifestations
Hypotension/ shock	Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/DIC	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of DIC
Convulsions	More than two generalized seizures in 24 h
Others	
Hemoglobinuria	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PDdeficiency)
Extreme weakness	Prostration; inability to sit unaided
Hyperparasitemia	Parasitemia level of >5% in nonimmune patients
Jaundice	Serum bilirubin level of >3 mg/dL) if combined with a

Treatment of Severe Malaria

- **First-line treatment**
  - **IV or IM artesunate (preferred)**
  - IM artemether (alternate)
  - IV quinine infusion (if artesunate is not available)
  - IM quinine (if artesunate is not available)

Treatment of Severe Malaria

- Artesunate dosing
  - 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12h and 24h, then daily for up to five days;
- Preparation:
  - Contains 60 mg powder within a 7 ml glass vial
  - First reconstitute by mixing with a 1 ml glass ampoule of 5% sodium bicarbonate solution (provided) then shaken 2-3 minutes for better dissolution.

Treatment of Severe Malaria

- For IV:
  - Add 5 ml of 5% glucose (D5W) or NS then infuse slowly intravenously (3-4 ml per minute IV)
- For IM
  - Add 2 ml of 5% glucose (D5W) or NS to the reconstituted 7 ml vial to make 3 ml of artesunate (20 mg/ml) for IM injection

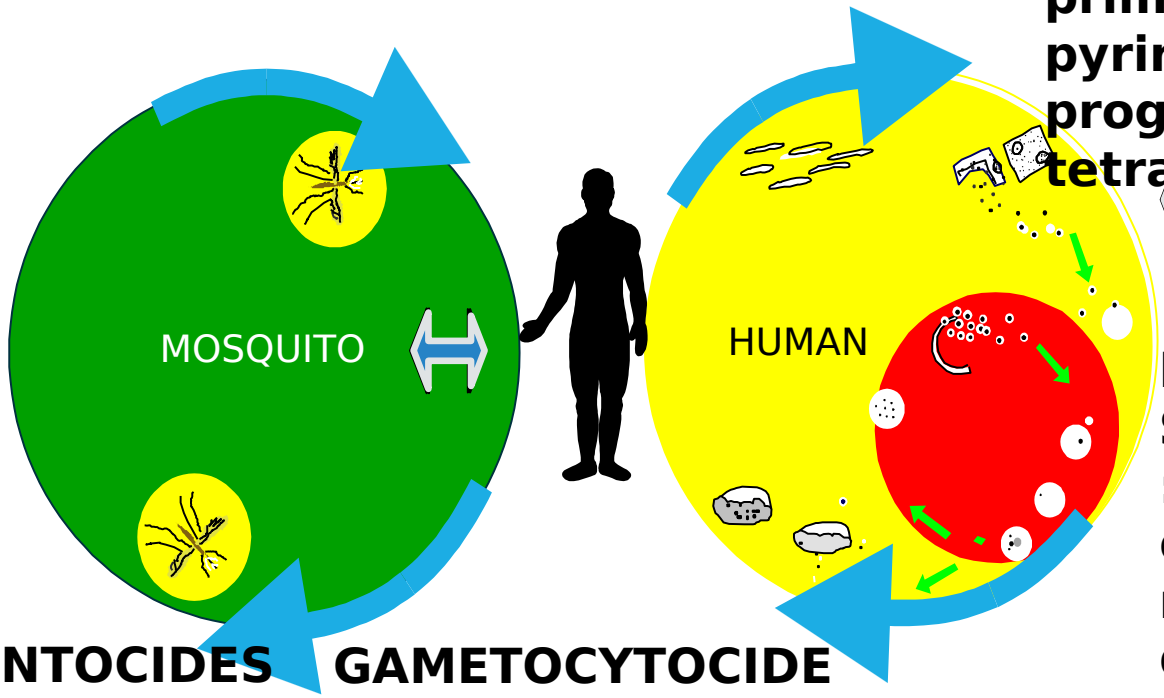
Malaria in Pregnant Women

- The first-line treatment for *P. falciparum* infection in pregnant women in the first trimester of pregnancy is oral quinine administered at 10 mg/kg (up to 600 mg) three times a day for seven days
- If pregnant women have *P. falciparum* or mixed infection and are in their second or third trimester, they will be treated with AL.
- Pregnant women with only *P. vivax* will be treated with chloroquine in all trimesters
- The recommended treatment for severe malaria in all patients including pregnant women is artesunate infusion, or alternatively quinine infusion or alternatively artemether IM

Drugs Used to Treat Malaria

- Chloroquine
- Amodiaquine
- Quinine and
- Mefloquine
- Halofantrine
- Atovaquone-proguanil
- Atemisinin derivatives

Sites of Action for Antimalarial Drugs



TISSUE SCHIZONTOCIDES:
primaquine
pyrimethamine
proguanil
tetracyclines

BLOOD SCHIZONTOCIDES:
chloroquine
mefloquine
quinine/quinidine
tetracyclines
halofantrine
sulfadoxine
pyrimethamine
artemisinins

SPORONTOCIDES:
primaquine
pyrimethamine
proguanil

GAMETOCYTOCIDES:
primaquine

Antimalarial drug actions

- **Actions**
  - **Blood schizontocidal** drugs (suppressive or clinical)– attack parasite in RBC, preventing or ending clinical attack
  - **Gametocytocidal** – destroy sexual forms in human, decreases transmission
  - **Hypnozoitocidal** – kill dormant hypnozoites in liver, antirelapse drugs
  - **Sporontocidal** – inhibit development of oocysts in mosquito, decreases transmission

Antimalarial Chemoprophylaxis

- Consider:
  - Immune status
  - Intensity/duration of exposure
  - Parasite drug resistance
  - Resources for diagnosis and treatment

Drugs for prophylaxis

- **Atovaquone/proguanil (Malarone®):** 250/100 mg once daily
  - Start 1 day earlier
  - continue throughout the stay and for 7 days after returning.
  - Chloroquine or mefloquine – resistant
- **Doxycycline**: 100mg QD
  - Chloroquine – or mefloquine – resistant
  - Start 2 days before
  - Continue daily during travel

Personal Protection

- Protective clothing
- Insect repellants
- Household insecticide products
- Window and door screens
- Bed nets

ONCOLOGIC DISORDERS

Chapter Three

Assefa M, MSc, Addis Ababa University

CANCER – THE BASICS

Introduction

- Cancer is a diverse group of diseases with the common theme of:
  - Uncontrolled growth of less differentiated cells
  - Local tissue invasion, and
  - Can spread to other parts of the body, **metastasize**
- A normal cell turns into a cancer cell because of
  - One or more mutations in its DNA, which can be acquired or inherited
- Two gene classes, oncogenes and tumor-suppressor genes, play a major role in the pathogenesis of cancer.

Introduction

- Damage to cellular DNA can result in mutations that lead to
  - Development of oncogenes & loss or inactivation of tumor suppressor genes
- Oncogenes are genes whose over activity or presence in certain forms can lead to the development of cancer.
- Oncogenes arise from normal genes called **proto-oncogenes** through genetic alterations such as
  - Chromosomal translocations, deletions, insertions, and point mutations

Introduction

The activation of proto-oncogenes to oncogenes

- Proto-oncogenes are genes that normally control cell division, apoptosis and differentiation ,
  - But which can be converted to oncogenes that induce malignant change by viral or carcinogen action

The inactivation of tumor suppressor genes

- Normal cells contain genes that suppress malignant change, termed tumor suppressor genes (antioncogenes),
  - Mutations of these genes are involved in many different cancers
- The loss of function of tumour suppressor genes can be the critical event in carcinogenesis

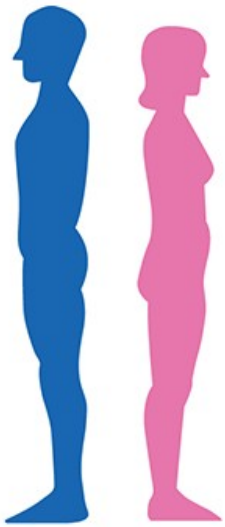
Cancer Epidemiology

- Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately **14 million** new cases in 2012
- Cancer is the 2nd leading cause of death globally; 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer.
- In fact more people die from cancer than from
  - AIDS, malaria and tuberculosis put together
  - Where 12.5% of all deaths each year

Estimated 2019 cancer incidences and deaths in the US

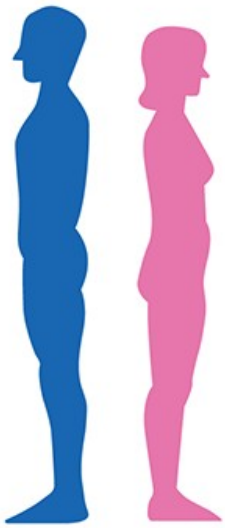
Estimated new cases

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,920	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	3%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**	**100%**	**All sites**	**891,480**	**100%**



Estimated deaths

Males			Females		
Lung and bronchus	76,650	24%	Lung and bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon and rectum	27,640	9%	Colon and rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver and intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver and intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain and other nervous system	7,850	3%
All sites	**321,670**	**100%**	**All sites**	**285,210**	**100%**



Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition.
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Cancer Epidemiology

Cancer in Ethiopia

- One-third of cancer cases are preventable (many caused by infections and smoking)
- 2008 Incidence of Cancer (estimated by WHO)
  - 51,700 New Cases
  - 41,600 Deaths
  - Higher estimates have been made by other groups (up to 150,000 new cases of cancer per year)

Cancer Types

- **Carcinoma:**
  - A tumor derived from **epithelial cells**, those cells that line the surface of our **skin** and organs
  - Accounts for 80-90% of all cancer cases
- **Sarcoma:**
  - a tumor derived from **muscle, bone, cartilage**, fat or **connective tissues**.
- **Leukemia:**
  - a cancer derived from **white blood cells** or their precursors.
- **Lymphoma:**
  - A cancer of bone marrow derived cells that affects the **lymphatic system.**

Tumor Classification by Tissue Type

Tissue of Origin	Benign	Malignant
Epithelial Tissue		
Surface epithelium	Papilloma	Carcinoma
Glandular epithelium	Adenoma	Adenocarcinoma
Connective Tissue		
Fibrous tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Fat		Liposarcoma

Tumor Classification by Tissue Type

Tissue of Origin	Benign	Malignant
Neural Tissue		
Glial tissue	Glioma	Glioblastoma Multiforme
Nerve Sheath	Neurofibroma	Astrocytoma Neurofibrosarcoma
Melanocytes	Pigmented Nevus	Melanoma
Lymphoid Tissue		Lymphoma
Hematopoeitic Cells		

Characteristics of Cancer Cells

1. **Excessive autonomous cell growth**
   - Tumor cells **produce growth factors** that stimulate their own proliferation
   - Abnormal receptors signal cell division
   - Loss of growth inhibitory signals
2. **Invasiveness**
   - Ability to grow into adjacent tissue
3. **Ability to metastasize**
   - Spread to new sites and form new growths
4. **Defective differentiation and immortality**
   - Proliferated cells don't divide (differentiation)
   - Failure of cancer cells to undergo programmed cell death

Risk Factors for Cancer?

1. Environmental exposures
2. Occupational environment
3. Lifestyle
4. Genetic predisposition
5. Drug exposure
6. **Sometimes we just don’t know!**

Environmental Exposures

Risk Factors	Associated Cancers
Ionizing radiation	Leukemia Thyroid cancer Breast cancer Lung cancer
UV radiation-tanning beds	Melanoma
Viral causes (EBV, HPV, Hepatitis)	Leukemia and Lymphoma Nasopharyngeal cancer Cervical cancer

Occupational Environment

Risk Factors	Sources/Uses	Associated Cancers
Asbestos	Vinyl floor tile, insulation, shingles, fireproofing	Lung cancer Mesothelioma
Chromium	Mining, textile dyes, printer inks and toners	Lung cancer
Aniline dye	Dyes, rubber additives, photography chemicals	Bladder cancer
	Solvent in inks,	

Lifestyle Risks

Risk Factors	Associated Cancers
Alcohol	Head and neck cancers Liver cancer Stomach cancer
Diet and Obesity	Colorectal cancer Breast cancer Endometrial ca Esophageal ca kidney cancers
Tobacco	Lung cancer- (80% of lung cancers) Head and Neck cancers Bladder cancers

Genetic Predisposition

Syndrome	Genes	Associated Cancers
Hereditary Breast & Ovarian Cancers	BRCA1 and BRCA2	Breast, Ovarian, Prostate, Pancreatic cancers
Li-Fraumeni Syndrome	BRCA2, p53, CHEK2	Soft tissue and osteo-sarcoma Breast cancer Leukemias Brain tumors
Cowden Syndrome	PTEN	Breast and endometrial cancers Thyroid cancer
Lynch Syndrome (HNPCC)	MLH1, MSH2, MSH6	Colon, endometrial, ovarian, pancreatic, stomach cancers
Von Hippel-Lindau	VHL	Renal Cell Carincoma

Drug Exposure

Risk Factors	Associated Cancers
Estrogens and Tamoxifen	Breast & Endometrial cancer
Diethylstilbestrol (DES)	Vaginal cancer (in female offspring)
Alkylating agents	Leukemia Bladder cancers
Immunosuppressants (adalimumab, infliximab)	Lymphoma

Cancer Prevention

- Smoking cessation;
- Limit alcohol
- Drug Rx: e.g. Tamoxifen for breast ca, Finasteride for prostate ca
- Treat infections and disease states that are risk factors
  - Antibiotic eradiation of H. pylori in Gastric ca; HIV, HPV
- Diet: Increase intake of fruits and vegetables
- Avoid mutagenic chemical exposure

Cancer Screening

- Helps detect cancer in the early stages
- Can help to cure (for some type of cancer) or decrease progression
  - If surgery is done before cancer metastasizes
- Examples
  - Mammogram or breast exam for breast Ca
  - Colonoscopy for colon Ca
  - Pap smear for cervical Ca
  - PSA & digital rectal exam for prostate Ca

Types of Cancer Treatment

- Often **in combination**, either simultaneously or sequentially:
  - **Surgery:** Often **the first line** of treatment for many **solid** tumors. If the cancer is detected **at an early stage**, surgery may be sufficient to **cure** the patient.
  - **Radiation:** The goal of radiation is **to kill the cancer cells** directly by damaging them with **high energy beams.**
  - **Chemotherapy:** A term used for a wide array of drugs used to kill cancer cells.
  - **Hormonal Treatments:** These drugs are designed to **prevent cancer cell growth** by **preventing the cells from receiving signals** necessary for their continued growth and division.

CHEMOTHERAPEUTIC AGENTS

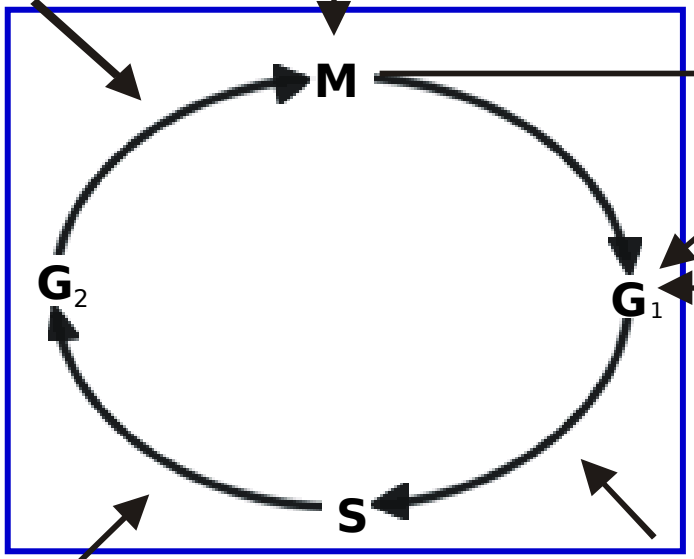
Chemotherapy

- **Cell cycle phase – specific**
  - Agents with major activity in a particular phase of cell cycle
  - Schedule dependent
  - Antimetabolites, antimitotics (taxenes, vinca alkaloids), DNA-repair enzyme inhibitors/ TI-II (etoposides), bleomycin
- **Cell cycle phase – non-specific**
  - Agents with significant activity in multiple phases
  - Dose dependent
  - Alkylating agents (including platinum analogs), anthracyclines, other –mycins, TI-I inhibitors (tepotecan)

The cell cycle

- Cancer cells, as with normal cells, proceed through the cell cycle.
- The cell cycle contains four phases (**M, G1, S & G2**).
- **M phase:** the cell undergoes **m**itosis (cell division)
- **G1 phase:** is the first **g**ap or resting phase where the cell makes the enzymes necessary for DNA synthesis.
- **S phase**: **s**ynthesis of DNA
- **G2 phase:** is a second **g**ap phase where RNA & other proteins are synthesized to prepare for cell division during the M phase
- The cells that complete mitosis may
  - Continue to proceed the cell cycle to divide again
  - Differentiate (mature into specialized cells) & eventually die, or
  - Enter a third resting phase called G0

l-cycle and phase specificity of some cytotoxic



Vincristine, Vinblastine
Paclitaxel,
Docetaxel

Cyclophosphamide
Bleomycin
Actinomycin D

Hydrocortisone

Purine antagonists
Methotrexate
Cyclophosphamide
5-Fluorouracil
Cytosine arabinoside
Daunomycin

Actinomycin D
5-Fluorouracil
Cytosine arabinoside
Methotrexate
6-Mercaptopurine
6-Thioguanine

G_0 = Resting phase

G_1 = Rrereplicative phase

G_2 = Postoperative phase

S = DNA synthesis

M = mitosis or cell division

Principles of Chemotherapy

- The main goals of treatment with chemotherapy are determined by
  - Cancer type
  - Stage
- Goals
  - To cure the cancer
  - To control the cancer
  - To relieve symptoms caused by the cancer

Principles of Chemotherapy

- **Primary induction chemotherapy**
  - When surgery isn't an option and chemotherapy will be administered on its own
- **Adjuvant chemotherapy**
  - When the most appropriate course of action is **surgery** but when it is **followed by chemotherapy**
  - The goal is **to prevent recurrence** using chemotherapy to kill microscopic cells not removed during surgery
- **Neoadjuvant chemotherapy**
  - Giving chemotherapy before **surgery to de-bulk the tumor**, making its removal easier.
  - Chemotherapy can also be combined with radiation therapy.

Principles of Chemotherapy

- **Consolidation or intensification chemotherapy**
  - Used to **eliminate** any **remaining leukemia cells.**
  - Is chemotherapy that is given to sustain a remission once a remission is achieved.
  - High dose + shorter Rx duration
- **Maintenance chemotherapy**
  - **Prevent disease recurrence** once remission has been achieved.
  - Is chemo given at lower doses to prolong remission.
  - It is only used for certain types of cancer (e.g. ALL)
  - Low dose + longer Rx duration

Principle of Chemotherapy

- Single drugs at tolerable doses rarely able to cure cancers
- Combinations of chemotherapeutic agents are often used to take advantage of:
  - **Different mechanisms** of action **to avoid resistance** (attack multiple targets)
  - Possible **synergistic** actions
  - Different **toxicity** profiles (to minimize risk of permanent organ damage or lethal toxicity)
- All drugs used in the combination must **be active alone.**

Chemotherapy Cycles

- Generally chemotherapy doses are administered in cycles
  - It gives the patient **time to recover** from the toxicities.
  - Cycles are courses of chemotherapy and are usually **defined by number of days.**
  - Cycles may be the same each time or vary based on toxicity concerns or the protocol being used.
- Chemos are thus given in cycles with **optimal doses** and schedules to **maximize cell kill** & **avoid unnecessary toxicity, drug resistance**

Chemotherapy Cycles

- **Dose-Dense Chemotherapy (DDC)**
  - Shortens the time between cycles
  - Shorten the overall time of therapy and
  - Decrease the amount of time that the tumor can grow between cycles,
  - But it usually requires the use of colony-stimulating factors (CSFs) to shorten the length of neutropenia (due to repeated use of cancer drugs)
- **Dose-Intense Chemotherapy (DIC)**
  - Involves increasing the total dose of chemo given during a fixed cycle period.

Calculating Chemo Doses

- Using Body Surface Area (BSA); because BSA
  - Estimates blood volume, cardiac output, and resulting drug distribution to the kidneys and liver
  - Provides an accurate comparison of activity & toxicity
- **DuBois equation for BSA:**
  - **$BSA(m^2) = 0.007184 \times weight\ (kg)^{0.425} \times height\ (cm)^{0.725}$**
- **Mosteller equation for BSA:**

Measurements Necessary to Administer Chemotherapy

- Blood cell count (CBC)
  - WBC >2,500 cells/mm3 or
  - ANC of >1,000 cells/mm3
    - **ANC** = WBC x % granulocytes (segs plus bands)
  - Platelet count of >75,000 cells/mm3
  - NB: these parameters may not apply when the cancer is of the bone marrow such as with leukemia
- Renal Function: CrCl

Supportive therapy to reduce toxicity

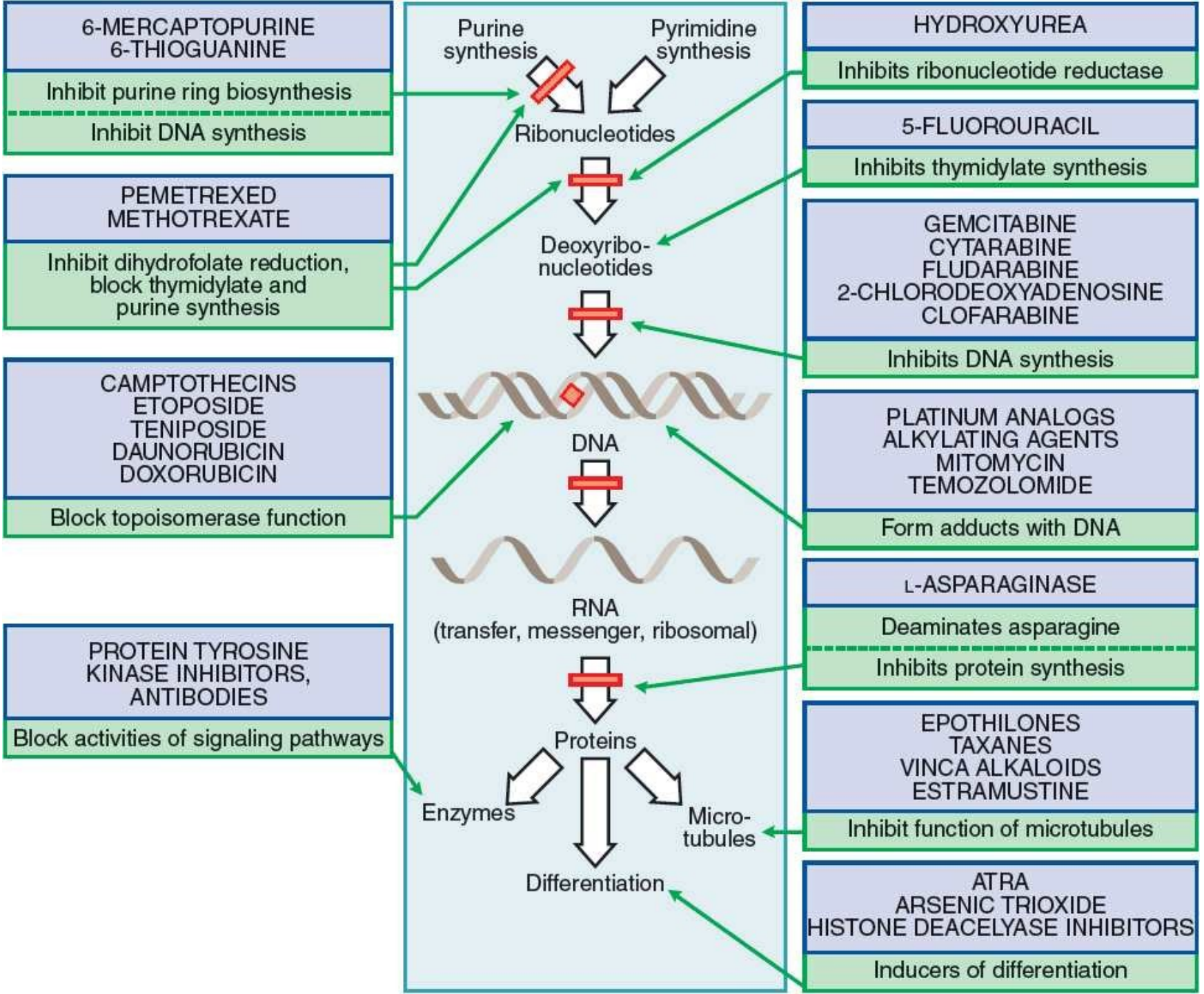
- **Antiemetics** (5-HT_3 –antagonists like Ondansetrone)
- **Antibiotic** prophylaxis and therapy (for neutropenic fever if **ANC <500 and T≥38.3c**)
- Prophylaxis of **urate nephropathy** (**allopurinol**)
- Enteral and parenteral **nutrition**
- **Pain** – analgesic drugs
- **Psychological support**

Supportive therapy to reduce toxicity

- **Hematotoxicity** – bone marrow transplantation, hematopoietic growth factors
- **Specific antagonists**: antifolate (methotrexate) – folate (leucovorin)
- **MESNA (2-mercaptoethanesulfonate)** - donor of –SH groups, decrease urotoxicity of **cyclophosphamide** (nephrotoxicity)
- **Dexrazoxane**: **chelates iron**, reduce anthracycline cardiotoxicity
- **Amifostine:** reduces hematotoxicity, ototoxicity and neurotoxicity of **alkylating agents**

Classes of Chemo

- **Cell cycle specific**
  - Antimetabolites (5FU, MTX, 6-MP),
  - Antimitotics (taxenes, vinca alkaloids),
  - DNA-repair enzyme inhibitors / Epipodophyllotoxins (- “posides”),
  - Bleomycin (antitumor antibiotic)
- **Cell cycle non-specific agents**
  - Alkylating agents (including platinum analogs)
  - Anthracyclines
  - other antitumor antibiotics – “mycins”
  - Camptothecins – “tecans”(e.g. tepotecan)


6-MERCAPTOPURINE
6-THIOGUANINE
Inhibit purine ring biosynthesis
Inhibit DNA synthesis
PEMETREXED
METHOTREXATE
Inhibit dihydrofolate reduction, block thymidylate and purine synthesis
CAMPTOTHECINS
ETOPOSIDE
TENIPOSIDE
DAUNORUBICIN
DOXORUBICIN
Block topoisomerase function
PROTEIN TYROSINE KINASE INHIBITORS, ANTIBODIES
Block activities of signaling pathways
Purine synthesis
Pyrimidine synthesis
Ribonucleotides
Deoxyribo-nucleotides
DNA
RNA
(transfer, messenger, ribosomal)
Proteins
Enzymes
Micro-tubules
Differentiation
HYDROXYUREA
Inhibits ribonucleotide reductase
5-FLUOROURACIL
Inhibits thymidylate synthesis
GEMCITABINE
CYTARABINE
FLUDARABINE
2-CHLORODEOXYADENOSINE
CLOFARABINE
Inhibits DNA synthesis
PLATINUM ANALOGS
ALKYLATING AGENTS
MITOMYCIN
TEMOZOLOMIDE
Form adducts with DNA
L-ASPARAGINASE
Deaminates asparagine
Inhibits protein synthesis
EPOTHILONES
TAXANES
VINCA ALKALOIDS
ESTRAMUSTINE
Inhibit function of microtubules
ATRA
ARSENIC TRIOXIDE
HISTONE DEACELYASE INHIBITORS
Inducers of differentiation

1. Alkylating Agents

- Impair cell function by **forming covalent bonds** with amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules (DNA)
- Classical alkylating agents
  - Nitrogen mustards
    - **Cyclophosphamide**, **Chlorambucil**, **Ifosfamide**
  - Nitrosoureas:
    - **Carmustine**, **Lomustine**
- Nonclassical Alkylating Agents
  - **Dacarbazine**, **Procarbazine**
- Alkylating-like
  - Platinum-based agents: **Cisplatin**, **Carboplatin**, **Oxaliplatin**
  - Do not have **alkyl** group, but still damage DNA

Nitrogen Mustards

- The metabolites of these compounds are:
  - **Highly reactive in aqueous** solution, in which an active alkylating moiety, the **ethylene imonium ion**, binds to DNA.
  - **Cyclophosphamide**, Chlorambucil, Ifosfamide
- Adverse Effects:
  - Are powerful local **vesicants**
  - **Local tissue necrosis**
  - **Pulmonary fibrosis**
  - **Hemorrhagic cystitis**
  - **Neurotoxicity**

Cyclophosphamide & Ifosfamide

- Alkylating agents used in the treatment **of solid tumors and hematologic malignancies.**
- Neither agent is active in its parent form
  - Must be activated by hepatic oxidase enzymes including the cytochrome P450 (CYP) 2B6 and CYP3A4 enzymes.
- **Phosphoramide mustard** is cyclophosphamide active cytotoxic metabolite
- Ifosfamide is hepatically activated to

Cyclophosphamide & Ifosfamide: Renal Toxicity

- **Acrolein** is a metabolite of both agents that causes hemorrhagic cystitis
  - Prevented by 2-mercapto*ethane*sulfonate (mesna)
- Hemorrhagic cystitis
  - Excretion of acrolein into the urinary bladder
  - Greater with bolus regimen
  - Higher incidence with ifosfamide than equivalent doses of cyclophosphamide
  - Symptoms: dysuria and urinary frequency
  - Treatment: requires evacuation of clots and continuous bladder irrigation

Cyclophosphamide & Ifosfamide
Neurotoxicity

- **Neurotoxicity**
  - **Chloroacetaldehyde** metabolite penetrates BBB
  - CNS toxicity occur in patients receiving **high doses** of the drug, **less in cyclophosphamide**
  - Encephalopathy (CNS toxicity) following ifosfamide can occur within 48 to 72 hours following the infusion and is reversible
  - **Encephalopathy** is manifested by cerebral ataxia, mental confusion, complex visual hallucinations

Dacarbazine (DTIC)

Dimethyl triazeno-imidazole-carboxamide [DTIC]

- Non-classic alkylating agent
- Undergo demethylation to monomethyl triazeno-imidazole-carboxamide [MTIC]
  - MTIC interrupts DNA replication by causing methylation of guanine
- Commonly used as part of the **ABVD** chemotherapy regimen to treat **Hodgkin lymphoma**, and in the **MAID** regimen for **sarcoma**
- Dacarbazine is poorly absorbed, & must be administered by intravenous infusion
- Dacarbazine penetrates the CNS poorly

Platinum Compounds

- Alkylating-like agents including
  - **Cisplatin**, **Carboplatin**, **Oxaliplatin**
- Are platinum-based chemo drugs; complexes of platinum
- Broad spectrum anticancer drugs for solid tumors (high cure rate)
- Covalently bind **guanine**, inhibit DNA replication & transcription, DNA breaks and miscoding

Cisplatin Toxicity

Nephrotoxicity (kidney damage) is a major concern

- Reduce dose if the patient's CrCl is low
  - Nephrotoxicity is a dose-limiting side effect
- Preventive measures:
  - Aggressive saline hydration, pretreatment with amifostine, avoid other nephrotoxic agents
- Predisposing factors to developing nephrotoxicity include
  - Age ≥ 60 years, higher doses, pretreatment GFR < **75** ml/min, cumulative dose, low albumin (cisplatin has >90% protein binding; low albumin ↑its exposure)

Cisplatin Toxicity

- **Nausea and vomiting:**
  - Cisplatin is highly emetogenic agent
  - Rx: prophylactic antiemetics (ondansetron, granisetron, etc.) in combination with corticosteroids
  - Aprepitant + ondansetron + dexamethasone
    - **Better** for highly emetogenic chemotherapy than just ondansetron and dexamethasone
- **Ototoxicity (hearing loss):**
  - No effective treatment to prevent this side effect
  - Audiometric analysis to assess severity of ototoxicity
  - Avoid ototoxic drugs (e.g. aminoglycosides) in patients receiving cisplatin

Cisplatin Toxicity

- **Electrolyte disturbance:**
  - Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia
- **Myelotoxicity:**
  - This agent can also cause profound **bone marrow suppression**
  - Hemolytic anemia can be developed after several courses of cisplatin
  - It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis

Carboplatin Toxicity

- **Moderately emetogenic**
- **Renal impairment is rare**
  - Because it is excreted primarily in the kidneys as an unchanged drug, it is not directly toxic to the renal tubules
- **Neurotoxicity is rare**
- **Myelosuppression**
  - Especially thrombocytopenia
  - Dose-limiting toxicity, cumulative
- **Hypersensitivity reaction**
  - Thought to be due to type I hypersensitivity (IgE mediated)
  - Incidence of hypersensitivity correlated with increased number of cycles of carboplatin administered-6 to 8 cycle

Comparison of Platinum Toxicity

Comparative adverse effect profiles of platinum drugs			
Adverse effect	**Cisplatin**	**Carboplatin**	**Oxaliplatin**
Nephrotoxicity	++	+	-
GI toxicity (NV)	+++	+	+
Peripheral neurotoxicity	+++	-	++
Ototoxicity	+	-	-
Hematologic toxicity	+	++	+

2. Mitotic Inhibitors (Antimitotics)

- These drugs disrupt **microtubules** which are structures that pull the cell apart when it divides
  - Prevent mitosis/M phase
- Examples of mitotic inhibitors frequently used are: Vinca alkaloids & Taxanes
- Vinca alkaloids Taxanes
  - Vincristine - Paclitaxel
  - Vinblastine - Docetaxel
  - Vinorelbine

Vinca Alkaloids

- All vinca alkaloids are administered intravenously (IV)
- Vinblastine
  - Inhibits angiogenesis, or the process by which **new blood** vessels grow from pre-existing ones
  - Used to treat lymphoma, breast ca
  - Side effects: toxicity to WBCs, nausea, vomiting, constipation, dyspnea, tumor pain, wheezing
- Vincristine
  - Its inhibition of microtubule is especially powerful
  - Used to treat acute leukemia, lymphomas
  - Side effects: peripheral neuropathy, bone marrow suppression, constipation, nervous system toxicity, N &V

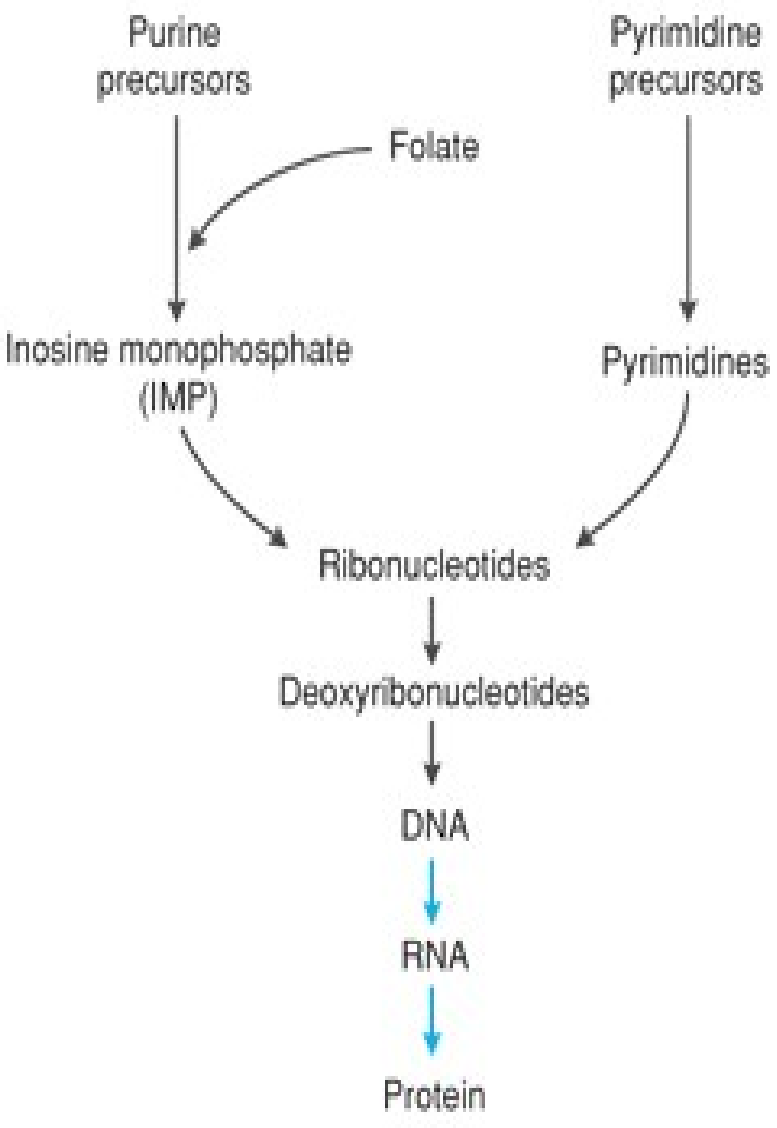
3. Antimetabolites

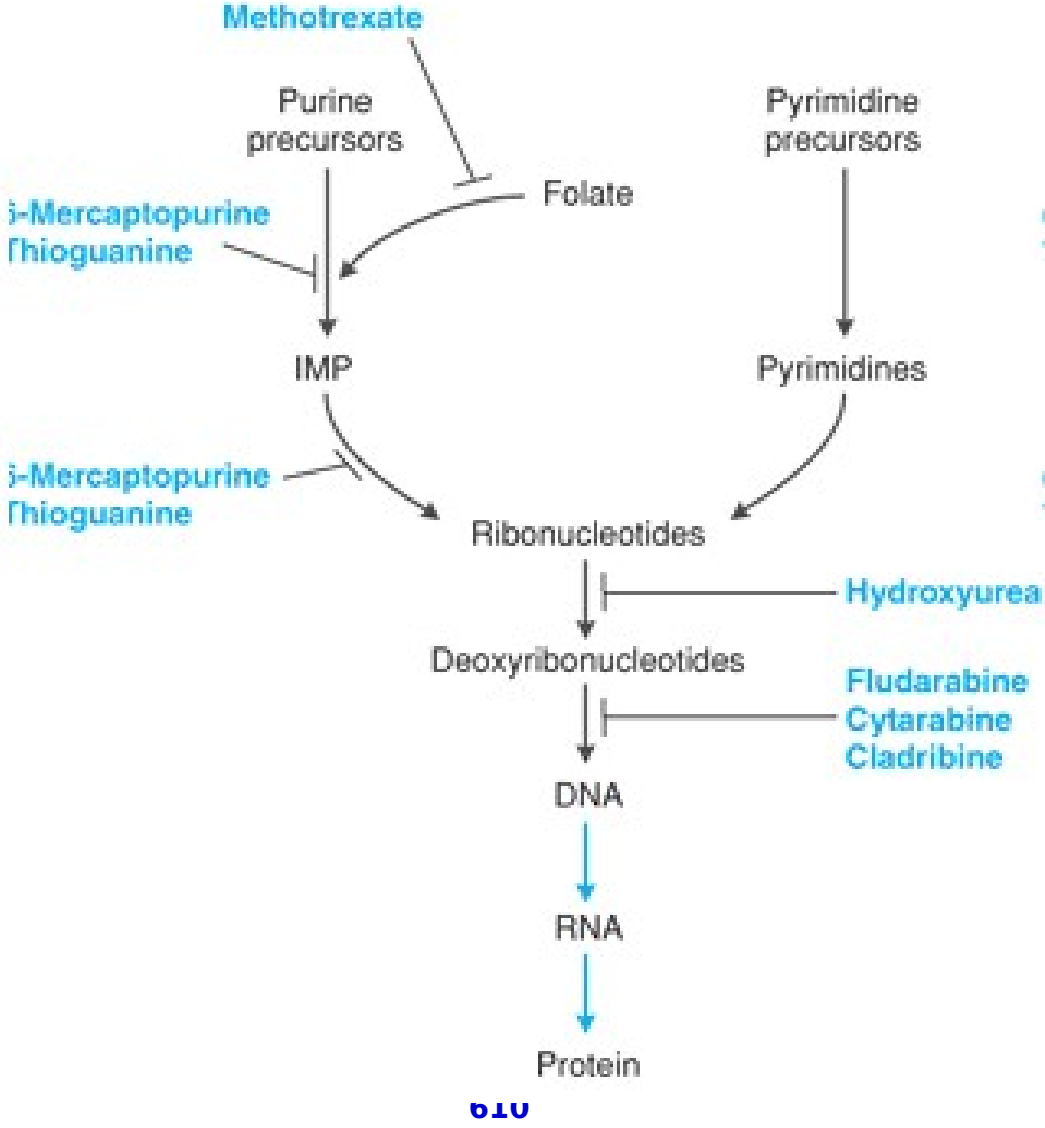
- Include folic acid, pyrimidine or purine analogues
- Induce cell death during **S phase** when incorporated into RNA & DNA or **inhibit enzymes** of nucleic acid production
- These agents are used for a variety of cancer therapies including leukemia, lymphoma, breast, ovarian & GI cancers

Drugs include:

- **Nucleoside analogs**
  - **Pyrimidine analog:** Fluorouracil, Cytarabine:
    - Gemcitabine: pro drug of Cytarabine
    - Capecitabine: pro drug of Fluorouracil
  - **Purine analog:** Mercaptopurine, thioguanine
- **Antifolate:** Methotrexate

Antimetabolites: Sites of Drug Action





Flurouracil (5-FU)

- Fluorinated analog of uracil
- **Cardiotoxicity**
  - Symptoms disappear on stopping
  - Occurs due to myocardial ischemia, potentially induced by **coronary vasospasm**
- Bolus: myelosuppression, oral mucositis, GI disturbances
- Continuous infusion regimen: hand-foot syndrome; less hematologic and GI toxicity
- Ocular Toxicity: Blepharitis (eyelid inflammation), conjunctivitis, excessive lacrimation, ocular pruritus and burning
- Hyperbilirubinemia
- 5-FU is not vesicant or irritant and is **low emetogenic**

Flurouracil (5-FU) toxicity

Hand-Foot Syndrome





Capecitabine

- Capecitabine is an **oral 5-FU** pro-drug
  - Enzymatically converted to **5-fluorouracil** by actions in liver and tumor cells
- Capecitabine toxicity
  - Gastrointestinal: NVD, abdominal pain, low emetic drug
  - Hand-foot syndrome (mimics 5-FU)
- Concomitant administration with warfarin is a Black Box Warning
  - Bleeding events have occurred within several days to several months after initiation of capecitabine therapy and, elevate prothrombin

Cytarabine

- Arabinose analog of cytosine
- Myelosuppression
- Gastrointestintal
  - Moderately emetogenic if > 1 gm/m^2
  - Stomatitis (inflammation of mucus membrane of mouth)
- CNS: **acute cerebellar syndrome**
  - Dysarthria (speech), dysdiadochokinesia (unable to perform rapid alternate movements), ataxia
- Ocular: conjunctivitis, excessive tearing, photophobia, pain, and blurred vision
  - Associated with high-dose cytarabine
  - Prophylactic use of corticosteroid eye drops
- Dermatologic: erythema of hands (hand-foot syndrome)
  - Can occur with HIDAC (High-dose cytarabine)
  - Alopecia

Folate Antagonists

- Folic acid is necessary for the production of nucleotides
- Tetrahydrofolic acid (THF), active folate, is a co-enzyme in the synthesis of purine bases and thymidine
  - THF is synthesized by dihydrofolate reductase (DHFR) enzyme
- **Methotrexate**: most commonly used folate antagonist
  - It is active in the S phase of cell growth and it works by binding to the enzyme DHFR reversibly
  - It is effective in many malignancies.

Methotrexate (MTX)

- **Doses**
  - Low dose: < 1 gram/m^2; High dose: 1 – 30 gram/m^2
- **High-Dose MTX**
  - Check **marrow, liver, and renal** function before therapy
  - Maintain **UOP > 100 ml/hr**
  - Hepls to decrease resistance
- MTX Drug Interactions
  - Avoid concomitant nephrotoxic agents (it has renal toxicity)
  - Salicylates and sulfonamides (e.g. Bactrim) may displace MTX from binding sites
  - Oral antibiotics may interfere with oral absorption of MTX and with enterohepatic recycling

MTX Toxicity

- **Myelosuppression**
- **Mucositis**
- **Nausea, vomiting and Diarrhea (NVD)**
- **Renal & Hepatic**
  - Vigorous hydration; adjust dose in renal & hepatic insufficiency
- **Pulmonary:** Less common, but potentially fatal
- **Neurotoxicity (IT therapy)**
  - Motor paralysis, seizures, coma during 2nd or 3rd week of treatment in patients with meningeal leukemia
  - Headache, nuchal rigidity (neck back), fever, vomiting - common, acute in onset
  - Coma – can occur months to years after treatment (irreversible)
- Others: rash, teratogenicity, alopecia

Leucovorin

- **Mechanism of action**
  - Derivative of THF and competes with MTX for active transport into cells
  - Enters folate cycle distal to MTX enzymatic block
  - Given AFTER MTX as “rescue” by repleting intracellular THF pools
  - Selective for rescuing normal cells more than malignant cells
  - May compromise antitumor efficacy if given early
- **Administration**
  - Started 24 hours after MTX
  - After 48 hours, MTX toxicity may not be reversible with leucovorin
  - 1:1 IV: po (100% bioavailability)

4. Antitumor Antibiotics

- Antitumor antibiotics are
  - Chemo treatments made from natural products produced by species of the soil fungus Streptomyces.
- Prevent cell division by either binding to DNA to prevent replication or inhibiting RNA synthesis.
- There are several types of antitumor antibiotics:
  - Anthracyclines: Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, and Idarubicin.
  - Chromomycins: Dactinomycin and Plicamycin.
  - Miscellaneous: Mitomycin and Bleomycin.

5. Topoisomerase inhibitors

- Topoisomerases are essential enzymes
  - That maintain the topology of DNA.
- Epipodophyllotoxins
  - Naturally occurring TI
  - Found in the root of American May-apple (Podophyllum peltatum).
- Semisynthetic derivative of Epipodophyllotoxin include
  - Etoposide,
  - Teniposide Topo I

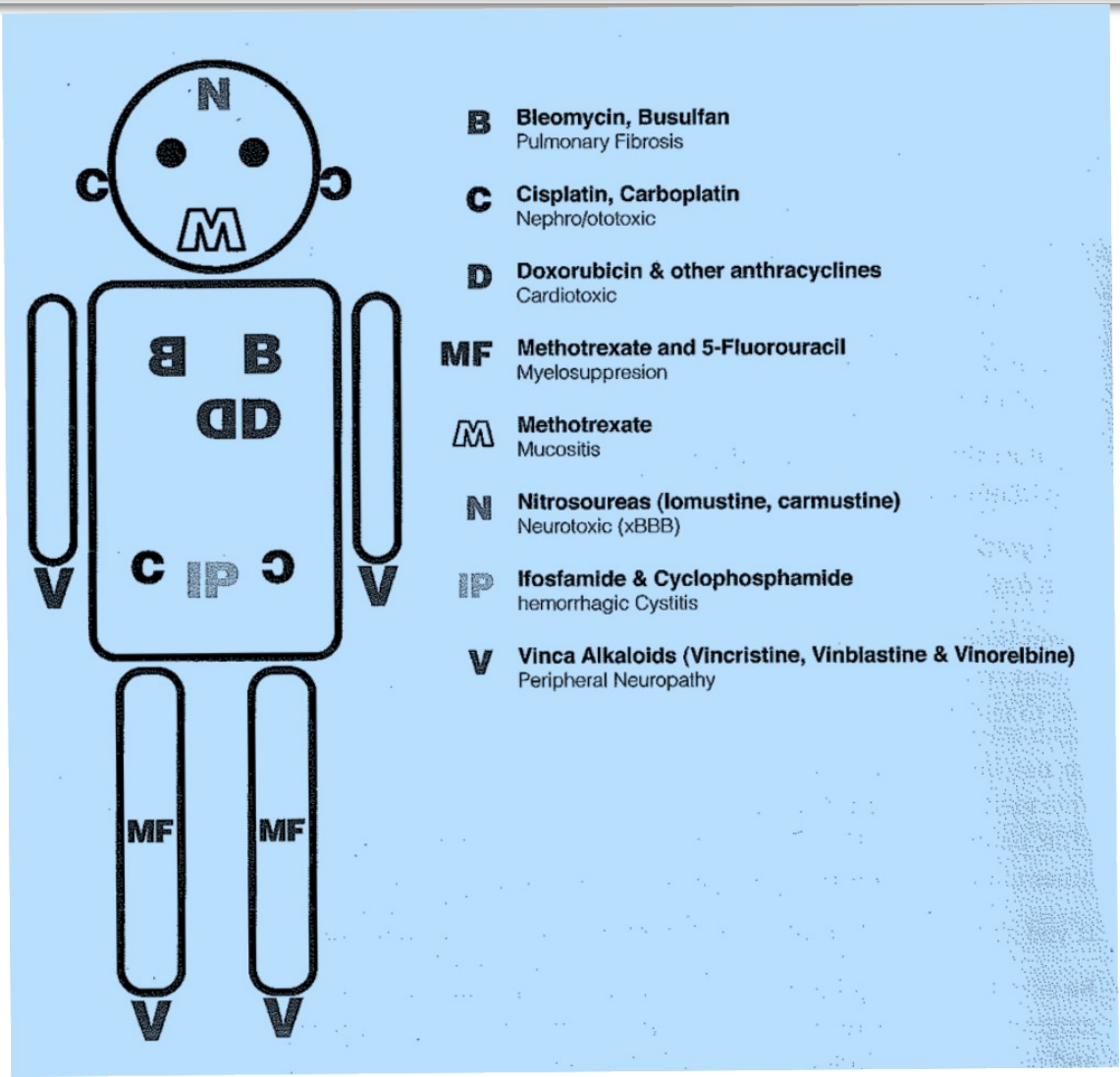
Topoisomerase inhibitors

- Two Types
  - Topo I inhibitors & Topo II inhibitors
- Inhibition of topoisomerases interferes with
  - Both transcription and replication of DNA by upsetting proper DNA supercoiling.
- Type I topoisomerase inhibitors
  - Camptothecins: **irinotecan** and topotecan.
- Type II inhibitors
  - Amsacrine, **etoposide**, etoposide phosphate, and teniposide.

6. Tyrosine Kinase Inhibitors

- ***Imatinib***
  - Imatinib was the first FDA-approved TKI
  - Designed to block the breakpoint cluster region tyrosine kinase (BCR-ABL) produced by the Philadelphia chromosome associated with CML and ALL
- Next-generation TKIs
  - **Dasatinib, Nilotinib, and Bosutinib**

Chemo Man


N
C
M
B
B
D
C
IP
C
V
V
MF
MF
V
V
B Bleomycin, Busulfan
Pulmonary Fibrosis
C Cisplatin, Carboplatin
Nephro/ototoxic
D Doxorubicin & other anthracyclines
Cardiotoxic
MF Methotrexate and 5-Fluorouracil
Myelosuppresion
M Methotrexate
Mucositis
N Nitrosoureas (lomustine, carmustine)
Neurotoxic (xBBB)
IP Ifosfamide & Cyclophosphamide
hemorrhagic Cystitis
V Vinca Alkaloids (Vincristine, Vinblastine & Vinorelbine)
Peripheral Neuropathy

7. Hormonal Therapy

- Hormone therapy can work by
  - Stopping the production of a certain hormone,
  - Blocking hormone receptors, or
  - Substituting chemically similar agents for the active hormone, which cannot be used by the tumor cell.
- The different hormone therapy types are categorized by their function and/or the type of hormone that is effected

Hormone Therapy

- **Hormone Therapy: Androgens**
  - Androgens are hormones such as testosterone and androsterone that produce or stimulate the development of male characteristics.
  - Fluoxymesterone, testosterone, testolactone
- **Hormone Therapy: Antiandrogens**
  - Antiandrogens are substances that block the effects of testosterone.
  - Bicalutamide, flutamide, nilutamide

Hormone Therapy

- **Hormone Therapy: Antiestrogens**
  - Tamoxifen, toremifene
- **Hormone Therapy: Aromatase inhibitors**
  - Aromatase inhibitors block the enzyme aromatase (found in the body's muscle, skin, breast and fat), which is used to convert androgens into estrogen.
  - Anastrazole, exemestane, letrozole

Hormone Therapy

- **Hormone Therapy: LHRH agonists (Lutenizing hormone-releasing hormone)**
  - LHRH agonists work by telling the pituitary gland located in the brain to stop producing leutinizing hormone, which (in men) stimulates the testicles to release testosterone and (in women) stimulates the ovaries to release estrogen.
  - Goserelin acetate, leuprolide acetate, triptorelin pamoate
- **Hormone Therapy: Selective Estrogen Receptor Modulators (SERMs)**
  - The term "SERMs" describes drugs that act like estrogen in some organs and as an anti-estrogen in

Hormones (Corticosteroids)

- Are thought to work
  - By blocking cell metabolism through their effect on specific genes.
  - However, the way these drugs work is under study.
  - In high doses, these synthetic hormones, relatives of the natural hormone cortisol, can kill malignant lymphocytes.
    - Dexamethasone
    - Methylprednisolone
    - Prednisone

8. Monoclonal Antibodies

- Are laboratory-produced proteins that can be infused to treat individuals with certain blood cancers.
- These agents target specific antigens on the surface of cancer cells to interfere with the cell's function and destroy the cell.
- Some monoclonal antibodies are linked to a toxin or radioactive substance.
  - Alemtuzumab
  - Ibritumomab tiuxetan
  - Ofatumumab
  - Rituximab
  - Tositumomab and iodine I 131 tositumomab

9. Miscellaneous Antineoplastics

- Several useful types of chemotherapy drugs are unique:
  - Ribonucleotide reductase inhibitor: **Hydroxyurea**.
  - Adrenocortical steroid inhibitor: Mitotane
  - Enzymes: **Asparaginase** and Pegaspargase.
  - Antimicrotubule agent: Estramustine
  - Retinoids: Bexarotene, Isotretinoin, Tretinoin (ATRA)

Review Questions

1. Which of the following terms refers to a gene that can help prevent abnormal cellular growth?
   A. Protooncogene
   B. Oncogene
   C. Tumor suppressor gene
   D. All of the above

Review Questions

2. A Breast CA stage II patient is about to get mastectomy followed by chemotherapy. This type of chemo is called:
   A. Adjuvant
   B. Induction
   C. Consolidation
   D. Neoadjuvant

Review Questions

3. If a chemo regimen given every 3 weeks instead the usual every 4 week cycle is called:
   A. Dose-Dense
   B. Dose-Intense

Review Questions

4. Which one of the following alternatives has incorrectly matched drug with the side effect
   A. Adriamycin Cardiotoxicity
   B. Cisplatin Nephrotoxicity
   C. Cytarabine Hand-foot syndrome
   D. Oxaliplatin Ototoxicity

Review Questions

5. Which one of the following is incorrect about chemotherapy cycles
   A. Cycles give the patient time to recover from the drug toxicities
   B. Cycles are courses of chemotherapy
   C. Cycles are similar each time until the patient completes full treatment
   D. Cycles are usually defined by number of days

Review Questions

6. Antimetabolite drug
   A. Mercaptopurine
   B. Cisplatin
   C. Bleomycin
   D. Vincristine

Review Questions

7. Which of the following chemotherapy agents inhibit topoisomerase function?
   A. Actinomycin D
   B. Etoposide
   C. Irenotecan
   D. Bleomycin
   E. Tamoxifen

Review Questions

8. Which of the following is **not** antimitotic agent?
   A. Doxorubicin
   B. Vincristine
   C. Vinblastine
   D. Paclitaxel

Review Questions

9. Which of the following are **TRUE** about the design of chemotherapy regimens?
   A. They are always designed with a cure in mind.
   B. Combination therapy is the standard of care for most types of cancer.
   C. Using drugs with the same mechanism of action is better than hitting multiple targets.
   D. Dose-intense chemotherapy means shortening the time between chemo cycles.

Review Questions

10. Which patient qualify to receive chemotherapy?

A. A leukemia patient with platelets count of 60,000

B. A patient with WBC of 1,500

C. A patient with ANC = 450

D. None of the above

Match

Drug	Class
1. Vincristine	A. Antimetabolites
2. Topotecan	B. Antimitotic
3. Bleomycin	C. Alkylating agent
4. Cytrabine	D. Antitumor Antibiotics
5. Mercaptopurine	E. DNA-Repair Enzyme Inhibitor
6. Cisplatin	

- How many vials of artesunate are required for the treatment of a 60 kg patient with sever p. falciparum malaria.
- Write the antimalarial agent that can have the radical cure for p.vivax
- Define neoadjuvant and adjuvant chemotherapy

BREAST CANCER

Epidemiology

- Breast cancer is the most common site of cancer and is second only to lung cancer as a cause of cancer death in American women
- In 2013
  - 234,580 new cases (**271,270 in 2019**)
  - 40,030 deaths (**42,260 in 2019**)
  - 2,240 cases of male (**2,670 in 2019**)

Common Terms

- **Carcinoma**
  - A cancer that **begins in the lining layer** (**epithelial cells**) of organs like the breast.
  - **Nearly all breast cancers are carcinomas** (either ductal carcinomas or lobular carcinomas).
- **Adenocarcinoma**
  - Carcinoma that **starts in glandular tissue** (tissue that makes and secretes a substance).
  - The **ducts** and **lobules** of the breast are glandular tissue (they make breast milk)

Carcinoma in situ

- Is an early stage of cancer
  - It is confined to the layer of cells where it began.
- In breast cancer, **in situ** means
  - The cancer cells remain confined to ducts (ductal carcinoma in situ) or confined to the lobules (lobular carcinoma in situ)
- The cells have not grown into (invaded) deeper tissues in the breast or spread to other organs in the body.
- Sometimes referred to as
  - **Non-invasive** or **pre-invasive** breast cancer

Ductal Carcinoma in Situ (DCIS)

- 14% to 50% of DCIS lesions will progress to invasive breast cancer
- Also known as **intraductal carcinoma**
  - Is **most common type** of non-invasive breast cancer.
  - Nearly all women diagnosed at this early stage can be **cured.**
- A **mammogram** is often the best way to find DCIS early.
- A more aggressive type of DCIS is when there is **tumor necrosis**
  - DCIS with necrosis is called **comedocarcinoma**

Lobular carcinoma in situ (LCIS)

- Generally no palpable mass, and no specific clinical abnormality is noted.
- Unlike DCIS, LCIS does not generally demonstrate calcifications on mammography
  - Undetectable by mammography
  - Detected by **biopsy** specimens
- Risk of developing into invasive carcinoma is about 0.5% to 1% per year

Risk factors for breast cancer

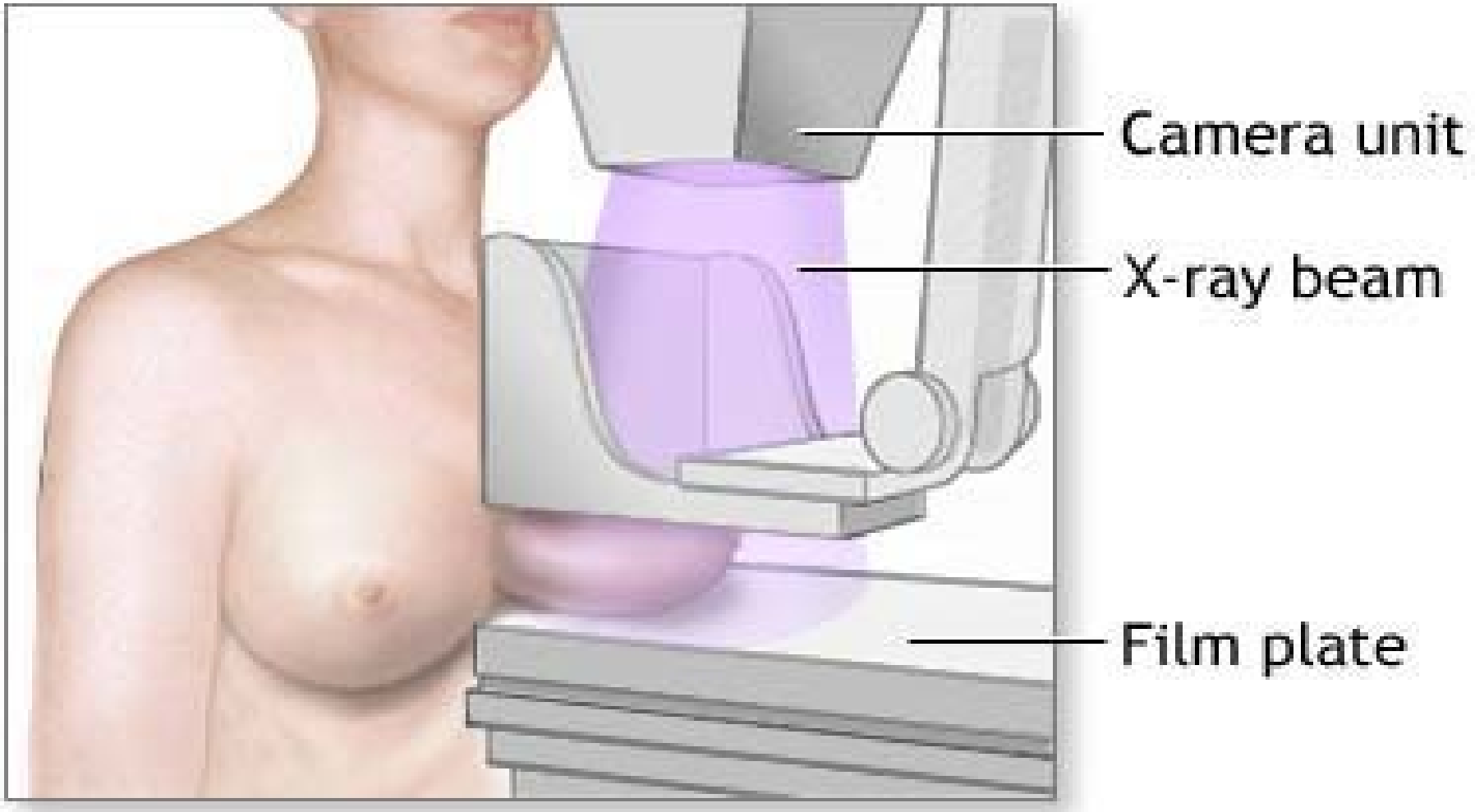
- Gender: risk of female to male is 100 : 1 proportion
- Genetic: BRCA1 and BRCA2 mutate genes
- Family history
- Age
- Race/ethnicity:
  - White (high risk) Vs blacks (more death)
  - Dense breast tissue has high risk
- More menstrual cycles
  - Menstruation started at early age (before age 12) and/or went through menopause at a later age (after age 55)
- Having children, pregnancy at young age reduces the risk
  - **No children** or first child after age 30 years higher risk
- Oral contraceptive use; Hormone Rx after menopause
- Alcohol (≥ 2 drinks/day); Obesity

Breast Cancer Prevention

- **Tamoxifen and Raloxifene**: approved by FDA as prevention
  - Competitive estrogen antagonist for estrogen receptor (block effect of estrogen on breast tissue)
  - For women at high risk
  - Tamoxifen side effects: (less in Raloxifene)
    - Increased risks of **endometrial** (**uterine**) **cancer** (in women who have gone through menopause) and serious **blood clots**
- **Aromatase inhibitors**: not approved by FDA
  - Drugs: anastrozole, letrozole, and exemestane
  - By inhibiting aromatase, the conversion of androstenedione to estrone, and testosterone to estradiol, is prevented; estrogen
  - Side effect: joint pain & stiffness and bone loss, leading to a higher risk of osteoporosis
- **Preventive (prophylactic) mastectomy**
  - Both breast removal: up to 97%

Screening

- Women age **40 and older** should have a screening **mammogram** every year.
- Despite its limitation (missing some cancers)
  - It is a very effective and valuable tool for decreasing suffering and death from breast cancer
- Women in their **20s and 30s**
  - Should have a clinical breast exam (CBE) as part of a periodic (regular) health exam at least every 3 years.
- CBE is a complement to mammograms



In mammography, each breast is compressed horizontally, then obliquely and an x-ray is taken of each position

A.D.A.M.

Signs and symptoms of Breast Cancer

- The most common symptom of breast cancer is a new **lump** or **mass**
  - A painless, hard mass that has irregular edges is more likely to be cancerous, but breast cancers can also be tender, soft, or rounded & painful
- Other possible signs of breast cancer include:
  - **Swelling** of all or part of a breast (even with no distinct lump)
  - **Skin irritation** or dimpling (slight depression)
  - **Nipple retraction** (turning inward)
  - Redness, scaliness, or thickening of the nipple or breast skin
  - Nipple discharge (other than breast milk)
- Sometimes a breast cancer lump or swelling may spread to lymph nodes under the arm or around the collar bone and
  - This could happen even before the original tumor in the breast tissue is large enough to be felt

Estrogen receptor (ER) and progesterone receptor (PR) status

- Normal breast cells and some cancer cells contain:
  - Receptors that attach to estrogen and progesterone.
- These 2 hormones fuel the growth of breast cancer cells.
- Cancer cells may contain neither, one, or both of these receptors; so breast cancers are classified as
  - *ER-positive* (or ER+) cancers or *PR-positive* (or PR+) cancers
- If either type of receptor is present, the cancer is said to be **hormone receptor-positive.**
- About ⅔ of breast cancers have at least one of these receptors.
- This percentage is higher in older women than in younger ones.

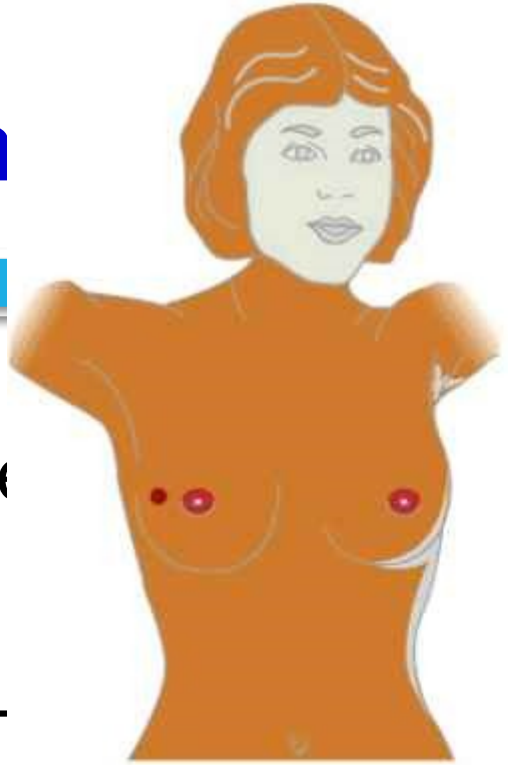
HER2/neu status

- About ⅕ breast cancers have:
  - Too much of a growth-promoting protein called *HER2/neu* often just shortened to HER2
  - The HER2/neu gene instructs the cells to make this protein
- Tumors with increased levels of HER2/neu are referred to as HER2-positive.
- Women with HER2-positive breast cancers tend to grow and spread more aggressively than other breast cancers
- HER2-positive cancers **much more likely** to benefit from treatment with drugs
  - That target HER2/neu protein include:
    - Trastuzumab, Lapatinib

The TNM staging system

- Classifies cancers based on their T, N, and M stages
- **The letter T**
  - Followed by a number from 0 to 4 describes the **tumor's size** and spread to the skin or to the chest wall under the breast
- **The letter N**
  - Followed by a number from 0 to 3 indicates whether the cancer has spread to **lymph nodes** near the breast and, if so, how many lymph nodes are affected
- **The letter M**
  - Followed by a 0 or 1 indicates whether the cancer has spread to distant organs; for example, the lungs or bones

The TNM staging system



Primary tumor (T) categories

- **TX:** Primary tumor cannot be asse
- **T0:** No evidence of primary tumo
- **Tis:** Carcinoma in situ (DCISand L
- **T1:** Tumor is **2 cm** (of an inch) **or less** across.
- **T2:** Tumor is **more than 2 cm but not more than 5 cm** (2 inches) across.
- **T3:** Tumor is **more than 5 cm** across.
- **T4:** Tumor of any size growing into the chest wall or skin.

The TNM staging system

Nearby lymph nodes (N)

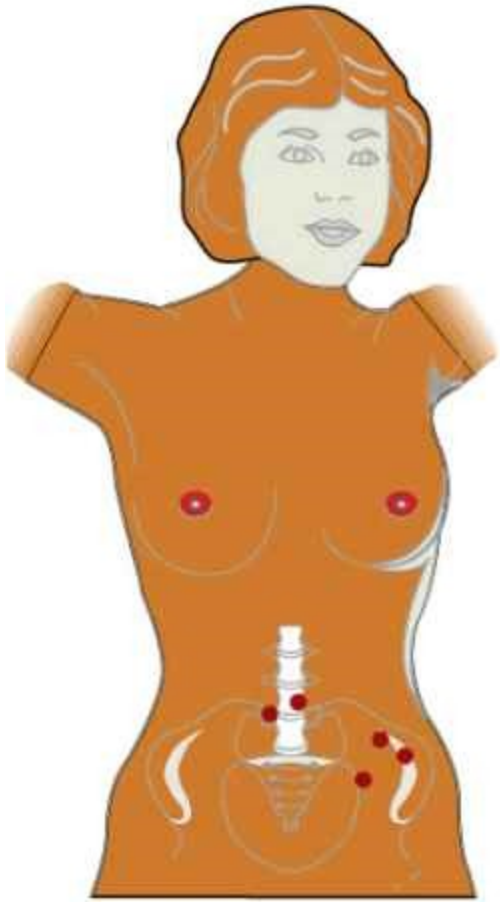
- **NX:** Nearby lymph nodes **cannot be assessed** (for example, removed previously).
- **N0:** Cancer has **not spread** to nearby lymph nodes.
- **N1:** Cancer has **spread to 1 to 3 axillary** (underarm) lymph node(s), and/or tiny amounts of cancer are found in internal mammary lymph nodes (near breast bone)
- **N2:** Cancer has **spread to** 4-9 axillary lymph nodes
- **N3:** >10 axillary lymph nodes



The TNM staging system

Metastasis (M)

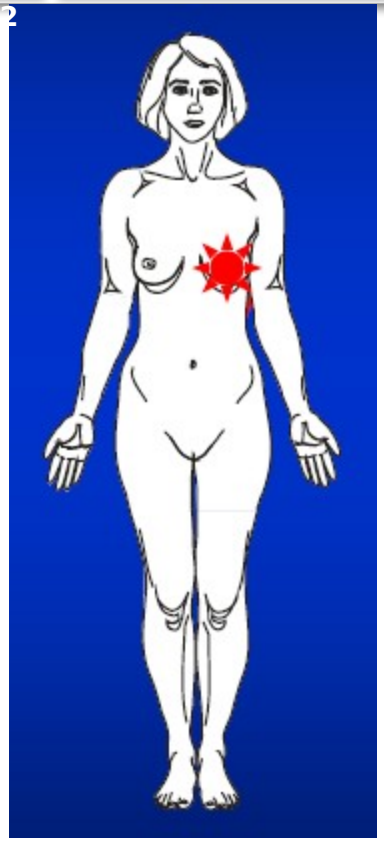
- **MX:** Presence of distant spread (metastasis) cannot be assessed.
- **M0:** No distant spread is found on x-rays (or other imaging procedures) or by physical exam.
- **M1:** Spread to distant organs is present. (The most common sites are **bone, lung, brain,** and **liver**.)



TNM Staging

0	Tis	N0	M0
IA	T1mi	N0	M0
IB	T0 or T1 mi	N1	M0
IIA	T0 or T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0 or T1 or T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

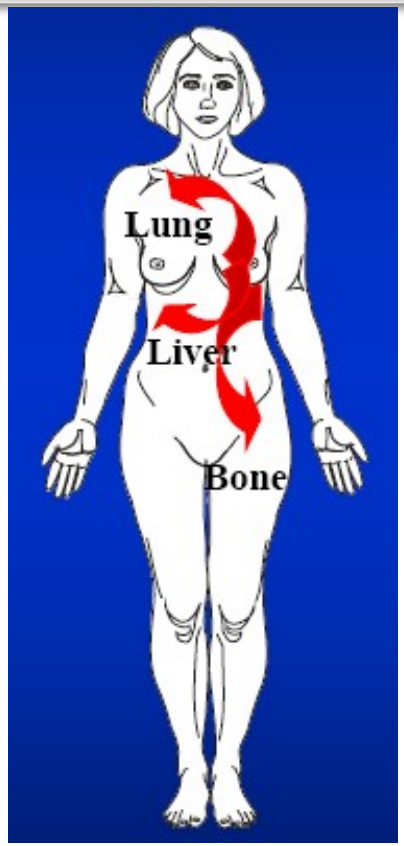
Breast Ca Treatment



Natural history

Therapy

- Surgery
- Radiation therapy
- Systemic therapy
  - ✓ Hormonal therapy
  - ✓ Chemotherapy
  - ✓ Biologic therapy

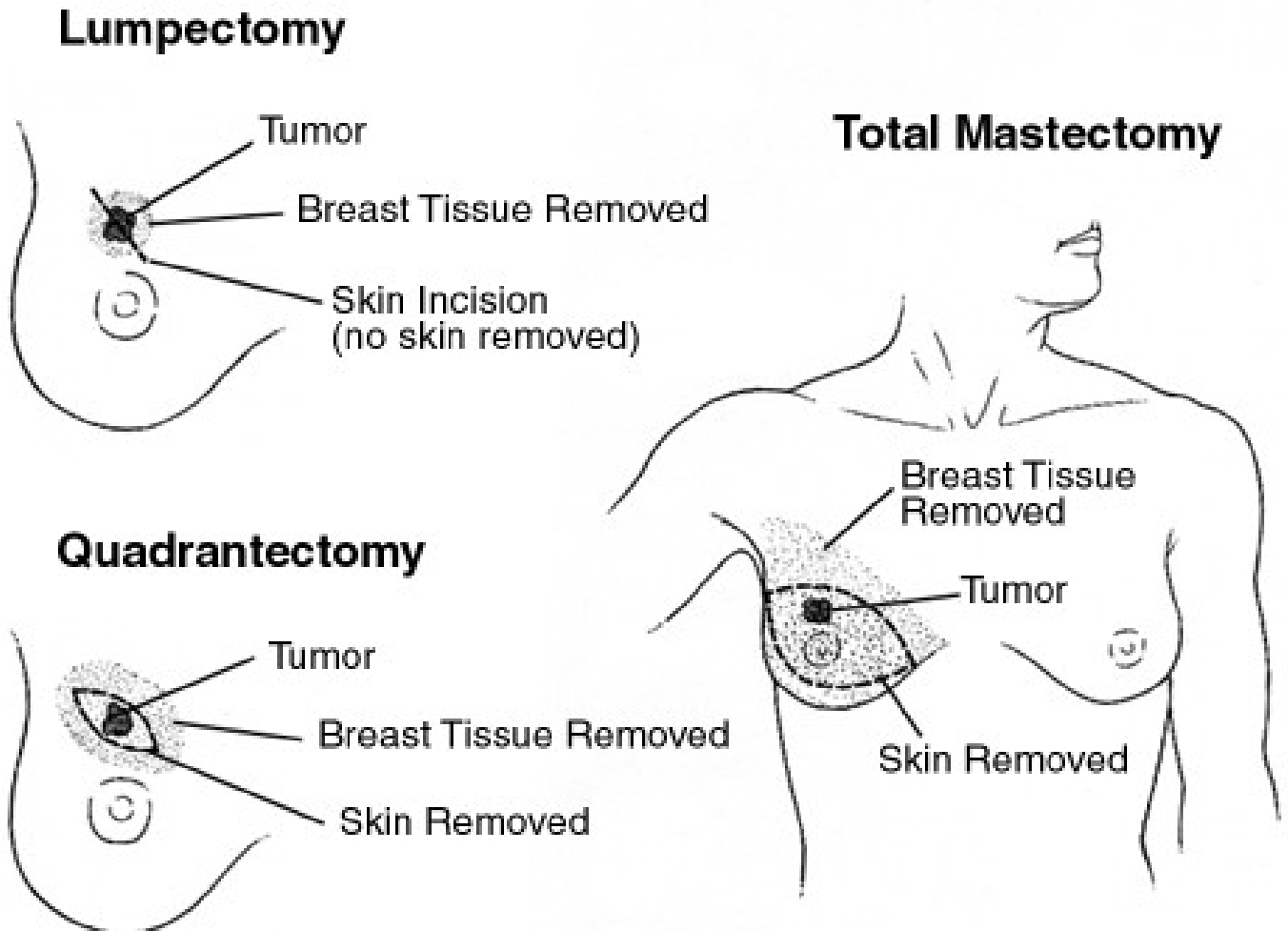


Localized disease
CURABLE

Metastatic disease
INCURABLE

Early Stage Breast Cancer (Stage I and II)

- **Lumpectomy**: Breast conservation (wide local excision
- **Mastectomy**: Remove the breast



Adjuvant Hormonal Therapy

- After surgery
- Block estrogen-related cell proliferation in breast cancer via blocking the oestrogen-receptor (ER) or inactivating estrogen-production
- Hormonal therapy with tamoxifen or aromatase inhibitor should only be considered in patients with ER positive tumours
- **Pre**-menopausal women, and **post**-menopausal women at **low-risk** should be offered tamoxifen
  - **Post-menopausal** women **not** considered to be at low-risk should be offered an aromatase inhibitor (anastrozole or letrozole)

Adjuvant Hormonal Therapy

- **Side effects of tamoxifen:**
  - Venous thromboembolism
  - Hot flushes, altered libido,
  - Gastrointestinal upset, weight gain
  - Vaginal discharge or dryness,
  - Menstrual disturbance,
  - Endometrial cancer (investigate any reported vaginal bleeding)
  - Decrease in bone mineral density in pre-menopausal women.
- **Side effects of aromatase inhibitors**
  - Hot flushes (less than tamoxifen),
  - Joint and muscle pains, osteoporosis, fatigue, vaginal dryness

Adjuvant Chemotherapy

- Combination chemotherapy with **anthracycline and taxane based regimens** improves survival
- Adjuvant **taxane** based regimens may improve disease-free survival over standard anthracycline-based therapy

Trastuzumab

- Monoclonal antibody; bind HER2; causes antibody-dependent cellular cytotoxicity
- Indicated in **HER2-positive** early invasive breast cancer
  - Given after surgery, chemotherapy, and radiotherapy
- Offered as an adjuvant treatment, given at **3-week intervals** for one year or until disease recurrence (whichever is the shorter)
- Cardiac side effects: mainly heart failure; not give in patients with CHF, LVEF <55%, uncontrolled arrhythmias or hypertension

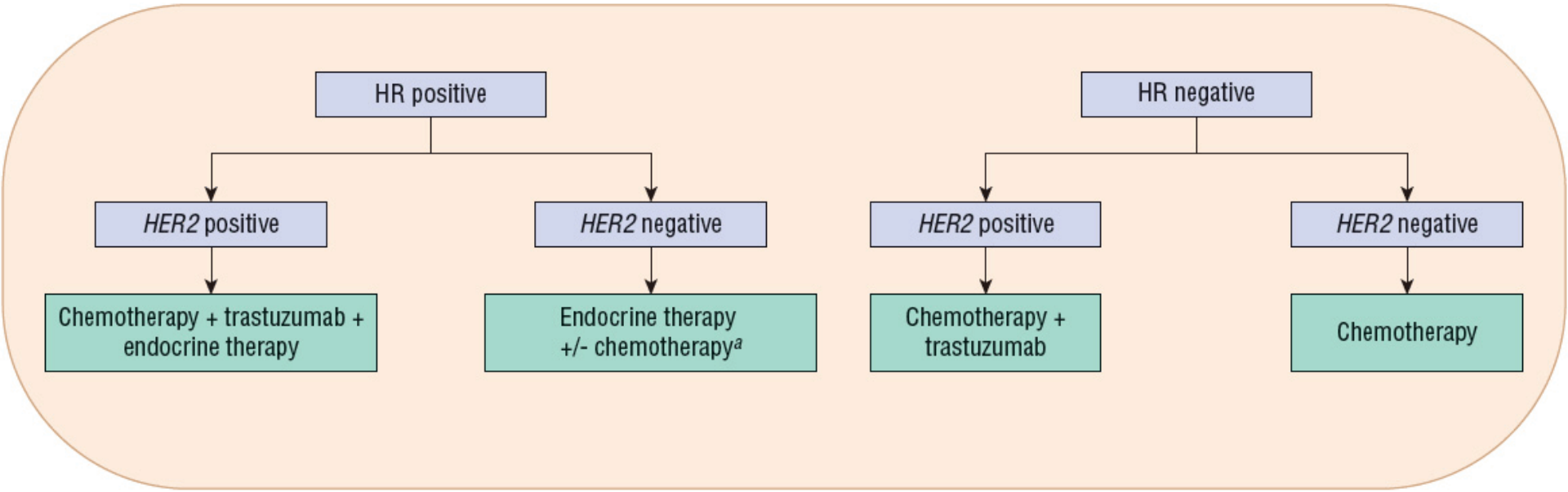
Adjuvant Chemotherapy Regimens

AC[b]	TC[a,c]
Doxorubicin 60 mg/m² IV, day 1 Cyclophosphamide 600 mg/m² IV, day 1 Repeat cycles every 21 days for 4 cycles	Docetaxel 75 mg/m² IV, day 1 Cyclophosphamide 600 mg/m² IV, day 1 Repeat cycles every 21 days for 4 cycles
FAC[d,m]	**TAC[a,e]**
Fluorouracil 500 mg/m² IV, days 1 and 4 Doxorubicin 50 mg/m² IV continuous infusion over 72 hours Cyclophosphamide 500 mg/m² IV, day 1 Repeat cycles every 21–28 days for 6 cycles	Docetaxel 75 mg/m² IV, day 1 Doxorubicin 50 mg/m² IV bolus, day 1 Cyclophosphamide 500 mg/m² IV, day 1 (doxorubicin should be given first) Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)
AC → Paclitaxel[a,j]	**Paclitaxel → FAC[g,m]**
Doxorubicin 60 mg/m² IV, day 1 Cyclophosphamide 600 mg/m² IV, day 1 Repeat cycles every 21 days for 4 cycles Followed by: Paclitaxel 80 mg/m² IV weekly Repeat cycles every 7 days for 12 cycles	Paclitaxel 80 mg/m² per week IV over 1 hour every week for 12 weeks Followed by: Fluorouracil 500 mg/m² IV, days 1 and 4 Doxorubicin 50 mg/m² IV continuous infusion over 72 hours Cyclophosphamide 500 mg/m² IV, day 1 Repeat cycles every 21–28 days for 4 cycles[o]
FEC[b]	**CEF[f]**
Fluorouracil 500 mg/m² IV, day 1 Epirubicin 100 mg/m² IV bolus, day 1 Cyclophosphamide 500 mg/m² IV, day 1 Repeat cycle every 21 days for 6 cycles	Cyclophosphamide 75 mg/m² per day orally on days 1–14 Epirubicin 60 mg/m² IV, days 1 and 8 Fluorouracil 600 mg/m² IV, days 1 and 8 Repeat cycles every 21 days for 6 cycles (requires prophylactic antibiotics or growth factor support)
CMF[i,k]	**Dose-Dense AC → Paclitaxel[a,l,n]**
Cyclophosphamide 100 mg/m² per day orally, days 1–14 Methotrexate 40 mg/m² IV, days 1 and 8 Fluorouracil 600 mg/m² IV, days 1 and 8 Repeat cycles every 28 days for 6 cycles *Or* Cyclophosphamide 600 mg/m² IV, day 1 Methotrexate 40 mg/m² IV, day 1 Fluorouracil 600 mg/m² IV, days 1 and 8 Repeat cycles every 21 days for 6 cycles	Doxorubicin 60 mg/m² IV bolus, day 1 Cyclophosphamide 600 mg/m² IV, day 1 Repeat cycles every 14 days for 4 cycles (must be given with growth factor support) Followed by: Paclitaxel 175 mg/m 2 IV over 3 hours Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)

Advanced Breast CA Treatment

- Hormonal Therapy
  - Tamoxifen, Aromatase Inhibitors
- Chemotherapy
  - Anthracyclines, Taxanes, Capecitabine, Vinorelbine, Gemcitabine
- Biological Therapy
  - Trastuzumab

Advanced Breast CA Treatment



Hormonal Therapies

- Are widely used for advanced breast cancer
  - Appropriate for approximately 70% of patients who have **ER-positive** disease.
- They have no role in **ER-negative** breast cancer.
- On **disease progression**, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy

Chemotherapy

- Chemotherapy regimens
  - CMF (Cyclophosphamide + Methotrexate + Fluorouracil)
  - AC (Doxorubicin + Cyclophosphamide)
  - CAF (Cyclophosphamide + Doxorubicin + Fluorouracil)
  - **Docetaxel**
  - Paclitaxel
- For patients not suitable for anthracyclines
  - First-line: single-agent **docetaxel**
  - Second-line: single-agent **vinorelbine** or **capecitabine**

Neoadjuvant chemotherapy

- Standard primary chemotherapy for locally advanced breast cancer (LABC)
  - Should include an **anthracycline** (FEC, AC, CAF)
    - FEC (fluorouracil + epirubicin + cyclophosphamide)
- Optimal duration is unknown but usually 4 -8 cycles

Metastatic Breast Cancer

- Nearly **50% of newly diagnosed** patients may eventually develop metastatic breast cancer
- Metastatic breast cancer is associated with a poor prognosis
  - Median survival is **2.7 years** from the onset of symptoms
- Mortality rates may decrease if there is increased awareness, early detection through screening, and improved treatment

Chemotherapy Metastatic Breast Ca

Single-agent chemotherapy	Combination chemotherapy
•Doxorubicin •Epirubicin •Paclitaxel ** •Docetaxel ** •Capecitabine ** •Vinorelbine	•CAF •AC •FEC •CMF •EC (epirubicin + cyclophosphamide) •AT (doxorubicin + docetaxel/paclitaxel) •CapeT (Docetaxel + capecitabine) ** •GT (gemcitabine + paclitaxel) ** •Paclitaxel + bevacizumab

** approved by the FDA

COLORECTAL CANCER

Colorectal Cancer (CRC)

- In 2019,
  - an estimated 145,600 new cases
  - An estimated 51,020 deaths

Colorectal Cancer (CRC)

- Colorectal cancer (CRC) starts in the **colon** or **rectum**
- Can be referred separately as **colon cancer** or **rectal cancer**, depending on where they start.
- CRC is the **3rd most common** form of cancer diagnosed in men and women in the US
- 90% of cases occurs after age 50
- Average lifetime risk for developing this cancer is 6%
- Men and women are affected equally
- African Americans & Hispanics have lower survival rate

CRC

- **Screening for/removing polyps** early is the best way to prevent and cure CRC
- Most colorectal cancers develop slowly over several years
- Before cancer develops, growth of tissue/tumor begins as non-cancerous **polyp** on the inner lining of colon/rectum
- Some polyps can change into cancer but not all do; chance of changing into a cancer depends upon the kind of polyp
- Pre-cancerous polyps

Risk Factors

- Age >50 yrs
- Dietary factors: High animal fat, low fiber diet
- IBD: Chronic ulcerative colitis and Crohn's disease
- Familial adenomatous polyposis (FAP)
- Family history
  - Colorectal adenomas, Colorectal cancer
- Personal history of
  - Colorectal adenomas, Ureterosigmoidostomy, Breast, Ovarian and Uterine cancers
- Racial, ethnic factors
  - African-Americans have increased risk
- Lifestyle: sedentary, obesity, smoking, alcohol
- Fruits & vegetables, exercise, folic acid, aspirin/NSAIDs, Calcium, vitamin D, screening: decrease risk

Screening

- Regular colorectal cancer screening is
  - One of **the most powerful weapons** for preventing colorectal cancer.
  - This is because **most polyps can be found** & **removed** before they have the chance to turn into cancer
  - It usually takes about **10 to 15 years** for polyps to develop into colorectal cancer
- Screening can also result in finding colorectal cancer early, when it is highly curable.
- CRC is **highly curable** when diagnosed at an early stage with 90% 5-year survival

Screening

- CRC screening should begin at **age 50**
- Start screening at a younger age and/or do more frequently screening is for those who have
  - A **family history** or **other risk factors** for colorectal polyps or cancer, such as inflammatory bowel disease
  - African-Americans need earlier screening starting at age 45
- Screening Tests that find polyps and cancer
  - Flexible sigmoidoscopy every 5 years
  - Colonoscopy every 10 years (Gold standard)
  - Double-contrast barium enema every 5 years
  - CT colonography (virtual colonoscopy) every 5 years
  - Fecal occult blood test (FOBT) every year
  - Fecal immunochemical test (FIT) every year

Clinical Manifestations

- Abdominal pain: 44%
- Change in bowel habit: 43%
- Hematochezia or melena: 40%
  - Passage of stools containing blood
- Weakness: 20%
- Anemia: 11%
- Weight loss: 6%
- 15 to 20% of patients have
  - **Distant metastatic** disease at the time of presentation
- 80% present with early disease

Stages of CRC

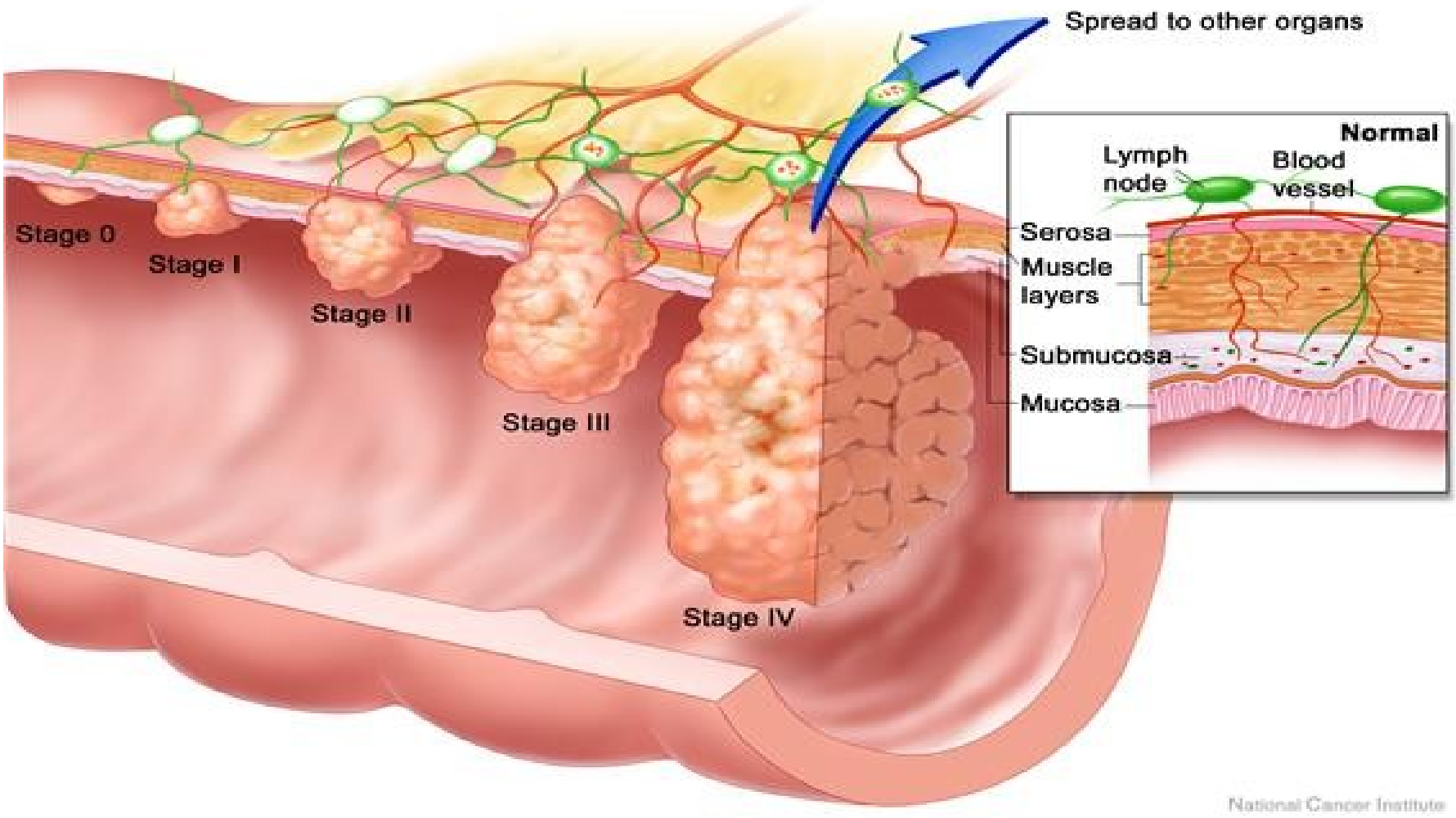
Three elements:

- **T = Tumor**
  - How large is the tumor?
- **N = Node**
  - Are cancer cells in the lymph nodes?
- **M = Metastases**
  - Has the cancer spread to other organs?

Four stages:

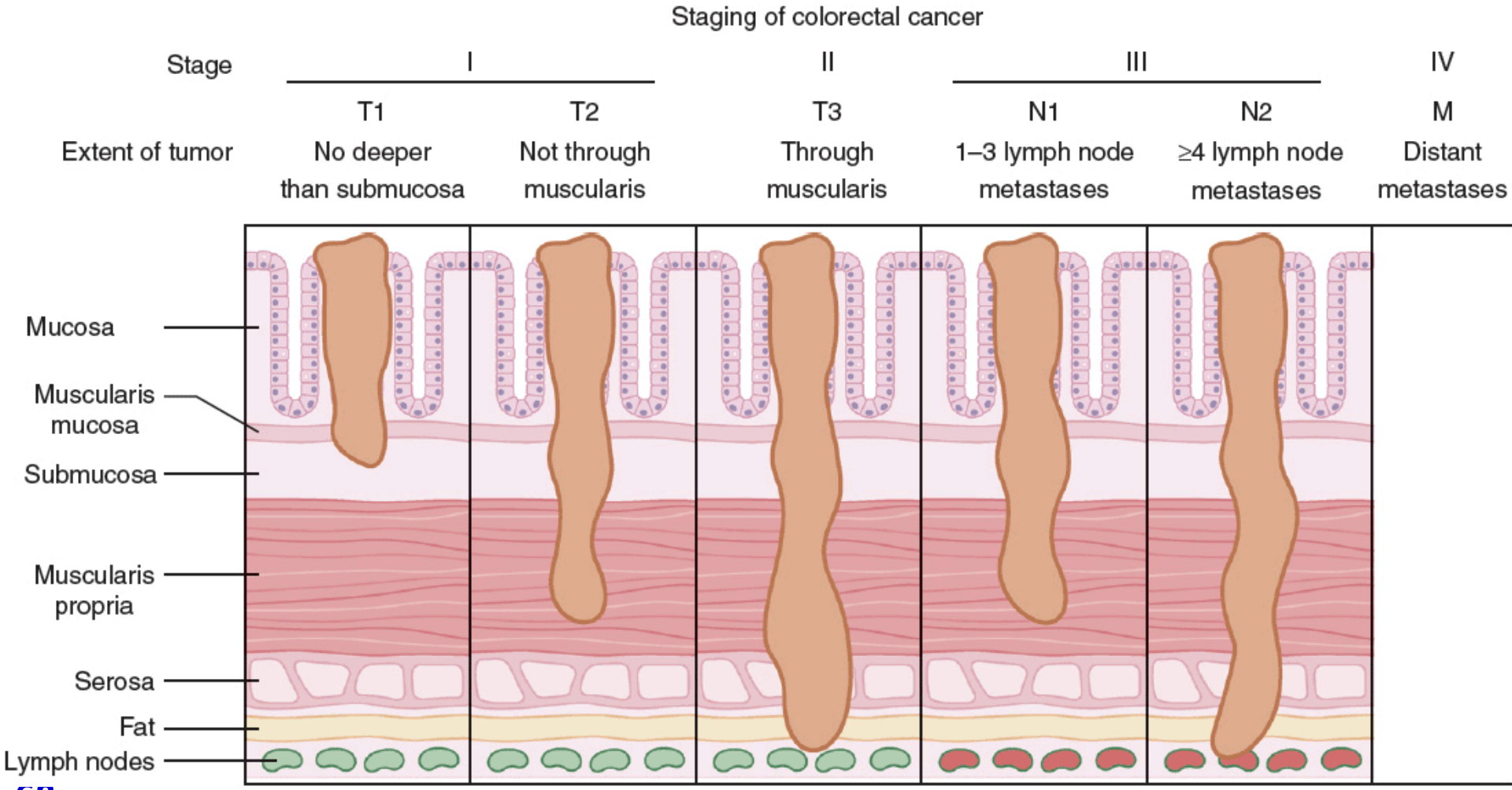
- **Stage I**
  - Spread to the middle layers of the colon or rectum
- **Stage II**
- **Stage III**
- **Stage IV**: Advanced disease, spread to other organs

Stages of CRC



Stages of CRC

686



Diagnostic Tests

- Barium enema (BE)
- Sigmoidoscopy,
- Colonoscopy (or colon endoscopy):
- Computed tomography (CT):
- Transrectal ultrasound (TRUS):
- Magnetic resonance imaging (MRI):
- Laparotomy (surgical incision of abdomen):

Treatment of CRC

- Operable Disease (Stages I–III)
  - Surgery
    - Stages I, II, and III—cancer
    - Laparoscopy/open surgical resection
    - Colostomy: temporary or permanent
  - Adjuvant Therapy
  - Radiation Therapy
    - Rectal Ca
- Metastatic Disease (Stage IV)
  - Chemotherapy

Drugs Used to Treat CRC

- Several drugs can be used to treat colorectal cancer.
  - Often, 2 or more drugs are combined to increase effectiveness
- The drugs most often used for colorectal cancer include:
  - **5-Fluorouracil (5-FU), given with leucovorin**
  - **Irinotecan**
  - **Oxaliplatin**

Targeted Therapies/Biologic Agents

- Targeted therapies work through specific pathways involved in cancer growth to attack cancer cells directly
  - EGFR inhibitors (Cetuximab and Panitumumab)
  - VEGFR inhibitors (Bevacizumab)
- Targeted therapies cause fewer side-effects since they attack cancer cells more specifically
- **Bevacizumab**: it is angiogenesis inhibitor (inhibit VEGF that stimulates new blood vessel formation)

Adjuvant Chemotherapy

Stage II		Stage III	
High Risk	**Low Risk**	**Good Performance status**	**Poor performance status**
Capecitabine or 5-FU plus leucovorin	Observation or clinical trial	**FOLFOX**	Capecitabine
FOLFOX	Capecitabine or 5-FU plus leucovorin	CapeOX	
CapeOx		FLOX	
FLOX		Capecitabine or 5-FU plus leucovorin	

Chemotherapy for Metastatic Colon

Good performance status
FOLFOX or FOLFIRI with bevacizumab
FOLFOX or FOLFIRI with cetuximab or panitumumab
FOLFOXIRI with or without bevacizumab
5-FU + leucovorin or capecitabine with or without bevacizumab
Poor Performance Status
Capecitabine or 5-FU plus leucovorin with or without bevacizumab

PROSTATE CANCER

Prostate cancer

- Prostate cancer is the most frequent cancer in men in the US
  - **238,590** new cases of prostatic carcinoma in 2013
    - 174,650 new cases in **2019**
  - **29,720** men died from this disease in 2013
    - 31,620 men died in **2019**
- **Second leading cause** of cancer related **deaths** among men in the US but the sixth common cause in the world
- **1 out of 6** men has a chance of developing prostate cancer in his lifetime
- Majority of cases occur after age 65

Diseases of the Prostate

1. **Prostate cancer**
   - Malignant growth of prostate cells, localised and may spread
   - Nearly all prostate cancers are **adenocarcinomas**, mainly occurring in peripheral zone of prostate gland
   - **Rare in men under 50**, and is more common with increasing age
2. **Benign prostatic hyperplasia**
   - **Non-malignant** increase in size of prostate with age
   - Rare in men under 50
3. **Prostatitis**: inflammation of the prostate
   - Can occur in men of any age

Risk factors

Risk factors	Possible relationship
Age	More than **70%** of cases are diagnosed in men older than **65** years
Race	**African Americans** have higher incidence and death rate
Genetic	Familial prostate cancer (inherited)
Occupational	Increased risk associated with **high-meat** and **high-fat** diets Increased risk associated with **cadmium** exposure Decreased intake of **1,25-dihydroxyvitamin D**, **Vitamin E**, **lycopene**, and **β-carotene** increases risk
Hormone	Does not occur in **eunuchs** Low incidence in **cirrhotic** patients. Up to 80% are hormonally dependent. **African Americans** have 15% increased testosterone

Clinical Features of Prostate Ca

- Prostate cancers (unlike BPH) tend to develop in the outer part of the prostate gland
- If the tumour is large enough:
  - It can cause lower urinary tract symptoms (LUTS)
    - Frequency, urgency, hesitancy, leaking
  - by the time this happens the cancer will usually have reached an advanced stage
- In about 20–30% of cases:
  - The first sign of prostate cancer arises from **metastases**,
  - For example, in patients with bone metastases who may present with bone pain.

Screening and Diagnosing Prostate Ca

- Digital Rectal Exam (“DRE”)
- Prostate Specific Antigen (“PSA”) blood test
- **Screening** (DRE, PSA) is recommended:
  - Annually for men 50+ years
  - At age **40 for higher risk patients**
    - African-American
    - Family history of prostate ca

Screening and Diagnosis

- Prostate cancer is usually detected by:
  - An elevated serum PSA & is asymptomatic at presentation
  - PSA >10 ng/mL – Prostate biopsy is uniformly recommended; 50% probability of cancer
  - PSA 4 to 10 ng/mL – Prostate biopsy is advised. Specificity is lower, 20% probability of cancer
  - PSA > **2.6 ng/mL** & if PSA velocity is **≥ 0.75 ng/mL per year** – Prostate biopsy is advised
  - PSA velocity **>2 ng/ml per year** is high risk for life threatening cancer

Screening and Diagnosis

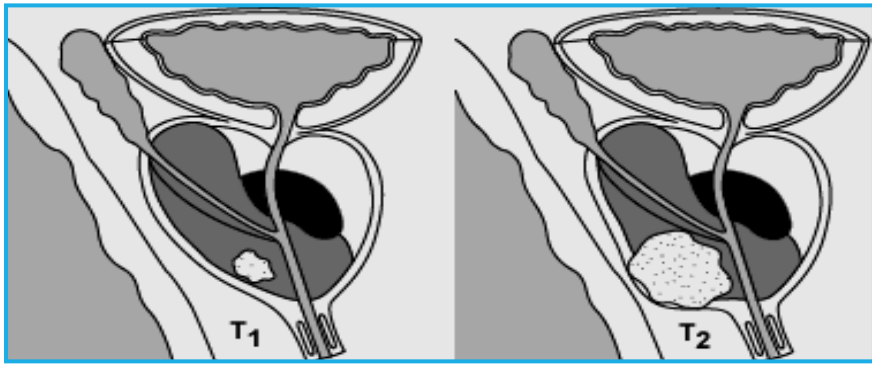
- If PSA or DRE is abnormal
  - **Additional tests** may be done to confirm presence of cancer:
    - Imaging of the prostate (ultrasound, MRI, CT)
    - Needle **biopsy**
- **Prostate biopsy** is the gold standard for diagnosis
- Transrectal ultrasonography (**TRUS**) biopsy is a relatively simple procedure done in the office
- Bone scan findings

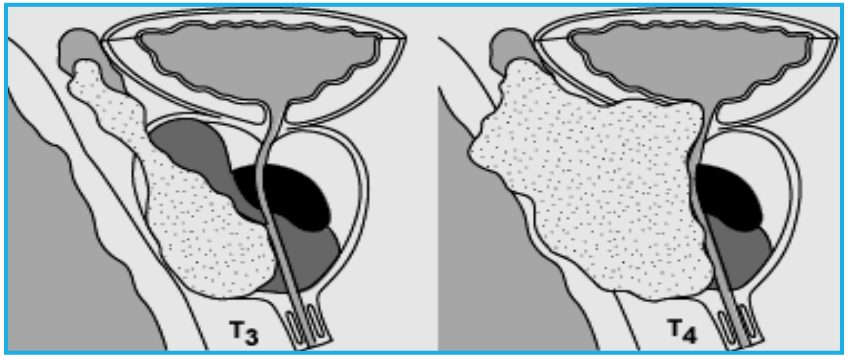
Testosterone Influence on Prostate Ca

- In preclinical models
  - Stimulates the growth of PC cells
- In clinical studies
  - Correlates with ↑ PAP
  - Correlates with ↑ PSA
  - Correlates with ↑ symptom flare
- FDA accepts T as surrogate endpoint for PC treatment

TNM Classification (T)

- **TX**: Primary tumor cannot be assessed
- **T1**: Clinically inapparent **tumor–not palpable** or **visible** by imaging
- **T2**: Palpable tumor confined within the prostate
- **T3**: Palpable tumor extending through prostate capsule and/or seminal vesicle(s)
- **T4**: Tumor is fixed or invades adjacent structures other than the seminal vesicles





TNM Classification (NM)

- Nodal Involvement (N)
  - **Nx**: Regional LN cannot be assessed
  - **N0**: No regional LN metastasis
  - **N1**: Cancer has spread to 1 LN
- Metastasis (M)
  - **MX**: Presence of distant metastases cannot be assessed
  - **M0**: No distant metastasis
  - **M1**: Distant metastasis

TNM Staging

Stage I	$T_{1a}N_0M_0$
Stage II	$T_{1a}N_0M_0$ $T_{1b/c}N_0M_0$ $T_2N_0M_0$
Stage III	$T_3N_0M_0$
Stage IV	$T_4N_0M_0$ $T_{any}N_1M_0$ $T_{any}N_{any}M_1$

AJCC Cancer Staging Manual, 5th edition, 199

Treatment Options

1. Watchful waiting
2. Surgery
3. External beam radiation therapy
4. Hormone therapy
5. Brachytherapy (seed implantation)
6. Combination Therapy

Treatment of Prostate Ca

Watchful waiting

- **May be used for slow-growing tumors or elderly patients**
- Requires frequent check-ups on progress of tumor

Surgery (Radical Prostatectomy)

- **Involves removal of entire prostate gland and surrounding tissue**
- Can be very effective if cancer is **confined to gland**
- Side effects include possible impotence and incontinence

Treatment of Prostate Ca

External Beam Radiation

- Uses radiation (x-ray) to destroy cancer cells
- A common treatment technique in **early cancers**
- **Requires daily treatment for 8-9 weeks**
- Side effects may include:
  - Incontinence: Urinary or rectal problems
  - Skin irritation
  - Impotence
  - Fatigue and bowel irritation

Treatment of Prostate Ca

Hormone Therapy

- It lowers level of male hormones (androgens) to shrink gland and slow tumor growth
- Sometimes used in combination with other therapies
- **A treatment but not a “cure”**

Brachytherapy

- Implantation of radioactive “seeds” directly into the prostate gland
- Seeds deliver high-dose radiation directly to the site of the cancer
- **Seeds release radiation over 3-9 months**

Treatment of Prostate Ca

For localised cancer:

- Active surveillance is one of the options; this involves
  - Regular monitoring of patients with the option for radical treatment should the cancer progress
- Other preferred options are
  - Prostatectomy
  - External beam radiotherapy
  - Brachytherapy

Treatment of Prostate Ca

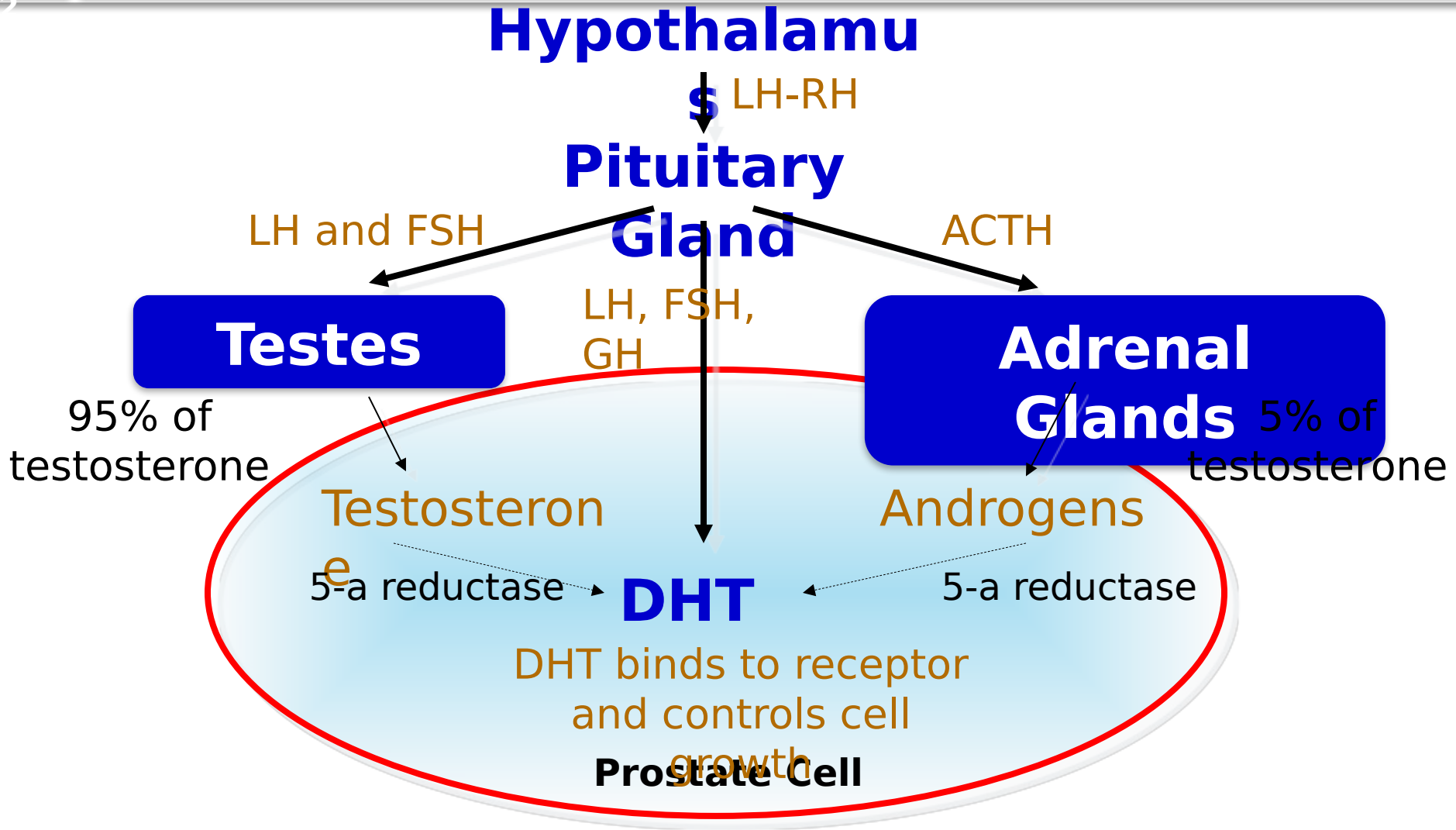
Metastatic Cancer:

- **Androgen deprivation** therapy is
  - The primary option for metastatic cancer
  - Can be considered as an **adjuvant** to radiotherapy.
- **Chemotherapy**,
  - **Docetaxe**l plus **prednisolone**, can be offered for hormone refractory cancer.
- **Bisphosphonates**
  - For bone pain in patients with advanced cancer,
  - But evidence is insufficient to recommend their routine use

Androgen Deprivation Therapy

- Prostate cells are physiologically dependent on
  - Androgens (mainly **testosterone**) to
    - **Stimulate growth**, **function and proliferation**
- The **testes** are the **source of**
  - **90–95% of androgens** (5–10% from **adrenal glands**)
- If prostate cells are deprived of androgenic stimulation
  - They undergo apoptosis (programmed cell death)
- **Androgen deprivation therapy (ADT**) is thus the main therapy for PC

Hormonal Regulation of the Prostate Gland



Androgen Deprivation Therapy

- Can be achieved by
  - **Suppressing** secretion of the **testicular** androgens.
    - This is obtained by
      - **Castration,**
      - **LHRH agonists**
  - **By inhibiting** the action of circulating androgens
    - Anti-androgens

Methods Used for Androgen Depletion

	Advantages	Disadvantages
Orchiectomy (surgical castration)	✓ Low cost in long term ✓ No other treatment is more effective	✓ Irreversible. ✓ Unacceptable to some men ✓ Leads to loss of libido and symptoms similar to the female menopause (eg hot flushes, osteoporosis)
LHRH agonists (medical castration) E.g. goserelin	✓ Reversible. ✓ Probably as effective as orchiectomy	✓ Side effects similar to those of surgery, but wider range of symptoms. ✓ **Initial** stimulation of

Methods Used for Androgen Depletion

	Advantages	Disadvantages
Anti-androgens Eg bicalutamide, flutamide, cyproterone	✓ Can be used with LHRH agonists to reduce tumour flare ✓ Can be used alone in certain circumstances. ✓ Side effects may be less severe than	✓ May be less effective than surgery or LHRH agonists, when used alone. ✓ Common side effects include gynaecomastia (breast pain and swelling) and risk of liver damage

Hormone Refractory Prostate Carcinoma

- Definition**:**
  - Disease progression despite castrate serum levels of testosterone
- Progression is defined by:
  - Increase in **size** of measurable lesions
  - Appearance of **new** measurable **lesions**
  - Increase in **PSA >50%** on at least 2 consecutive measurements
  - Increase **in pain** associated with new **bony lesions**
- Median survival approximately 1 year

Chemotherapy for Hormone-Resistant Cancer

- Chemotherapy drugs for prostate cancer include
  - Docetaxel, Mitoxantrone, Estramustine and
  - Platinum-based drugs: Carboplatin.
- These drugs are often combined with other cancer drugs such as 5-fluorouacil or corticosteroids (prednisone)
- FDA approved **docetaxel** in combination with **prednisone** for treatment of hormone-resistant prostate cancer
- Side effects may include: GI problems (NVD)

Skeletal Related Events (SRE)

- SREs include microfractures, new pain, and need for radiation therapy
- **Zoledronic acid**
  - Potent bisphosphonate given IV every 3-4 weeks
  - **Inhibits osteoclasts**
  - 35% reduction in SREs
  - Side-effects: nephrotoxicity, flu-like symptoms
- **Denosumab**
  - Monoclonal antibody (**osteoclast inhibitor**) given SQ every 3-4 weeks
  - Slightly better reduction in SREs than Zoledronic acid
  - Side-effects: hypocalcemia
- Both FDA-approved for castrate-resistant, bone metastasis

LEUKEMIA

INTRODUCTION TO LEUKEMIA

- Leukemia is a malignant disease characterized by unregulated proliferation of blood cell.
  - It may involve any of the cell lines or a stem cell common to several cell lines
- Leukemia is classified into 2 major groups:
  - **Chronic:** Insidious, less aggressive, and the cells involved are more **mature cells**
  - **Acute**: rapid, aggressive, and poorly differentiated cells with many blasts.

INTRODUCTION TO LEUKEMIA

Comparison of acute and chronic leukemia:

	Acute	Chronic
Age	All ages	Usually adults
Clinical onset	Sudden	Insidious (gradual)
Course (untreated)	6 mon or less	2 – 6 years
Leukemic cells	Immature, >30% blasts	More mature cells
Anemia	Prominent	Mild
Thrombocytopenia	Prominent	Mild
WBC count	Variable	Increased
Lymphadenopathy	Mild	Present; often prominent
Splenomegaly	Mild	Present; often

ACUTE LEUKEMIA

- It is characterized by a **rapid increase** in the number of **immature blood** cells.
- Crowding due to such cells makes the
  - Bone marrow **unable to produce healthy** blood cells.
- **Immediate treatment** is required in acute leukemia due to
  - The **rapid progression** and accumulation of the malignant cells, which then **spill over into the bloodstream** and **spread to other organs** of the body.

CHRONIC LEUKEMIA

- Is characterized by
  - The excessive buildup of **relatively mature**, but
  - Still abnormal, white blood cells
- Takes
  - **Months or years** to progress,
  - Resulting in many abnormal white blood cells.
- Treatment: watchful monitoring for some time
- Chronic leukemia mostly occurs in
  - **Older people,** but can theoretically occur in

INTRODUCTION

- When people develop leukemia, their abnormal **WBC's crowd out** the functioning of the RBC's, fostering the **tiredness** & **paleness** that are the hallmarks of anemia.
- These white blood cells also **do not effectively fight infections**, which can be fatal.
- A lack of functioning cells (platelets): people with leukemia prone to life-threatening bleeding episodes.
- Other symptoms include bone or joint pain, or enlarged organs.
- Untreated leukemia progresses rapidly to death

Epidemiology and Etiology

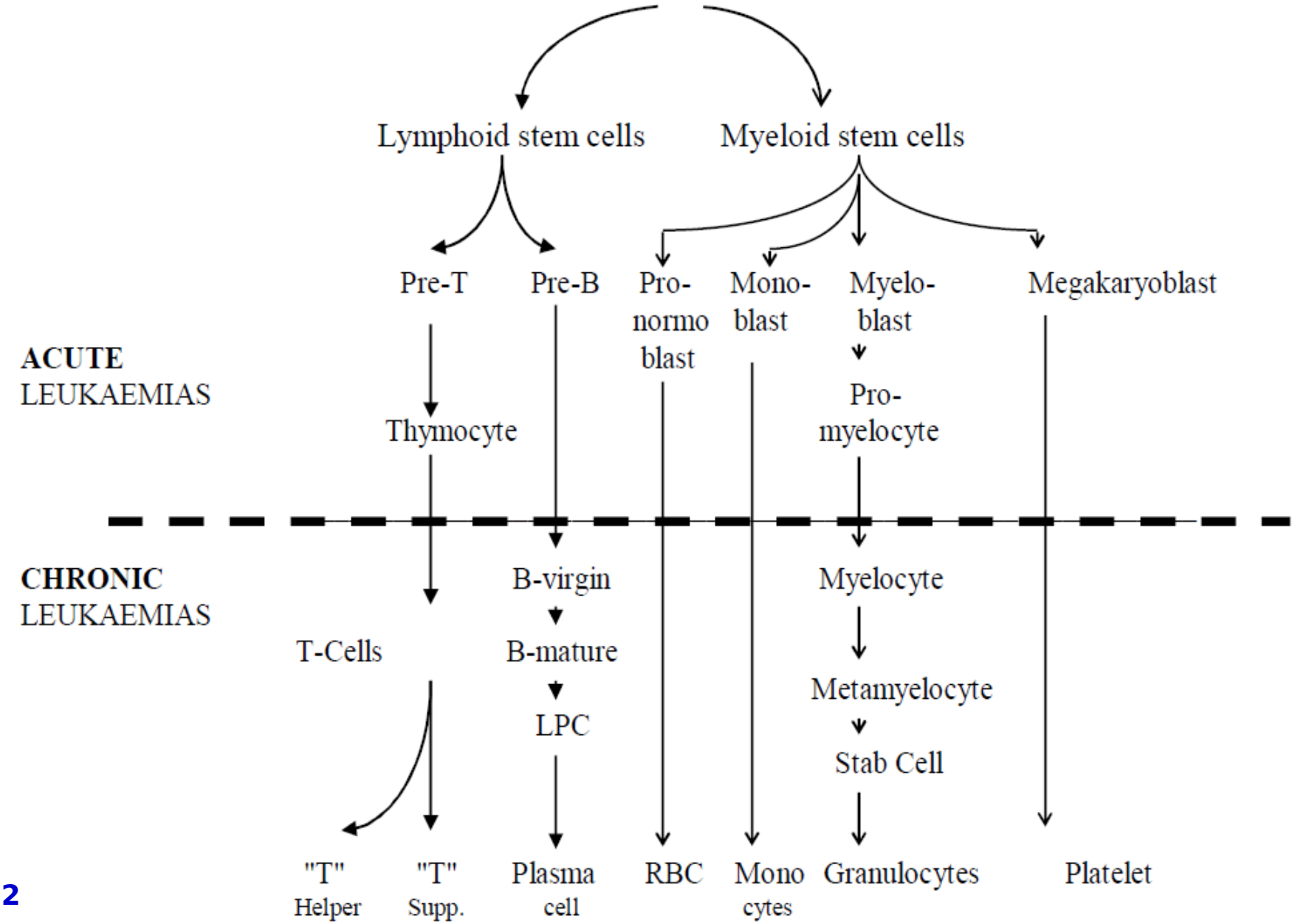
- Among cancer death, 3%; among all death, 0.35%.
- Among children with some form of cancer, about **a third** have acute lymphoblastic leukemia-ALL
- Boys are **more likely to develop** leukemia than girls, and
- **White American children** are almost **twice** as likely to develop leukemia than black American children

□ **Etiology**: predisposing factors can be predicted

- Host factors: Genetics
- Environmental factors:
  - ✓ Exposure to ionizing radiation, mutagenic chemicals and drugs; Viral infections

CLASSIFICATION

- According to which kind of blood cell is affected or the prominent cell line involved in the expansion
- This split divides leukemia into:
  - **Lymphocytic Leukemia:**
    - Leukemia of infection-fighting immune system cells such as **lymphocyte, the B cell**
    - The prominent cell line is of the **lymphoid** series
  - **Myeloid Leukemia:**


Lymphoid stem cells
Myeloid stem cells
Pre-T
Pre-B
Pro-
normo
blast
Mono-
blast
Myelo-
blast
Megakaryoblast
ACUTE
LEUKAEMIAS
Thymocyte
Pro-
myelocyte
CHRONIC
LEUKAEMIAS
B-virgin
Myelocyte
T-Cells
B-mature
Metamyelocyte
LPC
Stab Cell
"T"
Helper
"T"
Supp.
Plasma
cell
RBC
Mono
cytes
Granulocytes
Platelet

Four Basic Types of Leukemia

1. **Acute Myelocytic Leukemia – AML**
2. **Acute Lymphocytic Leukemia – ALL**
3. **Chronic Myelocytic Leukemia – CML**
4. **Chronic Lymphocytic Leukemia – CLL**

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- Estimated new cases of ALL (2011): 5,730
  - With 1,420 deaths
- Is the most common type of leukemia in
  - Young children.
- This disease also affects
  - Adults, especially those age 65 and older.
- Standard treatments involve
  - Chemotherapy and radiotherapy.
- The five-year survival rates vary by age
  - 85% in children and 50% in adults

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- Estimated new cases of CLL (2011): 14,570
  - With 4,380 deaths
- Most often affects
  - Adults over the age of 55
  - It sometimes occurs in younger adults, but it **almost never affects children.**
- **Two-thirds** of affected people are **men.**
- The **five-year** survival rate is 75%.
  - It is **incurable**, but has **many effective treatments**.

ACUTE MYELOID LEUKEMIA (AML)

- Estimated new cases of AML (2011): 12,950
  - With 9,050 deaths
- Occurs more commonly in
  - Adults than in children, and
  - More commonly in **men** than women.
- It is treated with chemotherapy.
- The five-year survival rate is 40%.

CHRONIC MYELOID LEUKEMIA (CML)

- Estimated new cases in 2011: 5,150
  - With 270 deaths
- Occurs mainly in adults;
  - A very small number of children also develop this disease.
- Treatment is with
  - Imatinib
  - The five-year survival rate is 90%.
- Imatinib - Tyrosine Kinase Inhibitor
  - The enzyme in abnormal gene (Philadelphia chromosome positive CML patients)

LEUKEMIA SIGNS AND SYMPTOMS

- **Thrombocytopenia**
  - May easily become bruised, bleed excessively, or develop pinprick bleeds (petechiae)
- **Frequent infections: m**any but dysfunctional WBC
- **Anemia**
- Other symptoms
  - Having fevers, chills, night sweats
  - Nausea or **a feeling of fullness** due to **enlarged liver and spleen**; this can result unintentional weight loss
- If the leukemic cells invade the CNS:
  - Neurological symptoms (**headaches**) can occur

DIAGNOSIS

- Is based on repeated
  - **CBC** and a **bone marrow examination** following observations of the symptoms;
  - **Blood tests:** done but may not show leukemia in the early stages or has entered remission.
  - **A lymph node biopsy**
- **Blood chemistry tests** done
  - To determine the degree of liver and kidney damage or the effects of chemotherapy on the patient.
- Many people: Up to one-fifth
  - Undiagnosed: because the symptoms are vague in some patients

LEUKEMIA TREATMENT

- There are **five general** types of therapy
  - Chemotherapy: usually a combination of drugs
  - Radiotherapy
  - Bone marrow transplant
  - Immunotherapy
    - Stimulate the patients **own immune system** to mount a response against the malignant cells
  - Monoclonal antibodies

ALL: TREATMENT

ALL treatment is divided into phases:

- **Induction chemotherapy**
  - Is used to bring about bone marrow **remission.**
- **Consolidation or intensification therapy** is to
  - Used to **eliminate** any **remaining leukemia cells.**
- **Maintenance treatments** is to
  - **Prevent disease recurrence** once remission has been achieved.

ALL risk groups

Low-risk ALL

- Age 1 and 10
- <50,000 white blood cells/mm3
- Leukemia cells with chromosome changes that respond well to treatment.
  - Translocation of chromosome 12 and 21 or three copies of chromosomes 4, 10 and 17.
- No leukemic cells in the cerebrospinal fluid (CSF), (negative CNS status)
- A good response to the first phase of chemotherapy (induction).

ALL risk groups

High-risk ALL

- Less than age one or older than ten years of age
- >50,000 white blood cells/mm3
- A large amount of leukemic cells in the spinal fluid (positive CNS status)
- Leukemia cells with chromosome changes that are more difficult to treat.
  - In these cells, a part of one chromosome breaks, and fuses to a gene on another chromosome involved in leukemia, called MLL.
  - This is called an MLL (mixed lineage leukemia) gene rearrangement.
- For example, a child with ALL who is 12 years old but has a white blood cell count less than 50,000/mm3 at diagnosis will be considered high risk.

ALL risk groups

Very high-risk ALL

- Chromosome changes inside leukemia cells.
  - Leukemia cells that have parts of chromosome 9 and chromosome 22 fused together.

  ↳This is called a **Philadelphia chromosome.**
- Leukemia cells which have too few chromosomes (hypodiploid)

Standard risk ALL

- Does not share any features with the low-risk or high-risk groups.

ALL Treatment: Induction Therapy

- For adults, standard induction plans include
  - **Prednisone, Vincristine,** and an **Anthracycline** drug;
- Other Drug Plans may Include
  - **L-asparaginase** Or **Cyclophosphamide**.
- **For children** with **low-risk** ALL
  - standard therapy usually consists of **three drugs**
  - Prednisone, L-asparaginase, and Vincristine
    - Given for the first month of treatment.

ALL Treatment: Consolidation

- Many different approaches to consolidation are available, but
  - It is typically a **high-dose**, **multidrug** treatment undertaken **for a few months**.
- Patients with low- to average-risk ALL receive therapy with
  - **Antimetabolite** drugs, such as
    - **Methotrexate** and **6-mercaptopurine** (6-MP).
  - High-risk patients receive higher doses of these drugs, plus additional drugs.

ALL: Maintenance therapy

- Maintenance therapy usually involves
  - lower drug doses, and may continue for up to 3 yrs.
- Alternatively
  - **bone marrow transplantation** may be appropriate for high-risk or relapsed patients
- CNS prophylaxis is used to
  - stop the cancer from spreading to the brain and nervous system in high-risk patients.
  - This includes **radiation** of the head and/or **drugs delivered** directly into the spine.
    - Prophylactic cranial irradiation; or intrathecal chemotherapy like MTX, Cytarabine

ALL treatment

Induction	Cyclophosphamide 1200 mg/m2 IV x 1 day 1
(Course I)	Daunorubicin 45 mg/m2/day IV day 1,2,3
	Vincristine 2 mg IV on day 1,8,15,22
	Prednisone 60 mg/m2 po days 1 –21
	L-asparaginase 6000 IU/m2 SQ /IM day 5,8,11,15,18,22
Early Intensification	Methotrexate 15 mg IT day 1
(Course IIA)	Cyclophosphamide 1000 mg/m2 IV x 1 day 1
	6 mercaptopurine 60 mg/m2 po day 1-14
	Cytarabine 75 mg/m2 SQ days 1-4, 8-11
	Vincristine 2 mg IV day 15, 22
	L-asparaginase 6000 IU/m2 SQ /IM day

ALL treatment

Early Intensification Continuation	Methotrexate 15 mg IT day 1
(Course IIB)	Cyclophosphamide 1000 mg/m2 IV day 1
	6 mercaptopurine 60 mg/m2 po day 1-14
	Cytarabine 75 mg/m2 SQ day 1-4, 8-11
	Vincristine 2 mg IV day 15, 22
CNS Prophylaxis and Interim Maintenance	Cranial XRT 2400 cGy day 1-12
(Course III)	Methotrexate 15 mg IT Day 1,8,15,22,29
	6 mercaptopurine 60 mg/m2 po

ALL treatment

Late Intensification	Doxorubicin 30 mg/m2 IV day 1,8,15
(Course IV)	Vincristine 2 mg IV day 1,8,15
	Dexamethasone 10 mg/m2 po day 1-14
	Cyclophosphamide 1000 mg/m2 IV day 29
	6-thioguanine 60 mg/m2 po day 29-42
	Cytarabine 75 mg/m2 SQ q day day 29-32, 36-39
Prolonged Maintenance	Vincristine 2 mg IV q week (day 1 of every week x 4)
(Course V)	Prednisone 60 mg/m2 po day 1 –5 of every 4 weeks
	6 mercaptopurine 60 mg/m2 po days 1-28

Chronic Lymphocytic Leukemia (CLL)

- Treatment is based on
  - Both the **stage** and **symptoms** of the individual patient.
  - A large group of CLL patients have **low-grade disease**, which does not benefit from treatment.
- Indications for treatment are
  - **Falling hemoglobin** or **platelet count**
  - **Painful**, disease-related **overgrowth of lymph nodes** or spleen
  - An increase in the **rate of lymphocyte**

Chronic Lymphocytic Leukemia (CLL)

- CLL is probably incurable by present treatments.
- Combination chemotherapy with
  - **Chlorambucil or cyclophosphamide, plus a corticosteroid such as prednisolone.**
- In resistant cases
  - Single-agent treatments with nucleoside drugs such as fludarabine, or cladribine may be successful antimetabolites/**purine** analogs
  - Younger patients may consider bone marrow transplantation.

Chronic Myeloid Leukemia

- The standard of care for newly diagnosed patients is imatinib therapy
  - Tyrosine kinase inhibitor: blocks proliferation and induces apoptosis
- Compared to most anticancer drugs, it has
  - Relatively few side effects and can be taken orally at home.
  - With this drug, more than 90% of patients will be able to manage the disease for five years
  - CML becomes a chronic, manageable condition.

Chronic Myeloid Leukemia

- In a more advanced, uncontrolled state, or
- When the patient cannot tolerate imatinib, or
- If the patient wishes to attempt a permanent cure,
  - ➲Then a **bone marrow transplantation** may be performed.
- This procedure involves
  - High-dose chemotherapy and radiation followed by infusion of bone marrow from a compatible donor.
- Approximately
  - 30% of patients die from this procedure

Acute Myeloid Leukemia

- Induction therapy
  - 7 + 3
    - Cytarabine for 7 days *plus* Anthracycline (idarubicin or daunorubicin) **or** mitoxantrone for 3 days (7+3),
  - Total Duration: 1 or 2 cycles
- Consolidation therapy:
  - High-dose cytarabine [HiDAC] and/or
  - Hematopoietic **stem cell transplantation** (HSCT).
- Although still considered investigatory
  - **Induction with HiDAC** may confer a disease-free survival advantage in patients aged 50 years& younger

Acute Myeloid Leukemia

- Pediatric patients
  - **Etoposide or thioguanine during induction**
- Patients with significant residual blasts need secondary induction with
  - **Cytarabine plus anthracycline or mitoxantrone**
- Patients receiving HiDAC should be monitored for signs of **neurotoxicity** and **renal** insufficiency.

LUNG CANCER

EPIDEMIOLOGY

- Lung cancer is a major cause of morbidity and mortality.
- It has reached epidemic proportions in many industrialized countries
- It is the most frequently fatal malignancy in the world.
- 228,190 new cases of lung cancer were diagnosed in the United States in 2013
- It remains the leading cause of cancer death in both adult men and women,
  - with about 159,480 deaths in 2013

ETIOLOGY

Gender

- Lung cancer incidence and mortality are slightly higher in **males**

- Rate (mortality) in females is expected to match that of males in future years owing to changes in smoking patterns

ETIOLOGY

Race

- No significant difference is noted in incidence or mortality between black and white females
- Black males have higher incidence and mortality rate than white males.
- Smoking habits, including cigarette type (i.e., increased menthol cigarette use) have a proposed contribution to this gap
- Black Americans also show a significantly lower 5-year survival rate than white

ETIOLOGY

- **Smoking**
  - The single most important risk factor for the development of lung cancer is smoking.
  - Total smoke exposure, as well as current use, correlates with the individual's risk of developing malignancy.
  - Total smoke exposure is reported as pack-years.
    - One pack-year is the equivalent of smoking 1 pack per day for 1 year.
    - A patient who smokes 40 cigarettes per day (2 packs) for 5 years would have a 10 pack-

ETIOLOGY

Other Air-Related Risks

- Environmental tobacco smoke (ETS) presents a significant occupational hazard for nonsmokers
- Other factors *radon*, *arsenic*, *nickel*, and *chloromethyl ethers*.
- High concentrations of combustion fumes

ETIOLOGY

- **Nutrition**
  - Not all heavy smokers develop lung cancer
  - Epidemiologic studies have shown ***reduced rates of lung cancer*** in individuals who report higher ***fruit and vegetable consumption*.**
  - Recommendations to patients who are at risk owing to smoking or other factors or those who are simply interested in reducing their risk of cancer should include an increase in dietary intake of fruits and vegetables.

ETIOLOGY

Hereditary or Genetic Risk Factors

- After adjustments for age, smoke exposure, occupation, and gender, relatives of a lung cancer patient have approximately a **two-fold risk** of developing lung cancer.

- **Lung cancer gene has not been identified**

ETIOLOGY

- **Hereditary or Genetic Risk Factors (2)**
- The damaging effects of tobacco smoke are thought be a result of bulky aromatic hydrocarbons that damage DNA
  - Phase I metabolic enzymes: activation
  - Phase II conjugating enzymes such as the glutathione-*S-transferases:* Deactivation
- High carcinogen
  - Elevated cytochrome CYP450 2D6, 1A1, or 1A2
  - Deficient phase II metabolism

Case study

A 53-year-old African-American man presents at your clinic complaining of new-onset cough. He has had several upper respiratory infections in the last 2 months, with occasional hemoptysis. He has consistently smoked 1.5 packs per day for the last 20 years. He has worked as a bartender at a local restaurant downtown for most of his life.

- What risk factors for lung cancer are present?
- Calculate this patient's pack-year history.

PATHOPHYSIOLOGY

- Most lung cancers are derived from the **epithelium** of the airways → **carcinomas.**
- Four major and several rare histologic types of lung cancer through similar mutagenic pathways

Histologic Classification

- Involves determining the cellular origin of the tumor
- ***Knowing the histology of the tumor influences treatment decisions as well as prognosis.***
- Four major histologic types of lung cancer that are divided into two classes:
  - *Small cell lung cancer (SCLC)* and
  - *Non–small cell lung cancer (NSCLC)*

Radiation

- The treatment of choice for ***limited-stage SCLC***
- Radiation therapy can be used in place of surgery with curative intent in localized NSCLC, [success rate approximately 50% that of surgery]
- **Advanced** SCLC & NSCLC: radiation is limited to palliation of symptoms caused by a local tumor.
  - Toxicity on normal tissue, and patients may experience esophagitis, pneumonitis, cardiac abnormalities, myelopathies, and skin irritation.

Chemotherapy

- Decision to start chemotherapy depends greatly on the overall patient picture, with emphasis on **performance status** and comorbid conditions.

Eastern Cooperative Oncology Group

ECOG Score	Patient Status
0	Unrestricted, asymptomatic
1	Able to complete light work activities but restricted from strenuous tasks. Otherwise ambulatory.
2	Ambulatory for more than 50% of waking hours. Able to care for self completely but unable to complete even light work.
3	Able to care for self on a limited basis, confined to bed or chair more than 50% of time awake. Unable to carry out work activities
4	Completely disabled, confined to bed or chair
5	Deceased

Chemotherapy

- **Performance status:**

- Measure of capability to tolerate systemic therapies that may severely compromise the patient's health.

- Patients who score **well** (0–1) are more likely to tolerate intense therapy, whereas patients who score **highly** (3–4) are considered unfit for chemotherapy or surgery.

- Controversy on score=2
  - At this point, treatment is aimed at treating comorbidities to improve the performance status or the use of palliative symptomatic therapy.

Chemotherapy

- Preventing and managing chemotherapy toxicity are crucial to optimizing patient outcomes
  - Curing,
  - Prolonging life, or
  - Palliating symptoms

Adjuvant Therapy

- The use of chemotherapy or radiotherapy following surgical resection of a tumor mass.

- The rationale behind adjuvant chemotherapy is to eradicate micrometastases or other tumor cells that may have been missed during removal of the primary tumor.

Adjuvant Therapy

Project	IATL	Intergroup JBR-10	CALGB 9633
Adjuvant therapy	Cisplatin	cisplatin-vinorelbine	Carboplatin-paclitaxel
Improvement in survival	4%	12%	15%

Carboplatin-Paclitaxel is current preferred regimen

Adjuvant Therapy

- *Adjuvant radiotherapy*, or postoperative radiotherapy (*PORT*), is thought to eliminate remnants of the resected tumor that might be deposited in nearby tissue.

- Clinical trials have clearly shown that PORT *decreases local recurrence*; however, a survival benefit has never been shown.

Neoadjuvant Therapy (*induction therapy*)

- The rationale behind neoadjuvant therapy is to decrease the size of the tumor so that it can be extracted more easily with clean margins, as well as to eliminate distant micrometastases before invasive local treatment
- Neoadjuvant chemotherapy has been shown to yield benefits in NSCLC (both local and locally advanced disease)
- Toxicity of induction regimens may delay surgery, and if the tumor does not respond to the treatment, there is a risk of disease progression

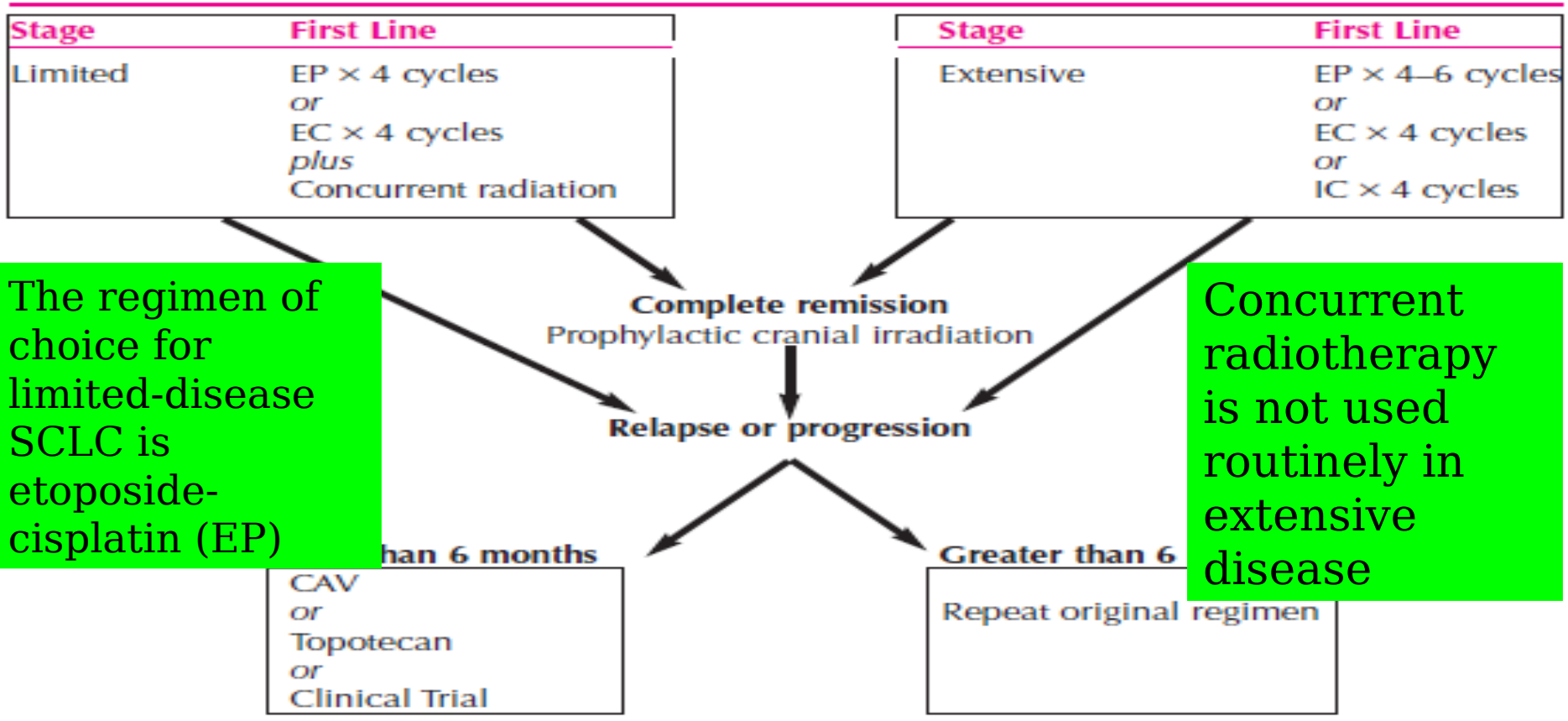
Chemotherapy for lung ca and associated toxicities

	Dose	Cycle Length	Neutropenia	
			Grade III	Grade IV
Non-Small Cell				
Paclitaxel-carboplatin-bevacizumab	Carboplatin, dose targeted to *AUC* of 6 IV (day 1), paclitaxel 200 mg/m² IVover 3 hours (day 1), bevacizumab 15 mg/kg IV (day 1)	21 days	N/A	24%
Cisplatin-paclitaxel	Paclitaxel 135 mg/m² IV over 24 hours (day 1) and cisplatin 75 mg/m² IV (day 2)	21 days	18%	57%
Cisplatin-docetaxel	Cisplatin 75 mg/m² IV (day 1) and docetaxel 75 mg/m² IV (day 1)	21 days	21%	48%
Cisplatin-gemcitabine	Cisplatin 100 mg/m² IV (day 1) and gemcitabine 1000 mg/m² IV (days 1, 8, 15)	28 days	24%	39%
Carboplatin-paclitaxel	Carboplatin, dose targeted to *AUC* of 6 IV (day 1), and paclitaxel 225 mg/m² IV over 3 hours (day 1)	21 days	20%	43%
Gemcitabine-paclitaxel	Paclitaxel 200 mg/m² IV (day 1) and gemcitabine 1000 mg/m² (day 1 and 8)	21 days	10%	5%
Gemcitabine-docetaxel	Gemcitabine 1100 mg/m² IV (days 1 and 8) and docetaxel 100 mg/m² IV (day 8)	21 days	11%	11%
Gemcitabine	Gemcitabine 1125 mg/m² (days 1 and 8)	21 days	19%	
Pemetrexed	Pemetrexed 500 mg/m² (day 1), vitamin B_{12} 1 mg IM 1–2 weeks before treatment initiation and every 9 weeks thereafter, folic acid 1 mg daily beginning 3 weeks before treatment initiation	21 days	5–6%	
Paclitaxel	Paclitaxel 200 mg/m² IV over 3 hours (day 1)	21 days	34%	3%
Docetaxel	Docetaxel 35 mg/m² IV over 1 hour (days 1, 8, 15)	28 days	5%	
Small Cell				
EP	Etoposide 100 mg/m² IV (days 1–3) and cisplatin 100 mg/m² IV (day 2)	28 days	85%	18%
CAV	Cyclophosphamide 800 mg/m² IV (day 1), doxorubicin 50 mg/m² (day 1), and vincristine 1.4 mg/m² (maximum of 2 mg) IV (day 1)	21–28 days	15%	72%
EC	Etoposide 100 mg/m² IV (days 1–3) and carboplatin *AUC* 5–6 IV (day 1)	21 days	10–20%	5–15%
IC	Irinotecan 60 mg/m² (days 1, 8, 15) and cisplatin 60 mg/m² (day 1)	28 days	40%	25%
Topotecan	Topotecan 1.5 mg/m² IV over 30 minutes (days 1–5)	21 days	18%	70%

Small Cell Lung Cancer

- The regimen of choice for limited-disease SCLC is etoposide-cisplatin (EP)
- Carboplatin may be substituted for cisplatin to reduce nausea and vomiting, nephrotoxicity, or neurotoxicity, although increased myelosuppression in the form of thrombocytopenia may result
- Poor performance status patients (3–4) typically are treated with palliative symptomatic therapies

Small Cell Lung Cancer



The regimen of choice for limited-disease SCLC is etoposide-cisplatin (EP)

Concurrent radiotherapy is not used routinely in extensive disease

CAV, cyclophosphamide, doxorubicin, vincristine; EC, etoposide carboplatin; EP, etoposide cisplatin; IC, irinotecan, cisplatin. See Table 87–4 for doses and schedules.

Non–Small Cell Lung Cancer

- Treatment options depend on the advancement of disease (i.e., *local, locally advanced, or metastatic*).

Local Disease

- Local disease encompasses stages *IA through IIA* and is associated with a favorable prognosis
- Stage **IA** tumors may be treated with **surgery alone**
- Stage **IB**, **IIA**, and **IIB** disease is treated with **adjuvant chemotherapy**. *Radiation* is added if surgical margins are positive.
- Benefit seen in clinical trials used **carboplatin-paclitaxel** or **cisplatin-**

Locally Advanced Disease

- Locally advanced disease (stages **IIB** and **IIIA**) still may be considered for surgery. Neoadjuvant chemotherapy with concurrent radiotherapy can be used prior to surgery,

Neoadjuvant therapy (chemo +radio)

+

Surgery

+

Adjuvant therapy

Advanced or Metastatic Disease (Stages IIIB and IV)

- Treated with chemotherapy if the patient has an acceptable ECOG **PS score (0–1).**

- **Platinum-containing doublets** have produced the highest overall response rates and survival times

Advanced or Metastatic Disease (Stages IIIB and IV)

- Paclitaxel-cisplatin
- Paclitaxel-carboplatin
- Cisplatin-gemcitabine
- Cisplatin-docetaxel
- Carboplatin-docetaxel
- Cisplatin-vinorelbine
- Gemcitabine-paclitaxel
- Gemcitabine-docetaxel

Recurrent (Progressive) Disease

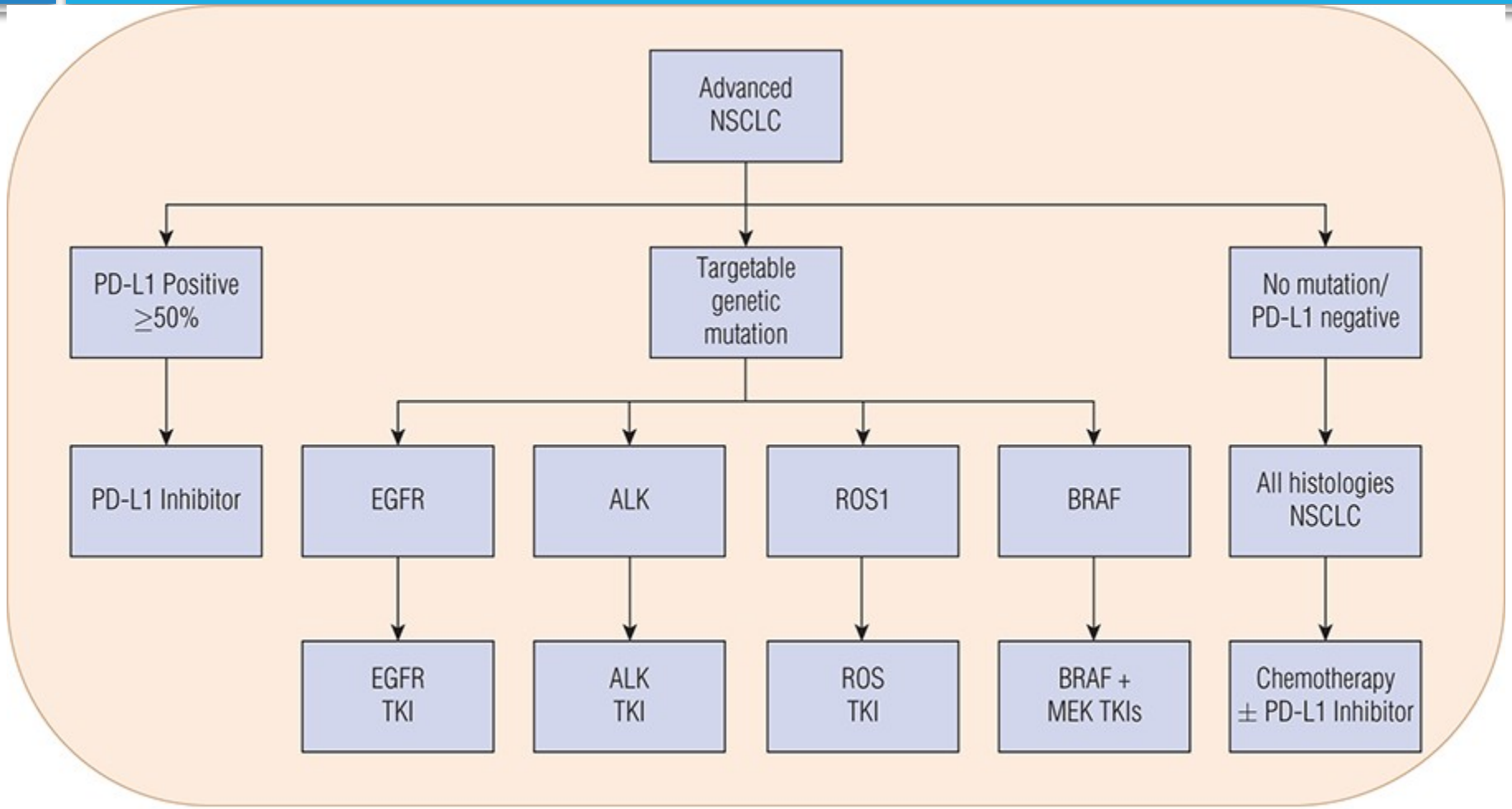
- Localized recurrence: Surgery options
- If the patient's PS remains acceptable (0–1), second-line systemic chemotherapy
  - Single-agent therapy with Docetaxel, Pemetrexed, or Erlotinib
- Recurrences in poorly performing patients (3–4) usually are not treated with chemotherapy and are instead treated with supportive.

Monoclonal Antibodies

- *Bevacizumab* is IgG monoclonal antibodies that have activity in NSCLC.
- Bevacizumab targets vascular endothelial-derived growth factor (VEGF), which is thought to facilitate angiogenesis, a process contributing to growth and maintenance of the tumor environment.
  - Synergistic with chemotherapy
  - Improve survival of advanced-stage NSCLC patients

Tyrosine Kinase Inhibitors

- Tyrosine kinase inhibitors (TKIs) work by targeting specific intracellular messenger proteins that transmit growth and survival signals.
  - *Erlotinib* and *Gefitinib*
- Target epidermal growth factor receptor (EGFR) a cytokine receptor on tumor cells that is frequently involved with tumor survival and proliferation.
- Erlotinib prolongs survival, whereas gefitinib does not



Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition.
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CERVICAL CANCER

Epidemiology

- Globally, cervical cancer is the third most common malignancy in women
  - the fourth most frequent cause of cancer-related death.
- In Africa, cervical cancer is the number one cause of cancer-related mortality among women
- It is estimated that 529,800 cases and 275,100 deaths occurred in 2008,
  - Overwhelmingly in developing countries (Southeast Asia, Africa and South America)
- It is estimated that 12,710 new cases and 4290 deaths in the U.S. in 2011

Etiology

- Cervical cancer is causally related to infection with oncogenic human papillomavirus (HPV) strains.
- Oncogenic HPV strains infect epithelium of lower anogenital tract, including the cervical squamo-columnar junction;
- More than 100 subtypes of HPV identified. **HPV-16** and **HPV 18** are responsible for more than 70%
- **HPV-6** and **HPV-11** are also associated with the development of genital warts
- Cervical dysplasia is precursor of cervical cancer

Risk Factors

1. **Human papilloma virus**; particularly infection with oncogenic subtypes 16 and 18
2. Early onset of **sexual activity**;
   - ✓ RR: 2-fold for younger than 18 yrs compared to 21 yrs or older
3. **Smoking**: nicotine and its' metabolites have been detected in cervical mucus, indicating that these carcinogenic substances can be transmitted by the blood to the cervix.
4. **Multiple partners**; RR is 3-fold with six or more partners compared to one partner
5. History of sexually transmitted diseases;
6. Chronically immunocompromised (e.g., HIV, organ transplants);
7. Lower socioeconomic status due to limited access to health care

Risk Factors

- Factors associated with decreased risk of cervical cancer:
  1. Nulliparity
  2. Abstinence
  3. Vaccination against HPV
  4. Sexual partners of circumcised males

Etiology of Pain in Cancer

C. Diagnostic or therapeutic procedures (20%)

- ✓ Procedure-related pain (i.e., bone marrow aspiration or biopsy, lumbar puncture)
- ✓ Acute postoperative pain or postsurgical syndromes (i.e., postmastectomy, postthoracotomy, postamputation syndromes)
- ✓ After radiation (injury to plexus or spinal cord, mucositis, enteritis)
- ✓ After chemotherapy (mucositis, peripheral neuropathy, aseptic necrosis)

D. Pain unrelated to the malignancy or its treatment (<10%)

MANAGEMENT OF CANCER PAIN

Pharmacologic Therapy

- Pharmacologic approaches are the most commonly used treatments for cancer pain, because they are effective, safe, and usually inexpensive.
- These are classified as:
  - ✓Non-opioids
  - ✓Opioids
  - ✓Adjuvant analgesics

MANAGEMENT OF CANCER PAIN

Mild to moderate pain:

- Aspirin, acetaminophen, or NSAIDs are preferred for mild to moderate pain
- If these do not provide adequate analgesia, codeine, oxycodone, or hydrocodone will frequently provide excellent relief
  - **Codeine:** 15 – 30mg IV/IM Q 3-4 Hrs. Ceiling for analgesia reached at doses >240 mg/day
  - **Tramadol:** 50–100 mg PO can be given every 3–4 hours, up to 400 mg daily.

MANAGEMENT OF CANCER PAIN

- For persistent or severe pain, codeine (or its congener) is replaced by a potent opioid, such as **morphine**.
- Patients with severe pain might need a strong opioid as initial therapy to ensure rapid pain relief.
  - **Morphine*:***
    - 30mg PO Q4–6Hrs.
    - 30mg PO (SR) Q 8–12 Hrs.
    - 10mg IV/IM Q 3–5Hrs.
  - **Meperidine*:***
    - 300 mg PO Q 3–6 Hrs.
    - 75 mg IV/IM Q 2–3 Hrs.

MANAGEMENT OF CANCER PAIN

Adjuvant Analgesics:

A. **Antidepressants:** Neuropathic pain
   - ✓ Amitriptyline
   - ✓ Nortriptyline
   - ✓ Desipramine

B. **Anticonvulsants:** Neuropathic pain, myoclonic jerks
   - ✓ Phenytoin
   - ✓ Valproic acid
   - ✓ carbamazepine.
   - ✓ Clonazepam
   - ✓ Gabapentin

MANAGEMENT OF CANCER PAIN

Adjuvant Analgesics:

C. **Corticosteroids:** Spinal cord compression, increased intracranial pressure, visceral distention
   - ✓ Methylprednisolone
   - ✓ Dexamethasone
   - ✓ Prednisone

D. **Benzodiazepines:** Muscle spasm, myoclonus, anxiety, insomnia
   - ✓ Diazepam
   - ✓ Lorazepam
   - ✓ Alprozolam
   - ✓ Midazalam
   - ✓ Temazepam

DIFFICULT-TO-MANAGE PAIN PROBLEMS

- **Difficult-to-manage pain problems are most common in patients with any of the following conditions:**
  - ✓Pain of neuropathic origin
  - ✓Episodic or incidental pain
  - ✓Impaired cognitive or communicative skills
  - ✓A history of substance abuse

CACHEXIA

The cachectic syndrome is defined by:

- Body weight loss of ≥10%,
- Reduced food intake (≤1500 kcal/day) and
- Systemic inflammation (C-reactive protein ≥10 mg/L).

CACHEXIA

Prevalence:

- The incidence of cachexia depends on tumor type:
  - ✓ Highest in patients with pancreatic and gastric cancer and
  - ✓ Lowest in patients with breast cancer and non-Hodgkin's lymphoma.
- Overall weight loss occurs in 30 to 80% of cancer patients and is severe (>10% of initial body weight) in 15%.
- Cancer therapies are also associated with the induction of anorexia and further weight loss

CACHEXIA

Treatment:

- **Progestins:**

↳ Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are two synthetic progestins derived from 17α-hydroxyprogesterone

  ↳ 160 to 1600 mg/day for MA and from 300 to 1000 mg/day for MPA.

CACHEXIA

TREATMENT

- **Corticosteroids:**
  - These include dexamethasone, prednisolone, and methylprednisolone. They induce a temporary effect on symptoms such as appetite,
  - Food intake, sensation of well-being, and performance status but show no beneficial effect on body weight.
  - They tend to be used in patients in the end stages of cancer in an attempt to improve the quality of life.

NAUSEA AND VOMITING

- Nausea and vomiting are common among the adverse effects most feared by patients.
- Although are usually self-limiting and seldom life-threatening, the deleterious effects on nutritional status and quality of life can be substantial.

NAUSEA AND VOMITING

- Five neurotransmitter receptor sites are of primary importance in the vomiting reflex:
  1. M1 – **Muscarinic**
  2. D2 – **Dopamine**
  3. H1 – **Histamine**
  4. 5-hydroxytryptamine (5-HT)3 – **Serotonin**
  5. Neurokinin 1 (NK1) receptor – **Substance P**

NAUSEA AND VOMITING

Antiemetics:

- **Neurokinin 1 receptor antagonist-** Aprepitant, fosaprepitant
- **5HT3 antagonists:** ondansetron
- **Dopamine antagonists:** Chlorpromazine**,** Metoclopramide.
- **Glucocorticoids:** good for early and delayed nausea.
- **Anti histamines:** Promethazine
- **Benzodiazepins:** Lorazepam-good for anticipatory emesis

Classification: Clinical Syndromes

1. Acute:

- Occur within 24 hours after the chemotherapy dose.
- Mostly with in 1-2 hrs (cyclophosphamide-9-18hrs)
- Most sever form drug induced nausea and vomiting
- 5HT-3 receptor antagonists are highly effective drugs against it

Classification: Clinical Syndromes

2. Delayed:

- Occur 24 or more hours after chemotherapy administration.
- Most severe and frequent after administration of high-dose cisplatin
- Poor control of acute nausea and vomiting are more likely to experience delayed nausea and vomiting
- NK-1 receptor antagonists are effective to prevent it

3. Anticipatory:

- Patients who have experienced poor control of emesis during previous courses of chemotherapy.
- The onset can occur before or during chemotherapy administration.

Risk Factors for CINV

Prior experiences with chemotherapy
Poor control in previous treatments increases the risk of N/V in subsequent cycles, especially anticipatory N/V
Psychosocial factors (anxiety, distress, etc.)
History of depression predisposes patients to increased N/V
Children have more N/V than adults
History of morning sickness with previous pregnancies
Women have more N/V than men
History of motion sickness

Emetogenicity of Chemotherapy Agents

Level-5 emesis: >90%

- ✓ Carmustine >250 mg/m^2
- ✓ Cisplatin ≥50 mg/m^2
- ✓ Cyclophosphamide >1500 mg/m^2
- ✓ Dacarbazine
- ✓ Mechlorethamine
- ✓ Streptozocin

Emetogenicity of Chemotherapy Agents

Level-4 Emesis: 60-90%

- ✓ Carboplatin
- ✓ Carmustine ≤250 mg/m^2
- ✓ Cisplatin <50 mg/m^2
- ✓ Cyclophosphamide >750 mg/m^2 and ≤1500 mg/m^2
- ✓ Cytarabine >1 g/m^2
- ✓ Doxorubicin >60 mg/m^2
- ✓ Epirubicin >90 mg/m^2
- ✓ Melphalan >50 mg/m^2
- ✓ Methotrexate >1000 mg/m^2
- ✓ Procarbazine (oral)

Emetogenicity of Chemotherapy Agents

Level-3 Emesis 30-60%

- Arsenic trioxide
- Cyclophosphamide ≤750 mg/m^2
- Cyclophosphamide (PO)
- Doxorubicin 20–60 mg/m^2
- Epirubicin ≤90 mg/m^2
- Idarubicin
- Ifosfamide
- Irinotecan
- Lomustine
- Methotrexate 250–1000 mg/m^2
- Mitoxantrone
- Oxaliplatin >75 mg/m^2

Emetogenicity of Chemotherapy Agents

Level-2 Emesis: 10-30%

- ✓ Cytarabine 100–200 mg/m²
- ✓ Capecitabine
- ✓ Cetuximab
- ✓ Docetaxel
- ✓ Doxorubicin (liposomal)
- ✓ Etoposide
- ✓ 5-Fluorouracil <1000 mg/m²
- ✓ Gemcitabine
- ✓ Methotrexate >50 mg/m2 and <250 mg/m²
- ✓ Mitomycin
- ✓ Paclitaxel
- ✓ Panitumomab
- ✓ Sorafenib
- ✓ Sunitinib
- ✓ Temozolomide
- ✓ Topotecan
- ✓ Tositumomab

Emetogenicity of Chemotherapy Agents

Level-1 Emesis: <10%

- ✓ Imitanib
- ✓ Melphalan (low dose, oral dosing)
- ✓ Methotrexate ≤50 mg/m2
- ✓ Pentostatin
- ✓ Rituximab
- ✓ Thioguanine (PO)
- ✓ Trastuzumab
- ✓ Vinblastine
- ✓ Vincristine
- ✓ Vinorelbine
- ✓ Alemtuzumab
- ✓ Bleomycin
- ✓ Bortezomib
- ✓ Chlorambucil (PO)
- ✓ Cladribine
- ✓ Denileukin diftitox
- ✓ Erlotinib
- ✓ Fludarabine
- ✓ Gemtuzumab ozogamicin
- ✓ Hydroxyurea
- ✓ Asparaginase
- ✓ Bevacizumab

Estimation of Emetogenic Potential of Combination Chemotherapy Regimens

Steps:

- Identify and classify most emetogenic agent.
- When considering the other components of the regimen, use the following rules:
  - Level 1 agents do not contribute to emetogenicity.
  - Adding level 3 or 4 agents increases emetogenicity by one level per agent.
  - Adding level 2 agents (regardless of number) increases emetogenicity by one level greater than the most emetogenic agent.

Estimation of Emetogenic Potential of Combination Chemotherapy Regimens

Regimen	Emetogenic Level of Agents in Regimen	Emetogenic Level of Regimen
CMF	3+2+2	4
CAF	3+3+2	5
Paclitaxel/ carboplatin	2+4	5
CVP	3+1+1	3

A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; M, methotrexate; P, prednisone; V, vincristine

Treatment of Acute and Delayed N/V

- Only the 5-HT3 receptor antagonists, metochlopramide and the new class of NK-1 receptor antagonists show marked activity against highly emetogenic chemotherapy.
- Combination antiemetic regimens
- Neurokinin-1 antagonists are only effective for delayed NV

Antiemetic Agents: Recommended Dosing

	Recommended Dose	
Antiemetic Agent	**Acute Emesis**	**Delayed Emesis**
5-HT3 Antagonists		
Ondansetron	0.15 mg/kg or 8 mg IV; 12–16 mg PO	8 mg PO bid × 2–3 days
Granisetron	1 mg IV or PO	
Dolasetron	1.8 mg/kg or 100 mg IV; 100–200 mg PO	
Palonosetron	0.25 mg IV	
Neurokinin-1 antagonists		
Aprepitant		125 mg PO (or 115 mg IV) day 1, then 80 mg days 2, 3
Corticosteroids		
Dexamethasone	8 mg IV or PO	4–8 mg PO bid days 2–4
Dopamine antagonists		
Metoclopramide	2–3 mg IV prechemotherapy, repeat 2 hr after chemotherapy	20–40 mg PO qid days 2–5
Prochlorperazine	10 mg PO or IV every 3–4 hrs as needed	
Haloperidol	1–3 mg IV or PO every 2–6 hrs as needed	
Benzodiazepines		
Lorazepam	1–2 mg IV every 4 hrs as needed	
Cannabinoids		
Dronabinol	5–10 mg PO every 3–4 hrs as needed	

Anticipatory Nausea and Vomiting

- For patients in whom anticipatory nausea and vomiting develop,
  - Treatment with anxiolytics such as the **benzodiazepines** is sometimes effective

Management Approach

- **For level 4 &5:** should receive routine prophylaxis for acute nausea and vomiting with a 5-HT3 receptor antagonist plus dexamethasone.
- ⇨ Because all of these patients also have substantial risk for delayed emesis, **aprepitant** should be added, and **palonosetron** should be considered the 5-HT3 antagonist of choice.
- **For level 3:** Well controlled with a 5-HT3 receptor antagonist plus dexamethasone; routine prophylaxis for delayed emesis is not necessary.
- **For level 1&2:** Do not require routine use of a 5-HT3 receptor antagonist and are usually managed effectively with either dexamethasone alone (category 2) or no prophylactic antiemetic therapy (category 1)

Radiation Induced Nausea & Vomiting

- The mechanism of radiation-induced emesis remains unclear, but release of serotonin from the GI enterochromaffin cells and subsequent involvement of the GI 5-HT3 receptors and vagal afferent fibers is most likely.
- Dexamethasone (4 mg orally daily, during the first 5 days only) or ondansetron (8 mg orally twice daily) improved results in patients receiving upper abdominal radiation therapy.
- Routine prophylaxis for acute and delayed nausea and vomiting should accompany total-body irradiation.

Definition of Febrile Neutropenia

- **Fever:** Single oral temperature ≥38.3°C or persistent temperature ≥38.0 °C for >1 hour.

- **Neutropenia:** ANC <0.5, or ANC <1.0 and a predicted decline to <0.5 over next 48 hrs.

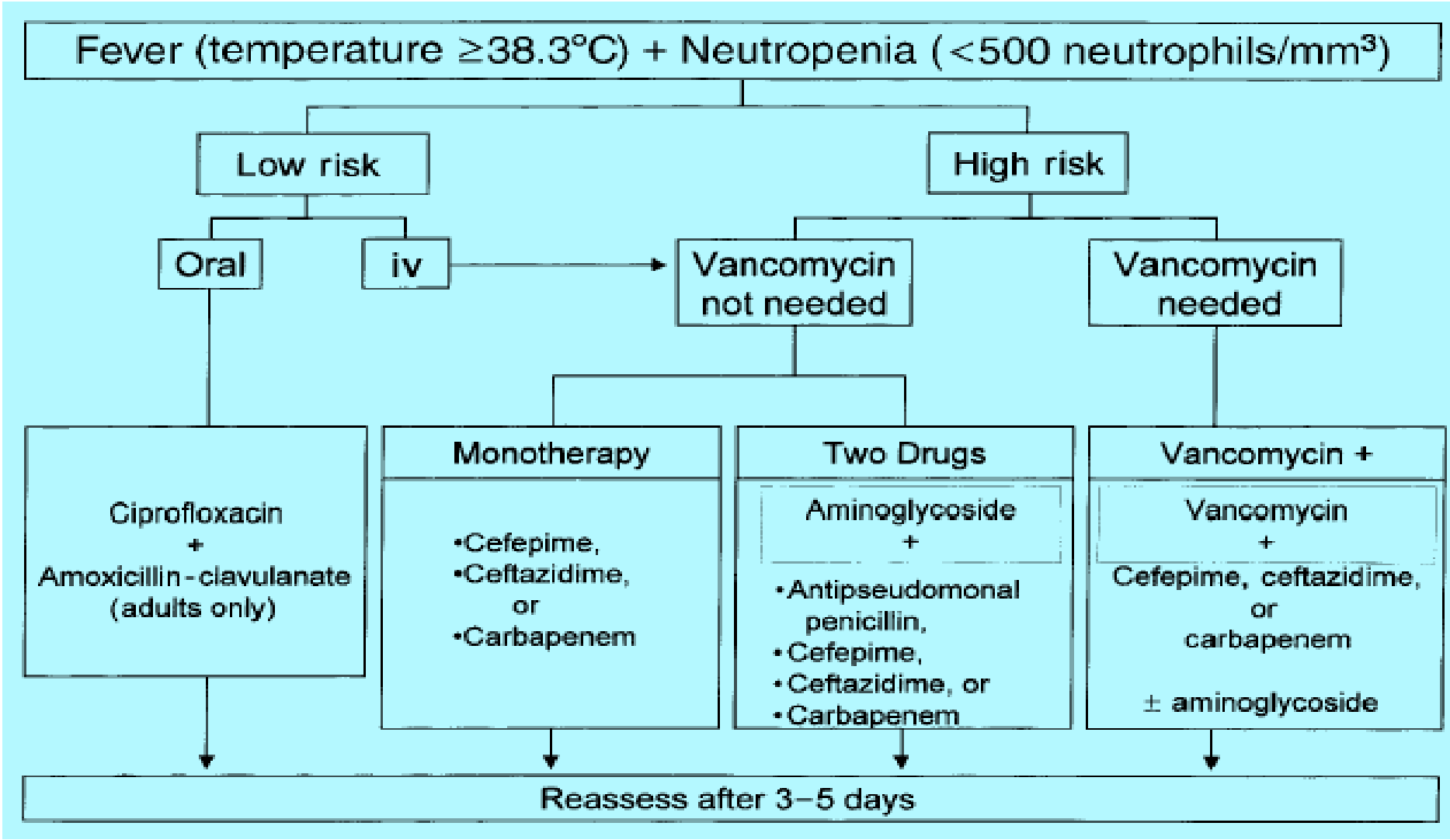
Neutropenic Fever

- Neutropenic fever is a medical emergency requiring initial intervention in the emergency room.
- Before empiric antibiotic therapy, infection accounted for **75% of all mortality** among patients receiving chemotherapy
- Early studies showed a **70% increase in mortality** with a delay in administration of empiric antibiotics once neutropenic fever was identified

Neutropenic Fever

- **To administer chemo:**
  - ✓ WBC > 3,000/mm³ or
  - ✓ ANC > 1,500/mm³ and
  - ✓ Platelets 100,000/mm³

Neutropenic Fever



Colony Stimulating Factors (CSFs)

- Filgrastim (Neupogen®)
  - ✓ 5mcg/kg/day-after 24 hrs. of administering of chemo
  - ✓ Recombinant human G-CSF (*E. coli*)
- Other rhG-CSF (recombinant human G-CSF).
  - ✓ PEG-filgrastim (**Neulasta®**) - longer half-life (6mg SC per chemo cycle)
  - ✓ Lenograstim (**Granocyte®**) - synthesized in Chinese Hamster Ovary cells (CHO cells).

Colony Stimulating Factors

- Not recommended
  - ✓ Patients who are neutropenic, but not febrile
- Recommended
  - ✓ Patients who are neutropenic and **febrile** in the presence of risk factors
  - ✓ ANC <100/mm^3, pneumonia, hypotension, multi-organ dysfunction, invasive fungal infection
  - ✓ May be used **with antibiotics**

Thrombocytopenia

- Defined as: Platelet count < 100,000/mm³
- Increased risk of bleeding occurs when
  - ✓ Platelet count ≤ **20,000/mm³**
- Thus require: **transfusion**
  - ✓ Most institutions do not transfuse until the patient becomes symptomatic such as:
    - ⇨ Ecchymosis, petechiae, hemoptysis, or heamtemesis
- When platelet count ≤ **10,000/mm³**
  - May lead to **spontaneous bleeding**

Cancer-Induced Hypercalcemia

- Hypercalcemia affects up to **10% to 30%** of cancer patients
- Cancer-related hypercalcemia is the **leading cause of** hypercalcemia in hospitalized patients.
- Patients with **breast cancer, lung cancer, and myeloma** are most commonly affected, but hypercalcemia can also occur with other malignancies
- Unfortunately, cancer-related hypercalcemia has a poor prognosis, as it is most often associated with disseminated disease.
- **Eighty percent of patients will die** within a year, and there is a median **survival of 3 to 4 months**.

Cancer-Induced Hypercalcemia

- The main pathogenesis of hypercalcemia in malignancy is **increased osteoclastic bone resorption**, which can occur **with** or **without bone metastases**.
- The main factor associated with cancer-related hypercalcemia is **parathyroid hormone–related protein**, which is produced by many solid tumours.
- Parathyroid hormone–related protein **increases calcium by activating parathyroid hormone receptors in tissue**, which results in osteoclastic bone resorption;

Cancer-Induced Hypercalcemia – Management

Hydration

- 2 to 3 L of normal saline per 24 hours until the patient is drinking well
- Hydration alone is not sufficient to achieve and maintain normocalcemia in cancer patients.

Intravenous bisphosphonates

- ✓ Should be given as soon as hypercalcemia is diagnosed
- ✓ Block osteoclast activity bone resorption.
- ✓ **Zoledronate**

Hair Loss

- Hair loss due to chemotherapy can be the most upsetting side effect for patients.
  - And it's not just hair on the head that can be lost.
    - Total body alopecia can occur, especially with **taxanes.**

Hair Loss

- **The good news** is that:
  - Hair grows back once chemo stops.
  - Hair loss usually **starts about 1 to 2 weeks** after a cycle of chemo.
  - Usually, hair will start growing back 1 to 2 months after chemotherapy is complete.
  - Often the hair that grows back after chemo is a different texture or may be somewhat lighter or darker in color.
- Hair loss is uncomfortable (itchy) and psychologically devastating to some patients, especially teenagers.

Fertility

Radiation

- Can significantly impact the female reproductive tract
  - Causing **irreversible damage to the ovaries** and loss of the menstrual cycle.
  - Makes the uterus more difficult to attain and maintain pregnancy.
- In men radiation can cause **testicular damage.**
  - **Sperm counts** may return to normal over a year or two
  - They may stay low, especially in men who've

Fertility

- **Alkylating agents:**
  - Cause amenorrhea in women and
  - Absent or prolonged low sperm counts in men.
- Men and women who desire children after chemotherapy or radiation are
  - Often counseled **to freeze eggs and sperm in advance**.
- And it's usually suggested that women wait at least 6 months after their last chemo cycle before trying to conceive.

MALNUTRITION

CHAPTER 4

Definition

- Malnutrition: over nutrition (obesity) and under nutrition
- Severe acute malnutrition (macro- and micronutrient deficiency)
  - ✓ Bilateral pitting edema or
  - ✓ WFH (weight for height) < 70 % or
  - ✓ MUAC < 11 cm or
  - ✓ Based on the Welcome classification, if the child has Kwashiorkor, Marasmus, or Marasmic-Kwash

Marasmus

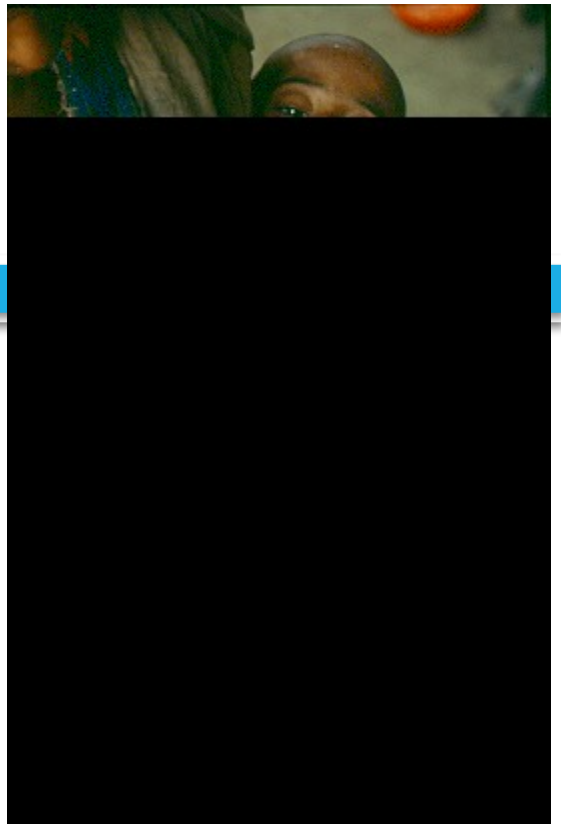
- Marasmus
  - You cannot tell whether a person is wasted by looking at the face



Marasmus



Marasmus



Severe wasting

- Note severe emaciation over ribs, thighs and extremely increased skin elasticity



Marasmus

Baggy pants



Marasmus



Bleached hair

Kwashiorkor

- The child has generalized edema, bleached hair the superficial skin has stripped off and he is miserable



Kwashiorkor



Bilateral pitting edema

Nutritional assessment

- Nutritional assessment is an interpretation of
  - Anthropometric,
  - Biochemical
  - Clinical and
  - Dietary survey data to tell whether a person/ group of people is well nourished or malnourished.

ANTHROPOMETRIC ASSESSMENTS

- Anthropometry comes from two words: Anthropo = Human, and Metry = measurement.

- **Definition**: - Anthropometry refers to measurement of – variations of physical dimension and gross composition of human body at different levels and degrees of nutrition

Anthropometric Assessments

- Anthropometric measurements could be used both
  - In the clinical and field set-ups.
  - In the clinical set-ups they are used to assess the nutritional status of:
    - Post-operative patient
    - Post traumatic patient (after acute trauma or surgery)
    - Chronically sick medical patient
    - Patient preparing for operation
    - Severely malnourished patient to assess the impact of nutritional intervention.

HEAD CIRCUMFERENCE (HC):

- Measured using flexible measuring tape around 0.6cm wide to the nearest 1mm.
- It is the circumference of the head along the supra orbital ridge anteriorly and occipital prominence posteriorly.
- HC is useful in assessing chronic nutritional problems in under two children.
- But after 2 years as the growth of the brain is sluggish it is not useful.

LENGTH

- A wooden measuring board (also called sliding board) is used for measuring length.
- It is measured in recumbent position in children <2 yrs old to the nearest 1mm.
- An assistance of two people is needed in taking the measurement

HEIGHT

- Is measured in children > 2 yrs and a adults in standing position to the nearest 0.1 cm.
- Knees should be straight and the heels buttocks and the shoulders blades, should touch the vertical surface of the stadiometer (anthropometer) or wall.
- Stadiometer or portable anthropometer can be used for measuring.

WEIGHT

- Weighing sling (spring balance) also called salter scale is used for measurement of weight in children < 2 years.
- In children the measurement is performed to the nearest 10g.
- In adults and children >2 years, beam balance is used and the measurement is performed to the nearest 0.1 kg.

Indices derived from these measurements

- **What is an index**? It is a combination of two measurements or a measurement plus age. The following are few of them:
  - Head circumference-for age
  - Weight -for-age
  - Height-for age
  - Weight for height

Meanings of the indices derived from growth measurements

- 100
- 100
- 100

Indices

- Both weight for age and weight for height are indices sensitive to acute changes to nutritional status
- Height for age of children in a given population indicates their nutritional status in the long run.

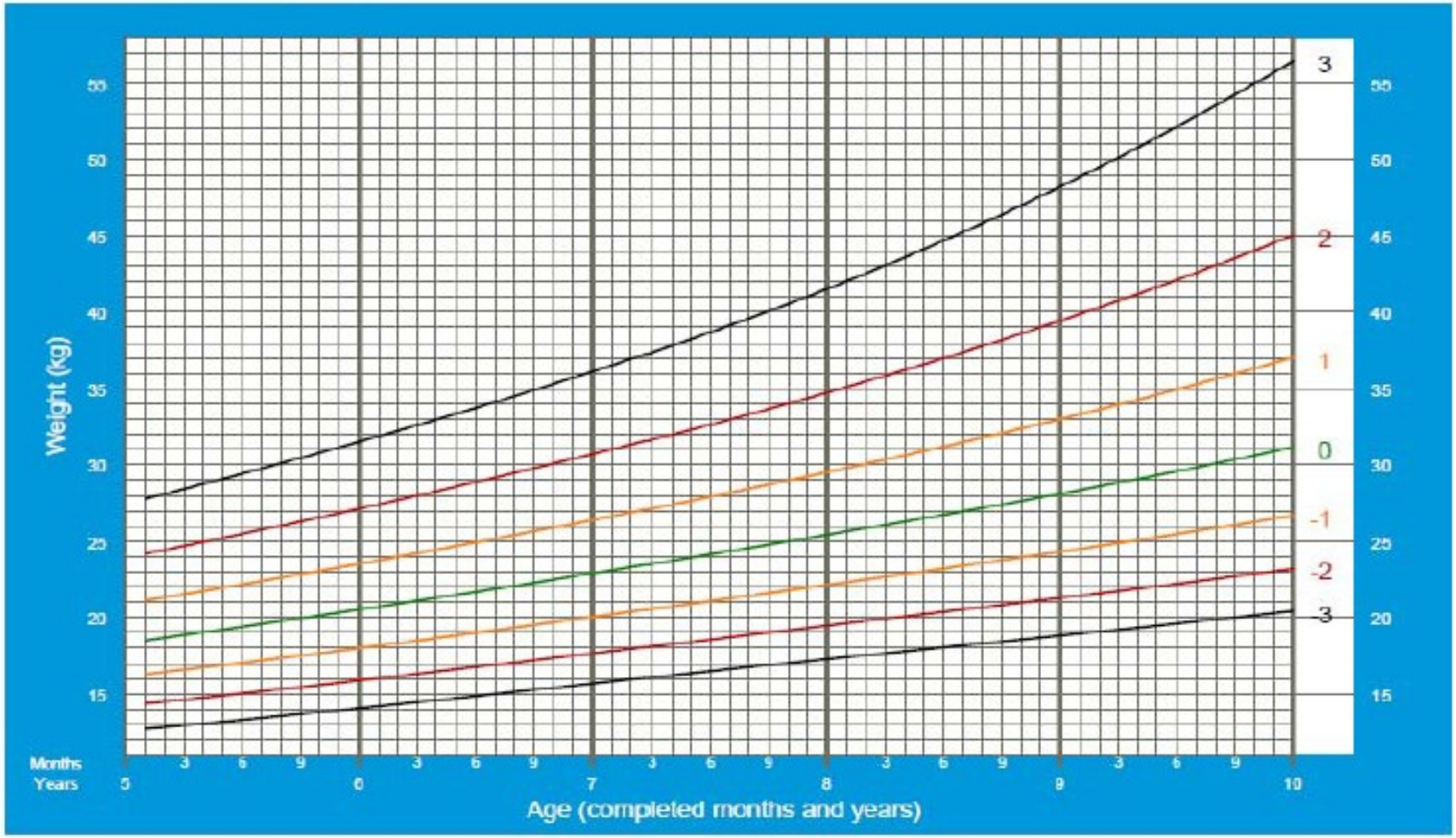
Growth Indices

- **Height-for-age**: measure of achieved linear growth relative to age
  - Low HFA (**shortness)** reflects a pathological process called **stunting**.
  - It could also be a normal variation
- **Weight-for-age**: reflects body mass relative to chronological age
  - Low WFA (**lightness)** reflects **underweight**
- **Weight-for-height:** measures body weight relative to height
  - Low WFH (**thinness)** reflects **'wasting'** in children
  - High WFH (**overweight**) in children reflects gaining excess weight relative to height or from gaining insufficient height relative to weight
- **Head circumference-for-age:**
  - Reflects **chronic undernutrition** (protein-energy deficiency) for children < 2 yr

Weight-for-age BOYS

World Health Organization

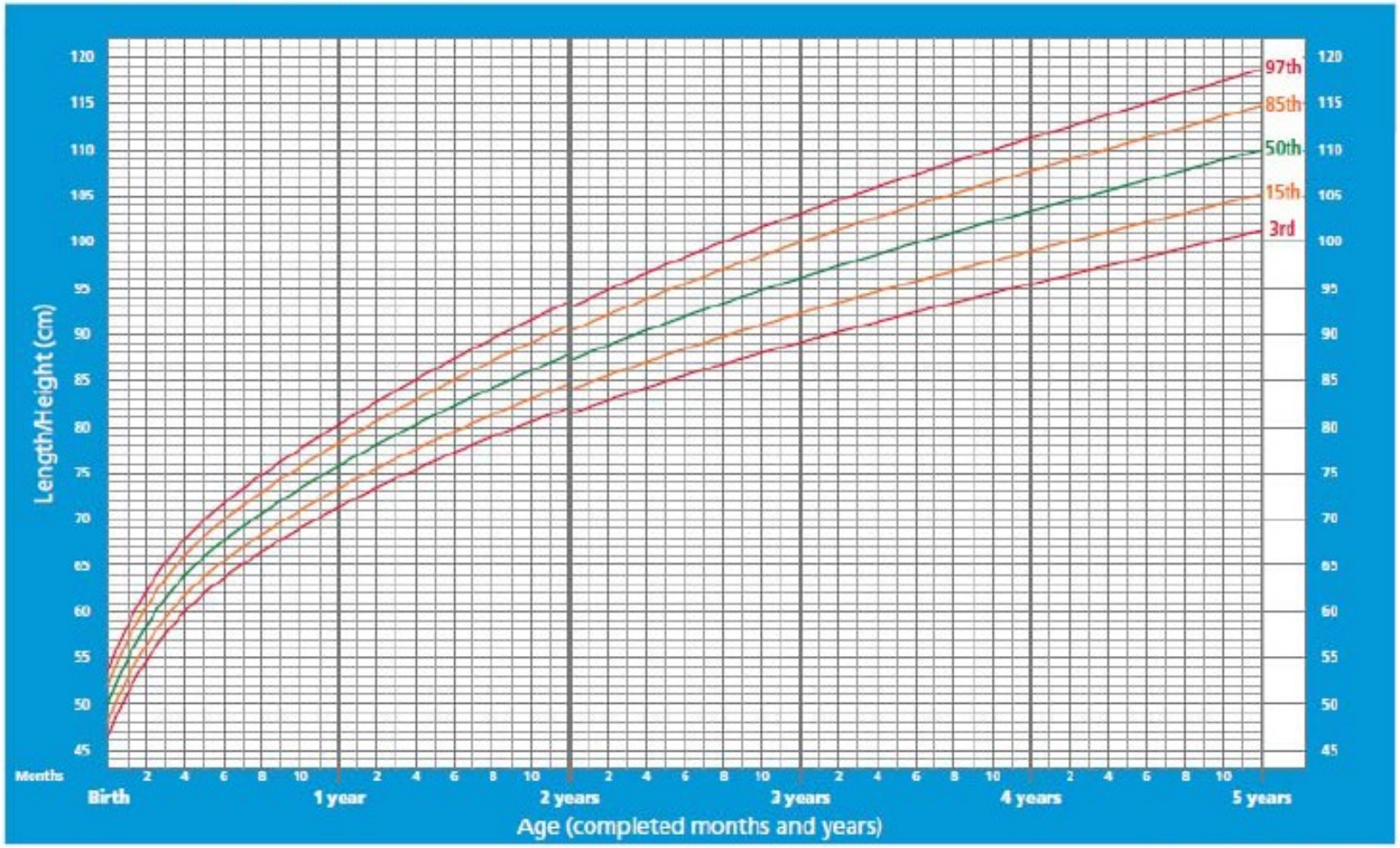
5 to 10 years (z-scores)



Length/height-for-age BOYS

Birth to 5 years (percentiles)

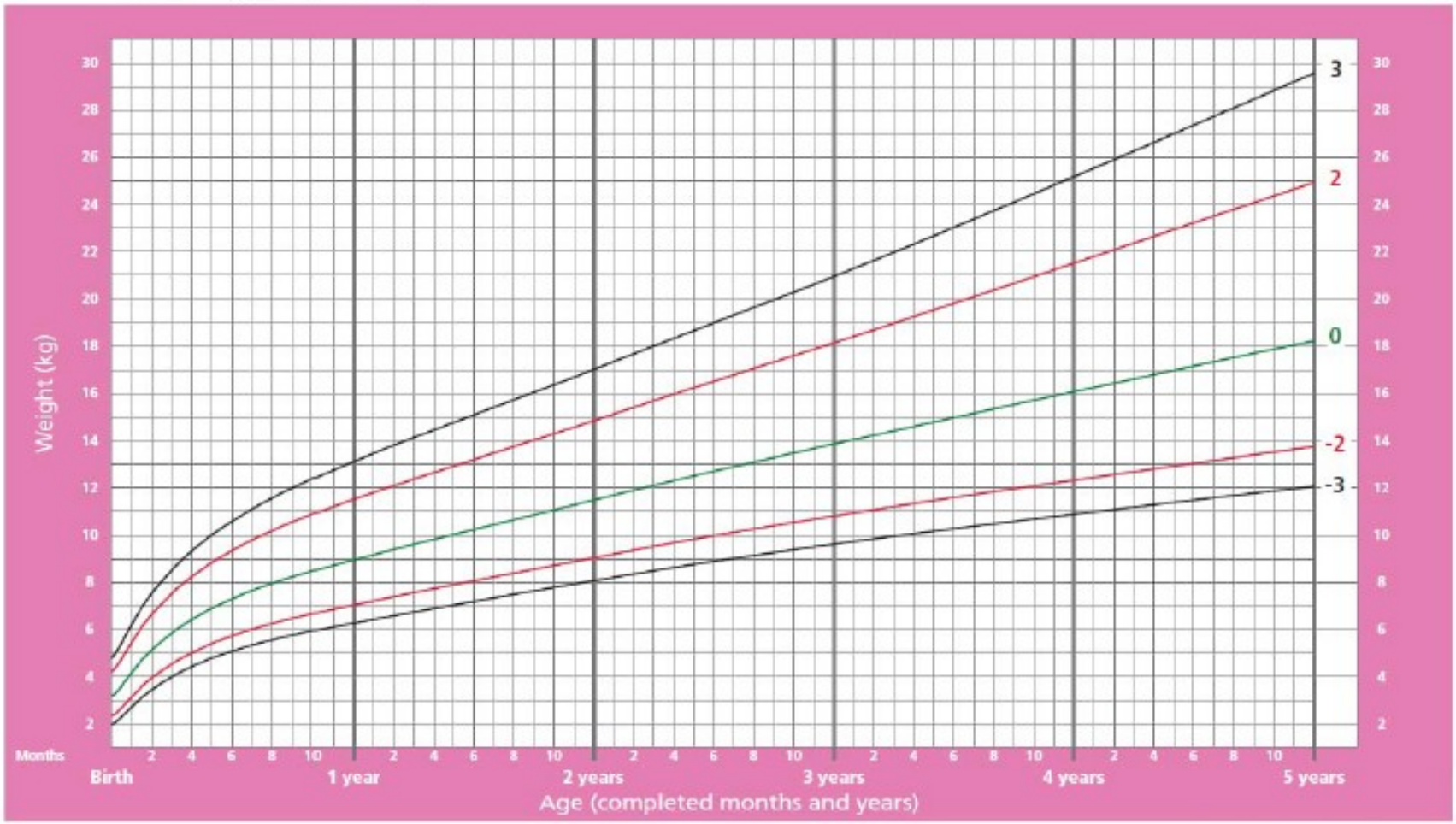
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Weight-for-age GIRLS

Birth to 5 years (z-scores)

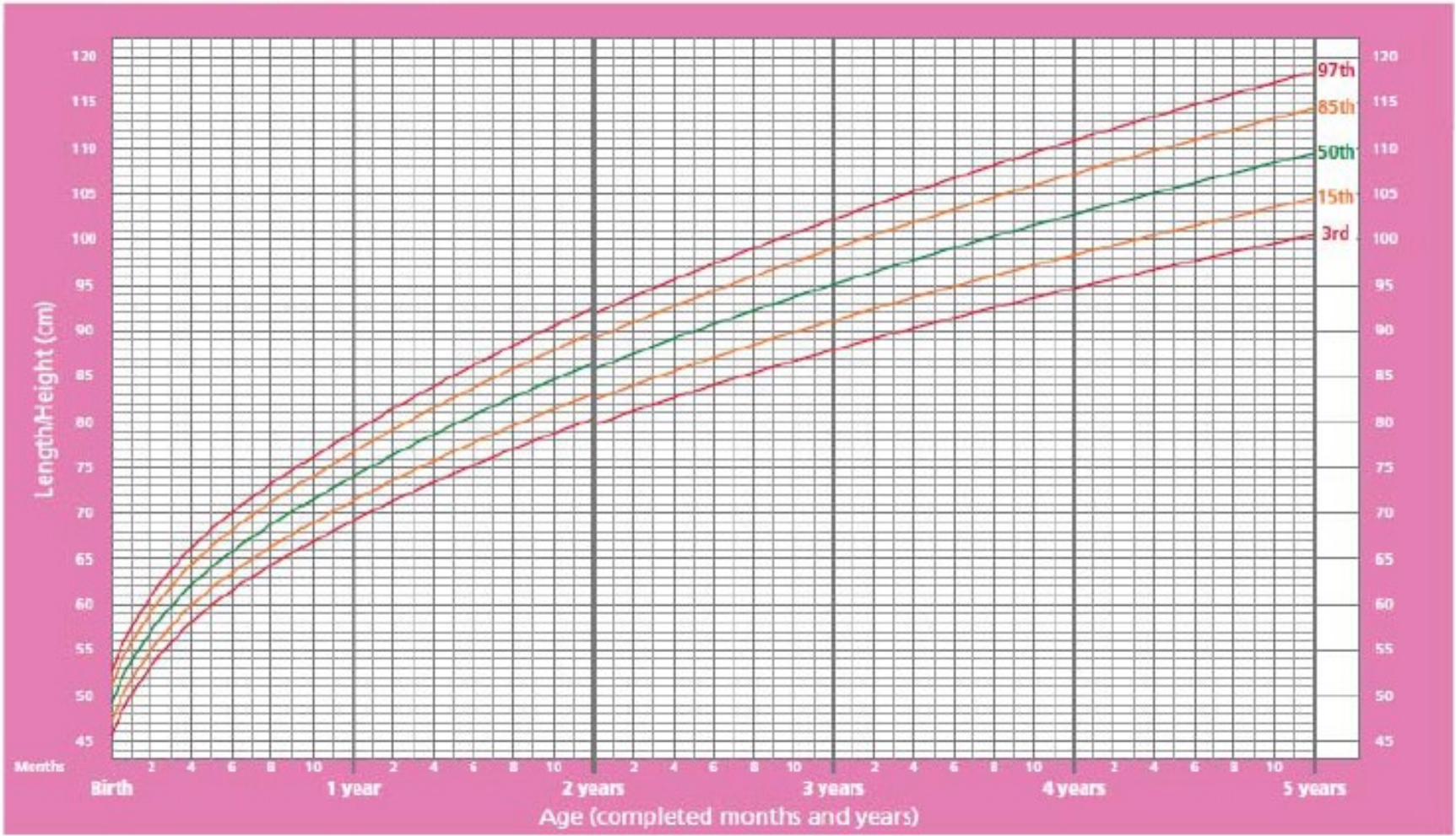
World Health Organization



Length/height-for-age GIRLS

World Health Organization

Birth to 5 years (percentiles)



Classification of nutritional status based anthropometric indices

- Gomez classification (weight-for-age)
- Well-come classification (weight-for-age)
- Waterlow Classification

Gomez classification (weight-for-age)

Percentage of NCHS reference	Level of malnutrition
90 – 109	Normal
75 – 89	Mild (Grade I)
60 – 74	Moderate (grade II)
<60	Sever (Grade III)

Disadvantages of Gomez classification

- The cut off point 90% may be too high as many well-nourished children are below this value.
- Edema is ignored and yet it contributes to weight and it does not indicate the duration of malnutrition
- Age is difficult to know in developing countries (agrarian society).
- It does not also differentiate between kwashiorkor and marasmus

Welcome classification (weight-for-age) (Welcome trust working party 1970)

Percentage (%) of NCHS reference	Level of malnutrition	
	Edema	No **Edema**
60 – 80	Kwashiorkor	Undernourished
< 60	Marasmic-Kwashiorkor	Marasmus

Welcome classification (weight-for-age) (Welcome trust working party 1970)

Disadvantages

- This method does not differentiate :
  - Acute malnutrition (for emergency planning)
  - Chronic malnutrition **(**for food security planning)
  - Depends on knowledge of the child’s age
  - Does not take height differences in to account

Waterlow Classification (Waterlow JC,1972)

Index	% of NCHS reference	Level of malnutrition	
Height for age	90 – 94	Mild	Stunting (Chronic malnutrition)
	85 – 89	Moderate	
	< 85	Sever	
Weight for height	80 – 89	Mild	Wasting (Acute malnutrition)
	70 – 79	Moderate	
	< 70	Sever	

Assessment of Body Composition

- Linear growth ceases at around the age of 25-30 years.
- Therefore, the main purpose of nutritional assessment of adults using anthropometry is determination of the changes of body weight and body composition

Body Composition…

- Weight relative to height: to take into account the effect of height
- Skin folds: estimate size of subcutaneous fat
- Waist circumference: proxy for central fat
- Waist-hip circumference ratio: regional distribution
- Mid-upper arm circumference (MUAC)
- Limb fat area

Weight relative to height

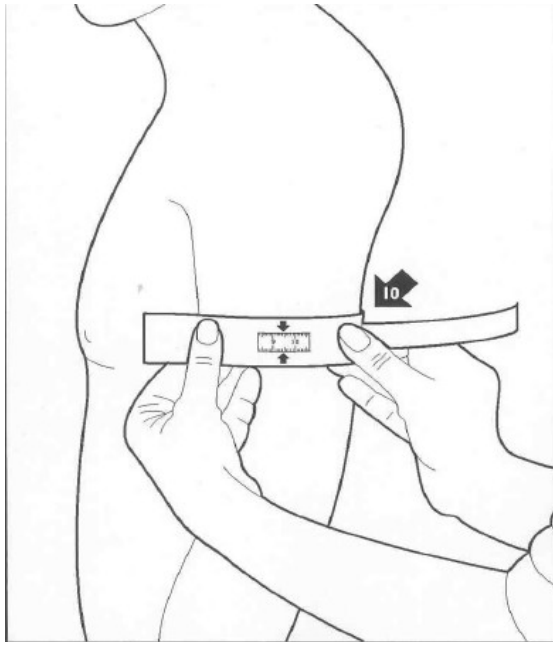
- To account the effect of height on weight value
- Weight to Height Ratio-wt/ht
- **Body Mass Index-wt/(ht)^2**
- Ponderal Index-ht/(wt)$^{1/3}$
- Benn's Index-wt/(ht)^p ; where p is calculated to minimize the direct relationship with height (Benn, 1971)

Mid upper arm circumference (MUAC)

- Is used for screening purposes especially in emergency situations where there shortage of human resource, time and other resources as it is less sensitive as compared to the other indices.
- It is measured half way between the olecranon process and acromion process using non stretchable tap
- In <5 yr children the cut-off points are:
  - Normal > 13.5 cm
  - Mild to moderate malnutrition 12.5-13.5 cm
  - Severe malnutrition < 11 cm

MUAC…

- It is a sensitive indicator of risk of mortality
- Useful for screening of children for community based nutrition interventions
- Useful for the assessment of nutritional status of pregnant women



Measurements used to assess fat mass:

- Body mass index
- Waist to Hip circumference ratio
- Skin fold thickness

Indices derived from the measurements

- Different indices could be derived by measuring the weight and height of an adult
  - Body mass index (Quetelet's index) = Wt/(Height in meters)^2
  - Weight/height ratio (Benn's index)^P
  - Ponderal index = Wt/ (ht)^3

Body mass Index(BMI)

- Body mass index the best method for assessing adult nutritional status as the index is not affected by the height of the person
- Therefore, it is most frequently used for assessing adult nutritional status

Cut-off points for BMI

- > 40 kg/m² = very obese
- 30-40 kg/m² = obese
- 26-29.9 kg/m² = overweight
- **18.5-25kg/m² = Normal**
- 17-17.9 kg/m² = mild chronic energy deficiency
- 16-16.9kg/m² = Moderate chronic energy deficiency
- < 16 kg/m² = severe chronic energy deficiency

Skin fold thicknesses

- Skin fold thickness is done at the following anatomical sights:
  - Biceps skin fold
  - Triceps skin fold
  - Subscapular skin fold
  - Suprailliac skin fold
  - Mid axillary skin fold
  - Thigh skin fold
  - Calf skin fold

Waist Circumference

- Proxy for central fat
- No universally accepted method of measurement
- WHO- Taken around natural waist at its widest point
- Mark lowest rib margin; palpate iliac crest; locate midway

  OR
- Locate at 2.5 cm above the belt

Waist-hip circumference

- Waist-hip circumference ratio: regional fat distribution
- Distinguishes fatness in lower trunk (hip & buttocks)-mainly subcutaneous & in upper trunk (waist & abdomen)
- Correlates with total body fat; Elevated WHR strongly associated w/increased risk of CHD, stroke, type 2 DM
- It is the circumference of the waist measured
  - midway between the lowest rib cage and anterior superior iliac spine divided by the circumference of the hip measured at the level of the greater trochantor off the fumer
  - both are measured to the nearest 0.5 cm
- If the ratio is > 1 in male, and > 0.87 in female there is high risk of coronary heart disease.

B. Biochemical/biophysical (laboratory) methods

- This involves measurement of either total amount of the nutrient in the body, or its concentration in a particular storage site (organ) in the body or in the body fluids.
- This group includes those that are indicative of defect in intermediary metabolism
- The depletion could be detected
  - By biochemical tests and/or
  - By tests that measure physiological or behavioral functions dependent on specific nutrient.

1) Static biochemical tests:-

- This involves measurement a nutrient or its metabolites in pre-selected biological material (blood, body fluids, urine, hair, fingernails etc.)
- Example, e.g. Biochemical Tests (laboratory)
  1. Serum ferritin level
  2. Serum HDL
  3. Erythrocyte Folate
  4. Tissue stores of Vit. A, Vit D,

Factors affecting the validity of static biochemical tests

- **Physiological** factors (pregnancy, diurnal variation, homeostatic regulation, physical exercise, age, sex, recent dietary intake)
- **Pathological** (inflammatory stress, infection, weight loss)
- **Analytical** (sample collection, sensitivity & specificity of the test, hemolysis, sample contamination, accuracy and precision of the method)

2) Functional biochemical tests (Biophysical tests):

- Assess sufficiency of a specific nutrient to permit optimally intended nutrient dependent function
- These functional biochemical tests are also useful for:
  - Sub-clinical deficiency states
  - Based on measurement of functional impairment
- Have greater biological value and significance than static tests, because they measure the extent of functional consequence of a specific nutrient deficiency.

Biomarkers of Nutrients

Nutrient	Most sensitive	Less sensitive	Least sensitive
Protein	Plasma aminoacids, transferrin, free alkaline Rnase, urine 3-methylhistidine	Serum albumin, Urine hydroxyproline , urea, creatinine	Total serum protein
Lipids	Serum HDL	Serum cholesterol, triglycerides	
Vitamin A		Serum vitamin A, Retinol binding protein	
Vitamin D	Serum 25 (OH) D_3, 1,25$(OH)_2$ D_3	Serum alkaline phosphatase	Serum calcium and phosphorus
Vitamin E	Serum Tocoferol, H_2O_2 erythrocyte		
Vitamin K	Serum prothrombin	Bleeding and coagulation time	

C. CLINICAL METHODS

- This are detection of deviations from the normal state of nutrition just by observing and interpreting clinical signs and symptoms of deficiency or under intake.

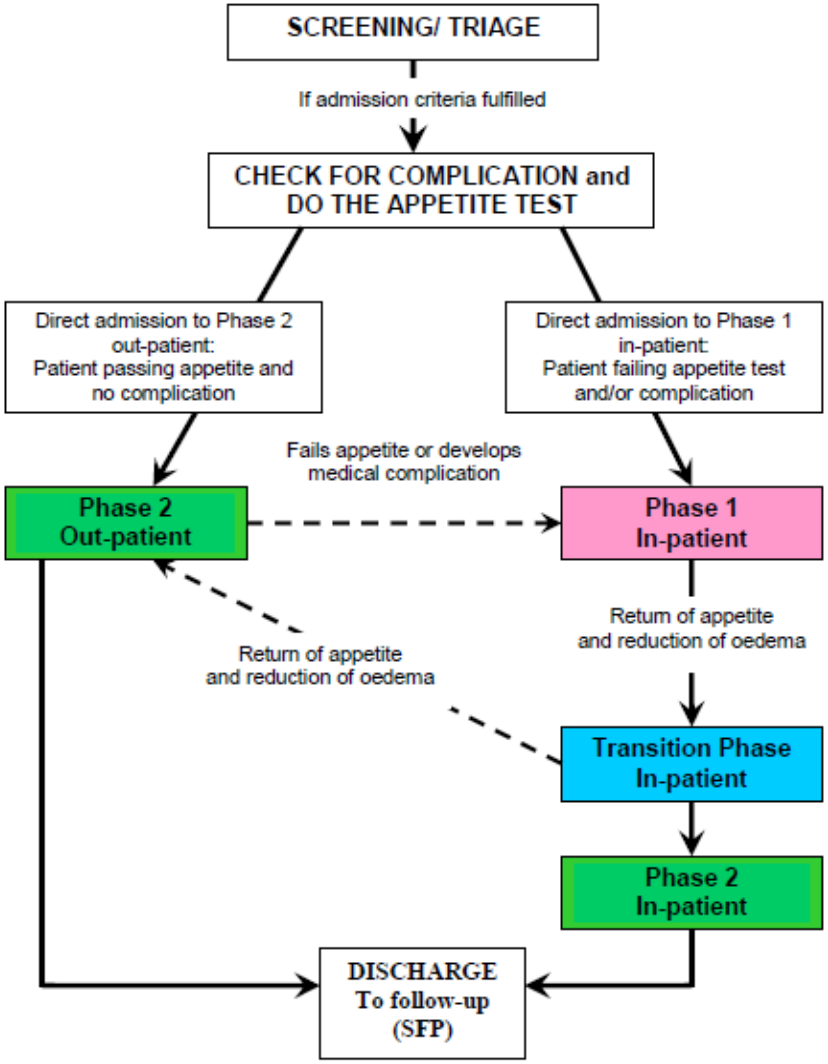
CLINICAL METHODS

Sign/ symptom	Nutritional abnormality
• Inability to see during the evening or dim light (Night blindness also called nyctalopia) • Bitot's spots	Vitamin A deficiency:
• Easy bruising of skin • Spongy bleeding gums	Scurvy (vitamin C deficiency)
• Pale: palms, conjunctiva, tongue • Easy fatigability, loss of appetite shortness of breath	Anemia: Which may herald, deficiency of: Iron, Vitamin B12, Folic acid, copper, protein (main causes of nutritional anemia)

4. Dietary Methods

- These methods include assessment of past or current intakes of nutrients from food by individuals or a group in order to know their nutritional status.
- At national level:-
  - Food balance Sheet also called National food disappearance data or food going in to consumption
  - Market data bases (for fortified foods by FDA)
- **At a household level**
  - Household food inventory method
  - Food account method
  - List recall method
  - Household food record method

Treatment


SCREENING/ TRIAGE
If admission criteria fulfilled
CHECK FOR COMPLICATION and DO THE APPETITE TEST
Direct admission to Phase 2 out-patient: Patient passing appetite and no complication
Direct admission to Phase 1 in-patient: Patient failing appetite test and/or complication
Fails appetite or develops medical complication
Phase 2 Out-patient
Phase 1 In-patient
Return of appetite and reduction of oedema
Return of appetite and reduction of oedema
Transition Phase In-patient
Phase 2 In-patient
DISCHARGE To follow-up (SFP)

Treatment

- **Phase I Feeding**
  - Feed the child a small amount of F-75
  - Eight feeds per day are given for 24h care units
  - No weight gain is expected
- **Transition Phase Feeding**
  - When the child has stabilized, transfer into transition phase and offer F-100 or RUTF
  - Higher calorie, higher protein “catch-up” feed
  - To progress from Phase 1 to transition phase:
    - Return of appetite (easily finishes 4-hourly feeds of F-75) and
    - Reduced oedema or minimal oedema (++ or less) and
    - No IV line, No NGT
  - The expected rate of weight gain is about 6 g/kg/day

Treatment

- **Phase 2 Feeding**
  - Transfer the child from transition phase to phase 2 if:
    - The child finish 90% of the F 100
    - If the child has oedema and will continue phase 2 as inpatient
  - The amount is unrestricted, usually 150kcal/kg/day

Treatment of medical complications

- **Dehydration:**
  - tends to be over diagnosed and its severity overestimated in severely malnourished children
  - Treatment
    - Do not use the IV route for rehydration except in cases of shock
    - Standard WHO ORS solution for general use has a high sodium and low potassium content, which is not suitable for severely malnourished children
    - Instead, give special rehydration solution for malnutrition, ReSoMal

ReSoMal

Ingredients	Amount
Water	2 L
WHO ORS	One 1 liter packet
Sugar	50 grams
Electrolytes/mineral solution*	40 mL

*45 ml of KCL solution (100gm KCL in one liter of water) can be used if electrolyte/mineral solution is not available

Hypothermia

- If the rectal temperature is below 35.5°C or axillary temperature below 35°C).
- Treatment
  - Feed the child immediately with F-75 and every 2-3 hours,
  - Use the “kangaroo technique” for children with a caretaker
  - The room should be kept warm, especially at night



Severe Anemia

- Haemoglobin concentration is less than 4g/dL
- **Treatment**
  - Give a Furosemide (1 mg/kg, given by IV)
  - Give 10ml per kg body weight of packed red cells or whole blood slowly over 3 hours, All children should be fasted during and for at least 3 hours after a blood transfusion

Hypoglycemia

- Blood glucose is <54 mg/dl
- Treatment: 50 ml of 10% glucose

Eye Problems

- If the child has any eye signs of vitamin A deficiency,
  - Give vitamin A orally on days 1, 2 and 14
    - Aged <6 months, 50 000 IU;
    - Aged 6–12 months, 100 000 IU;
    - Older children, 200 000 IU.

Antibiotics

- Antibiotics should be given to every patient with SAM
  - If no complications,
    - Give first line antibiotics: oral Amoxicillin for 7 days.
  - If complications present:
    - Gentamicin, plus IV Ampicillin for 2 days followed by Amoxicillin for a total treatment duration of 7 days

Deworming

- Albendazole or Mebendazole is given for children ≥1 year at the start of Phase 2 for patients that will remain as in patients

THANK YOU!