INTEGRATED THERAPEUTICS I

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Course Description

- Course name: **Pharmacotherapeutics**
- Course code:
- Credit hours: 4cr hr
- The course integrates the pathophysiology of disease state with concepts of
  - Drug selection
  - Dose optimization
  - Monitoring of therapeutic outcomes for safety & efficacy

Course objectives

- **At the end of this course, you are expected to:**
  - Recognize the various factors that may influence drug therapy in a patient;
  - Gather relevant patient information during drug therapy;
  - Interpret common diagnostic tests;
  - The etiology, pathophysiology, diagnosis, treatment and monitoring parameters of therapy outcomes in the management of common gastrointestinal diseases.

Pharmacotherapeutics I: Contents

- Chapter one: General principles
- Chapter two: Diagnostic tests
- Chapter three: Pharmacotherapy in special populations
- Chapter four: Pharmacotherapy of GI Diseases

Delivery Methods

- Interactive presentations and group discussions
- Individual and group exercise and assignments
- Case studies
- Brain storming
- Individual/group presentations
- Video dispalys

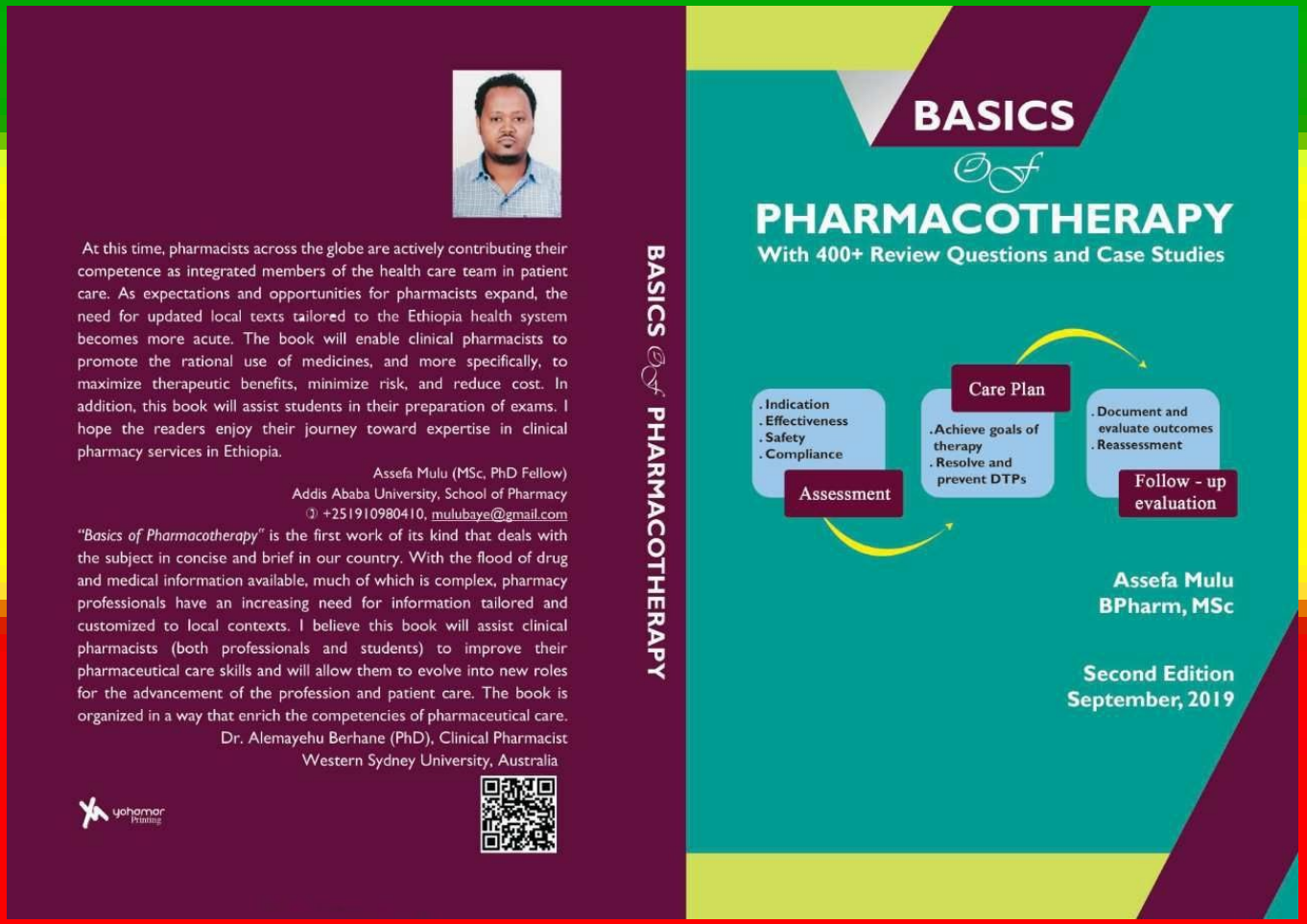
Methods of Assessment

- **Tests**: 20%
- **Individual and group presentations**: 10%
- **Midterm examination**: 30%
- **Final examination**: 40%

References

1. Marry Lee (ASHP). Basic skills in interpreting laboratory data 6th 2017
2. A Practical Guide to Pharmaceutical Care, American Pharmacists Association, latest edition.
3. Dipiro JT, Talbert RL, Yee GC, *et.al*. Pharmacotherapy, A Pathophysiologic Approach. 10th or later edition.
4. Koda - Kimble MA, Young LY, Kradjan WA, *et.al*. Applied Therapeutics, The Clinical Use of Drugs. 11th or later edition.
5. Assefa M. Basics of Pharmacotherapy. 2nd Ed September 2019.

References



At this time, pharmacists across the globe are actively contributing their competence as integrated members of the health care team in patient care. As expectations and opportunities for pharmacists expand, the need for updated local texts tailored to the Ethiopia health system becomes more acute. The book will enable clinical pharmacists to promote the rational use of medicines, and more specifically, to maximize therapeutic benefits, minimize risk, and reduce cost. In addition, this book will assist students in their preparation of exams. I hope the readers enjoy their journey toward expertise in clinical pharmacy services in Ethiopia.

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"Basics of Pharmacotherapy" is the first work of its kind that deals with the subject in concise and brief in our country. With the flood of drug and medical information available, much of which is complex, pharmacy professionals have an increasing need for information tailored and customized to local contexts. I believe this book will assist clinical pharmacists (both professionals and students) to improve their pharmaceutical care skills and will allow them to evolve into new roles for the advancement of the profession and patient care. The book is organized in a way that enrich the competencies of pharmaceutical care.

Dr. Alemayehu Berhane (PhD), Clinical Pharmacist
Western Sydney University, Australia

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BASICS of PHARMACOTHERAPY

BASICS
of
PHARMACOTHERAPY
With 400+ Review Questions and Case Studies

. Indication
. Effectiveness
. Safety
. Compliance
Assessment

Care Plan
. Achieve goals of therapy
. Resolve and prevent DTPs

. Document and evaluate outcomes
. Reassessment
Follow - up evaluation

Assefa Mulu
BPharm, MSc

Second Edition
September, 2019



INTRODUCTION TO PHARMACOTHERAPY

Chapter One

Introduction

- The use of medications in the health care system provides enormous help to many;
  - Lives are saved or enhanced, and life spans are lengthened
- Prescription medications are used daily (US);
  - 48.5% of the population uses one prescription drug daily,
  - 1.7% use three or more drugs daily, and
  - 10.6% use five or more prescription drugs daily

Introduction

- Problems occurring with the use of drugs can include:
  - Medication errors
  - Suboptimal drug, dose, regimen, dosage form, and duration of use
  - Unnecessary drug therapy
  - Therapeutic duplication
  - Drug–drug, drug–disease, drug–food, or drug–nutrient interactions
  - Drug allergies
  - Adverse drug effects, some of which are preventable

Pharmacotherapy: General Principle

1. There should be a **justifiable & documented indication** for every medication that is used.
2. A medication should be used at the **lowest dosage** & for the **shortest duration** that is likely to achieve the desired outcome.
3. When a pt is adequately treated with a single drug, **monotherapy** is preferred.
4. Newly approved medications should be used only if there are **clear advantages over older** medications.
5. Whenever possible, the selection of a medication regimen should be **based upon evidence** obtained from controlled clinical trials.

Pharmacotherapy: General Principle

6. The **timing of drug administration** should be considered as a possible influence on drug efficacy, adverse effects & interactions with other drugs & food.
7. A medication regimen should be **simplified** as much as possible to enhance pt adherence.
8. A **pt's perception** of illness or risks & benefits of therapy may affect adherence & treatment outcomes
9. Careful **observation of a pt's response** to treatment is necessary to confirm efficacy, prevent, detect, or manage adverse effects, assess compliance & determine the need for dosage adjustment or dc of drug therapy.
10. A medication should not be given by **injection** when giving it by mouth would be just as effective & safe.

Pharmacotherapy: General Principle

11. Before medications are used, **lifestyle modifications** should be made, when indicated, to obviate the need for drug therapy or to enhance pharmacotherapy outcomes.

12. Initiation of a drug regimen should be done with full recognition that a **medication may cause a disease, sign, symptom or abnormal laboratory test**.

13. When a variety of drugs are equally efficacious & safe, the drug that results in the **lowest health care cost** or is **most convenient for the pt** should be chosen.

14. When making a decision about drug therapy for individual pts, **societal effects** should be considered.

Pharmacotherapy: General Principle

15. Possible **reasons for failure** of medication regimens

- Inappropriate drug selection
- Poor adherence
- Improper drug dose or interval
- Misdiagnosis
- Concurrent illness
- Interactions with drugs or foods
- Environmental factors
- Genetic factors



THERAPEUTIC DRUG MONITORING (TDM) | 2019

Therapeutic Drug Monitoring

- TDM involves the measurement & interpretation of the concentrations of drugs in the plasma/serum/blood of patients.
- PK concepts are used to individualize pt drug therapy.
  - Increase efficacy & decrease toxicity of many medications
  - Achieve safe & effective therapeutic mgt of drugs in an individual pt.

Therapeutic Drug Monitoring

Drugs that do not need TDM:

- Drugs used for treating diseases of w/c their clinical end points can easily be monitored, (BP, HR, blood sugar, b/d cholesterol and triglycerides)
- Drugs whose serum concentrations **do not correlate** with therapeutic or toxic effects.
- Drugs with less complicated pharmacokinetics properties.
- Drugs used to treat less complicated or not life threatening diseases

Therapeutic Drug Monitoring

Commonly monitored drugs

- **Bronchodilators**: Theophylline
- **Antibiotics**
  - ✓ Aminoglycosides: Gentamicin, Amikacin
  - ✓ Vancomycin
- **Anticancers**: Methotrexate, Cyclosporine, Tacrolimus
- **Antiepileptics**: Phenobarbital, Phenytoin, Carbamazepine, Valproate
- **Cardiac Drugs**: Digoxin, Procainamide, Lidocaine
- **Psychoactive Drugs**: Lithium, TCA

Criteria for TDM

1. Assay methods
2. Narrow therapeutic range
3. Poor relationship b/n dose & SDC
4. Non-linear pharmacokinetics
5. Good relationship b/n SDC & therapeutic/toxic effects
6. Lack of therapeutic effects is dangerous (life threatening)
7. Difficulty in interpreting signs & symptoms of toxicity or therapeutic failure or in evaluating therapeutic responses
   - ✓ Toxicity vs therapeutic failure
   - ✓ Therapeutic responses

Therapeutic Drug Monitoring

- **Types of Assay Required**
  - Total drug concentration
  - Free drug concentration
  - Metabolites

Clinical Usefulness of TDM

1. **Maximizing efficacy**
   - Epileptic pt. vs phenytoin
   - Asthmatic pt. vs theophylline
2. **Minimizing toxicity**
   - Differentiate adverse effects from disease states
     - Digoxin toxicity vs ventricular arrhythmias
     - Digoxin toxicity vs hypo-K or hyper-Ca
   - Altered pharmacokinetics

CLINICAL USEFULNESS OF TDM

3. Identifying therapeutic failure

- Non-compliance
- Subtherapeutic dose
- Bioavailability problem
- Malabsorption
- Drug interactions

4. Facilitating adjustment of dose

- New dose = Old dose X Desired C_{ss}/Old C_{ss}

5. Facilitating therapeutic effects

- Target drug conc: Antiepileptics

Factors Affecting SDC & Interpretation of SDC

- Disease states: renal, liver, cardiac, thyroid
- Habits: diet, smoking, drinking
- Pregnancy, age, weight
- Non-compliance
- Electrolyte balance: Digoxin vs K^+ & Ca^+
- Drug interactions
- Plasma protein binding
- Bioavailability
- Sampling time

Therapeutic Range for Commonly Monitored Drugs

Amikacin	20–30 µg/mL
Carbamazepine	4–12 µg/mL
Digoxin	0.5–2 ng/mL
Gentamicin	5–10 µg/mL
Lidocaine	1–5 µg/mL
Lithium	0.6–1.4 mEq/L
Phenytoin	10–20 µg/mL
Procainamide	4–10 µg/mL
Quinidine	1–4 µg/mL
Theophylline	10–20 µg/mL
Tobramycin	5–10 µg/mL
Valproic acid	50–100 µg/mL
Vancomycin	20–40 µg/mL

DRUG INTERACTIONS (DIs)

DRUG INTERACTIONS (DIs)

Definition

- The pharmacologic or clinical response to the administration of a drug combination different from that is anticipated from the known effects of the two agents when given alone.
- Drug interaction results when the effects of a drug are altered in some way by the presence of another drug, by food, or by environmental exposure.

Epidemiology of Drug-Drug Interactions

- The risk of developing an adverse drug reaction (ADR) secondary to a drug–drug interaction increases significantly with the number of medications a patient is receiving.

- Adverse drug reactions are estimated to be responsible for 4.2–6% of all hospital admissions in the US

Epidemiology of Drug-Drug Interactions

- **Risks**
  - Elderly
  - Polypharmacy
  - Pts receiving less common and/or OTC medications
- **Potential Consequences**
  - Pt injury (including death)
  - Disease progression
  - Lost wages
  - Health care costs

Types of Drug Interactions

- Pharmacokinetic
  - One drug alters the concentration of another by altering its absorption, distribution, metabolism, or excretion
  - Usually (but not always) mediated by cytochrome P450 (CYP)
- Pharmacodynamic
  - Related to the drug's effects in the body
  - One drug modulates the pharmacologic effect of another drug: additive, synergistic, or antagonistic

Pharmacodynamic Drug Interactions

- **Synergistic**
  - Pharmacologic effect > than the summation of the 2 drugs
  - Beneficial: aminoglycoside + penicillin
  - Harmful: barbiturates + alcohol
- **Antagonism**
  - Pharmacologic effect < than the summation of the 2 drugs
  - Beneficial: naloxone in opiate overdose
  - Harmful: zidovudine + stavudine
- **Additive**
  - Pharmacologic effect equals to the summation of the 2 drugs
  - Beneficial: aspirin + acetaminophen

Pharmacokinetic Drug Interactions

- **Absorption**: GI motility, pH, chelate formation
- **Distribution**: transport proteins; penetration into sanctuary sites, plasma protein binding
- **Metabolism**:
  - Phase I (CYP450)
  - Phase II (conjugation)
- **Elimination**: Renal (glomerular filtration; tubular secretion)

Alterations in Absorption: GI Motility

- Decreased GI motility via methadone increases didanosine (ddI) degradation & reduces ddI bioavailability
- Increased GI motility by metoclopramide reduces digoxin absorption

Alterations in Absorption: Chelation

- Definition: Irreversible binding of a drug in the GI tract
- Tetracyclines, quinolone antibiotics + ferrous sulfate (Fe^{+2}), antacids (Al^{+3}, Ca^{+2}, Mg^{+2}), dairy products (Ca^{+2})
- Usually separating administration of chelating drugs by 2+ hours decreases interaction effect

Alterations in Absorption: pH

- Some drugs require an acidic environment for optimal absorption in the GI tract
- Examples: Fe, atazanavir, itraconazole & ketoconazole.
  - H_2 blockers and PPIs reduce absorption of these drugs

Drug Interactions: Transport Proteins

- Transport Proteins
  - **Efflux**: extrudes drugs outside of cell
  - **Uptake**: facilitates intracellular movement of molecules

Drug Transport: Efflux

- **Efflux proteins: P-gp**
  - Located in GI tract, BBB, liver, kidney, lymphocytes.
  - Transports many chemically diverse compounds
  - Modulation of P – gp by one drug may alter the PK of another
  - Substrates: **digoxin**, **colchicine**, **fexofenadine**
  - Inhibitors: cyclosporine, verapamil, erythromycin, itraconazole
  - Inducers: phenobarbital, rifampin, phenytoin, St. John's wort

Drug Transport: Uptake

- **Uptake proteins: OCT, OAT**
  - Transport numerous amphipathic compounds
  - Some present only in the liver
  - Many present at the BBB, lung, heart, intestine, kidney.
  - Facilitate the influx of compounds
  - Fexofenadine and digoxin are well-defined OATP substrates
  - Fruit juices inhibit OATPs, along with quinidine, nelfinavir, saquinavir, and ketoconazole

Drug Transport: Uptake

- **GI**
  - Fruit juices (grapefruit juice, apple juice & orange juice) inhibit OATP and reduce fexofenadine absorption
- **Liver**
  - OATP 1B1 uptakes drug into the hepatocyte where it then undergoes subsequent metabolism.
  - Blockade of OATP 1B1 by LPV/r results in reduced metabolism and increased plasma drug concentrations of rosuvastatin

Distribution: Protein Binding Interactions

- **Non-restrictively** cleared drugs
  - Eliminating organ removing most of the drug being presented to it, including the fraction bound to plasma proteins
  - Increase in fu will not lead to a proportional increase in CL
  - No examples of clinically significant protein binding interactions have been identified with non-restrictively cleared drugs

Distribution: Protein Binding Interactions

- **Restrictively cleared drugs**
  - Small fraction of drug extracted during single passage through the eliminating organ
  - Only unbound drug in plasma can be cleared
  - Increase in fu leads to proportional increase in total drug CL and decrease in total drug Cpss
  - Only likely to clinically significant for drugs with long $T_{1/2}$, small Vd, narrow therapeutic range, high PPB
  - Example: warfarin displacement from serum albumin by Cotrimoxazole.

Drug Metabolism Interactions

- Typically occur in the liver and/or G.I. tract
- Inhibition or induction of CYP enzymes by one drug that results in altered metabolism of another coadministered medication

Drug Metabolism Interactions: Inhibition

- Usually by **competitive** binding to enzyme site
- Enzyme inhibition results in significant increases in the substrate medication
- Typically occurs quickly; depends on the time to steady-state of the inhibitor
- Time to maximum interaction effect dependent on time required for substrate drug to reach new steady-state

Drug Metabolism Interactions: Inhibition

- Some examples of strong inhibitors
  - **CYP1A2**: ciprofloxacin; fluvoxamine
  - **CYP2C8**: gemfibrozil
  - **CYP2C9**: fluconazole
  - **CYP2C19**: omeprazole, rabeprazole, lansoprazole
  - **CYP2D6**: fluoxetine
  - **CYP3A:** itraconazole, ketoconazole, HIV protease inhibitors, clarithromycin

Drug Metabolism Interactions: Inhibition

Key questions when assessing potential inhibition:

- What is the safety index of the substrate medication?
  - Can a small increase in conc. result in toxicity? (digoxin, warfarin, tacrolimus)
  - Can relatively large serum conc. be well-tolerated? (SSRIs)
- Is the substrate metabolized by one or multiple CYPs?
- Does the substrate have **active metabolites**?
- Can **pro-drugs** form the active metabolite?
  - Clopidogrel + CYP2C19 inhibitor (i.e. omeprazole)
    - The active metabolite isn't formed resulting in reduced pharmacologic (antiplatelet) activity

Drug Metabolism Interactions: Induction

- Gradual **onset** and **offset**
  - Involves increased DNA transcription and synthesis of new CYP enzymes – this takes time
  - Depends on $T_{½}$ of inducer, time to make new CYP proteins, and rate of degradation of CYP proteins
- Results in reduction of plasma concentration of substrate drugs
  - Risk of therapeutic failure
  - Induction may lead to formation of toxic metabolite
  - Removal of inducer may lead to toxic concentrations of substrate

Drug Metabolism Interactions: Induction

- Some examples of CYP inducers
  - **1A2:** tobacco, omeprazole, ritonavir
  - **2B6**: phenobarbital, phenytoin, rifampicin
  - **2C9**: rifampicin
  - **2C19**: carbamazepine
  - **2D6**: dexamethasone, rifampin
  - **CYP3A**: efavirenz, nevirapine, barbiturates, carbamazepine, rifampicin, rifabutin, glucocorticoids, phenytoin, St. John's wort

Drug Metabolism Interactions: Induction

St. John's wort





Drug Excretion Interactions

- Some drugs could either increase or decrease the excretion of other drugs.
  - ✓Probencid + Penicillin → enhanced effect of penicillin.
  - ↳Probencid decreases the secretion of penicillin

Evaluating potential DIs in the clinical setting: points of consideration

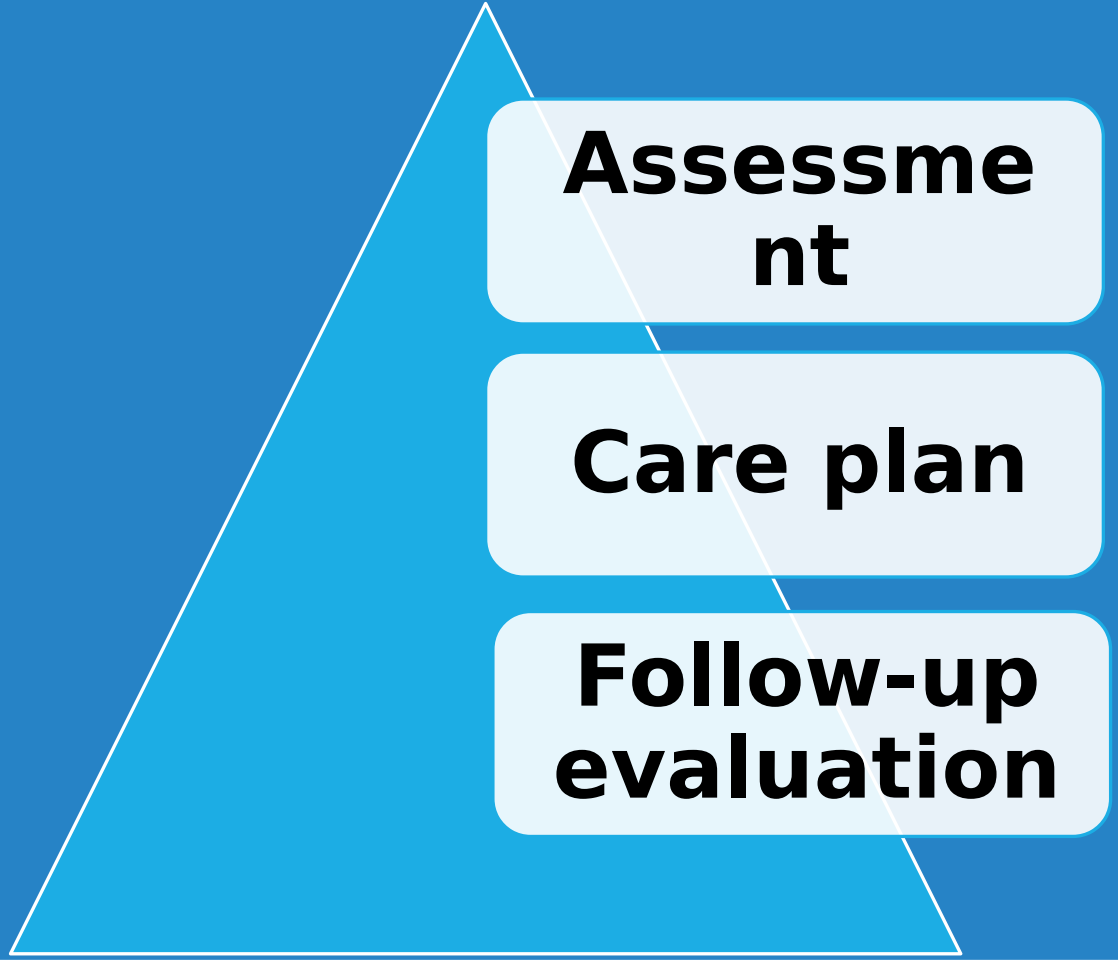
- Is the interaction clinically significant
- Therapeutic index of the “victim” drug
- How many drugs potentially involved?
- What is the likely time course of the interaction?
- Is inhibition/induction a class effect?
  - Cimetidine vs other H_2 blockers
- Options in managing the interaction
  - DC interacting drug, affected drug, or both?
  - Switch to another drug? Same drug class or another?
  - Change dose of affected drug?
  - Add another drug to circumvent the interaction (i.e. RTV)?

Drug Interactions: General Tools for Evaluation and Management

- Familiarity with metabolic pathways
- Know where to locate information on interactions
- Obtain thorough medication HX at each visit
- Maintain high index of suspicion when:
  - Therapeutic response is less than expected
  - Toxic effects are present
- Choose drugs that are less likely to interact
- Consider TDM in certain situations
  - When multiple DDIs are suspected, pregnancy, children, other special populations (liver disease, renal disease)

Drug Interactions: Resource examples

- Micromedex:
  - www.micromedex.com
- Natural Products Data Base:
  - http://www.naturaldatabase.com
- Lexi-Comp Lexi-Interact:
  - www.lexi-comp.com



PHARMACEUTICAL CARE

2019

Defining Pharmaceutical Care

- Pharmaceutical care is a patient-centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment.

THE CHANGING ROLE OF THE PHARMACIST

DISPENSING PHARMACY

1. Product business
2. Bring the product to consumer
3. Decisions focus on the business
4. Inventory generates revenue
5. Available service supports products

PHARMACEUTICAL CARE

1. Service (people) business
2. Bring the practitioner to patient
3. Decisions focus on the patient
4. Patient care generates revenue
5. Available products support service

DISPENSING PHARMACY	PHARMACEUTICAL CARE
6. Success measured as # of Rx	6. Success measured as patient outcomes
7. Space to display and sell	7. Space organized to meet patient needs
8. Records kept for legal purposes	8. Documentation to provide quality care
9. Visits determined by refill supply	9. Visits determined by patient risk/benefit
10. Business passive via prescriptions	10. Practice grows via patient recruitment

HEALTH CARE NEEDS OF A PATIENT



Pharmaceutical Care in Health Care

	Primary Focus	Knowledge Base	Responsibility in the drug use process
Medical Care	Diagnosis and treatment of the patient's disease	Pathophysiology	Prescribing
Nursing Care	Giving care to the whole patient during the cure or treatment	Biological, psychological, social, or spiritual human responses	Drug administration
Pharmaceu-tical	Identifying and meeting a patient's drug-	Pharmacotherapy	Identification, prevention, and

Pharmaceutical Care

- Pharmaceutical care is how a practitioner applies expert pharmacotherapeutic knowledge in practice to benefit the patient.

DRUG-RELATED NEEDS

During a pharmaceutical care encounter, the **patient, the patient's medical conditions**, and all of the **drug therapies** are assessed to determine if the following drug-related needs are being met

DRUG-RELATED NEEDS

1. **The medication is appropriately indicated**
   - ✓ There is a clinical indication for each medication being taken.
   - ✓ All the medication that is needed to treat each of the patient's medical conditions is being taken.

DRUG-RELATED NEEDS

2. The medication is effective

- The most effective product is being used.
- The dose of the medication is achieving the intended goals of therapy.

DRUG-RELATED NEEDS

3.The medication is safe

- There are no adverse reactions being experienced.
- There are no signs of toxicity.

DRUG-RELATED NEEDS

4. The patient is compliant

- The patient is able and willing to take the medications that have been determined to be appropriate, effective, and safe for the patient.

DRUG THERAPY PROBLEMS

- Drug therapy problems are undesirable events or risks that the patient experiences that inhibit or delay him/her from achieving the desired goals of therapy.

- The identification, resolution, and prevention of drug therapy problems are the heart and soul of pharmaceutical care practice

DRUG THERAPY PROBLEMS

1. **Unnecessary drug therapy**
2. **Needs additional drug therapy**

5. **Dosage too low**
6. **Dosage too high**

Indication → Drug product → Dosage regimen → Outcomes

Effectiveness

Safety

DRUG THERAPY PROBLEMS

Drug-related Needs

Indication

Effectiveness

Safety

Compliance

Drug Therapy Problems

Unnecessary Drug Therapy

Needs Additional Drug Therapy

Ineffective Drug

Dosage Too Low

Adverse Drug Reaction

Dosage Too High

Noncompliance

Indication

1. UNNECESSARY DRUG THERAPY

- **Causes**
  - ✓ No medical indication
  - ✓ Duplicate therapy
  - ✓ Non-drug therapy more appropriate
  - ✓ Treating avoidable adverse reaction

INDICATION

2. NEEDS ADDITIONAL DRUG THERAPY

- ✓ Untreated condition requires initiation of drug therapy
- ✓ Preventive therapy is required
- ✓ Synergistic or potentiating therapy required

Preventive drug therapy	Clinical indication
Aspirin	Prevention of heart attack and/or stroke
Calcium supplements	Prevention of osteoporosis
Folic acid supplement (during Px)	Prevention of neural tube defects
Pneumococcal vaccine	Prevention of pneumococcal pneumonia
Filgrastim	Prevention of infection in selected patients receiving anti-cancer drug therapies
Sunscreens	Prevention of sun-induced skin disorders
Dimenhydrinate	Prevention of motion sickness
Oral contraceptives	Prevention of pregnancy
Amoxicillin	Endocarditis prophylaxis in dental patients with cardiac lesions or prosthetic heart valves.
Colchicine	Prophylactic therapy for

EFFECTIVENESS

3. INEFFECTIVE DRUG

- ✓ More effective medication available
- ✓ Condition refractory to drug
- ✓ Dosage form inappropriate
- ✓ Drug not effective for condition

Effectiveness

4. DOSAGE TOO LOW

- ✓ Dose too low
- ✓ Frequency inappropriate
- ✓ Drug interaction
- ✓ Duration inappropriate

SAFETY

5. ADVERSE DRUG REACTION

- ✓ Undesirable reaction
- ✓ Unsafe drug for patient
- ✓ Drug interaction
- ✓ Dosage increased or decreased too fast
- ✓ Allergic reaction

SAFETY

6. DOSAGE TOO HIGH

- ✓ Dose is too high
- ✓ Frequency inappropriate
- ✓ Duration inappropriate
- ✓ Drug interaction
- ✓ Administered too rapidly

Compliance

7. NONCOMPLIANCE

- ✓ Patient does not understand instructions
- ✓ Patient prefers not to take the medication
- ✓ Patient forget to take medication
- ✓ Drug product is too expensive for the patient

THE PATIENT CARE PROCESS

- A guide for the practitioner
- A standard for the practice
- A comprehensive and consistent description of the practitioner's work
- A method that allows the practitioner to make rational (well-reasoned, scientific) decisions.
- An application of the problem-solving process

Patient Care Process

1. Assess the patient's drug-related needs
2. Develop a care plan
3. Complete a follow-up evaluation

Patient Care Process

Assessment

- Ensure all drug therapy is *indicated, effective* and *safe*.
- Patient can and will *comply* with instructions.
- Identify *DTPs*



Care plan

- Resolve drug therapy problem
- Achieve goals of therapy
- Prevent DTP



Follow-up evaluation

- Record actual outcome
- Evaluate status as progress in meeting in Therapeutic goals
- Re assess for new problem



The Patient Care Process

ESTABLISH A THERAPEUTIC RELATIONS



CONTINUOUS FOLLOW-UP

Assessment

- A systematic review of the patient's drug-related needs
- Performed by the pharmacist with the patient to ensure that all drug therapy is indicated, effective, safe, patient is compliant, and to identify drug therapy problems

Assessment

- The purpose of the assessment is three fold.
- Firstly, to understand the patient well enough to make rational drug therapy decisions with and for him/her.

- Secondly, to determine if the patient's drug therapy is appropriate, effective and safe, and to determine your patient's compliance with his/her medication regimens.

- Thirdly, the purpose is to identify drug therapy problems.

Assessment Decisions



Assessment

Primary sources of information:

Patient

Family

Caregivers

Texts

Literature

Assessment

Other sources of information:

Prescribers

Medication profiles

Medical chart

Laboratory test results

Assessment

1. Patient description (demographics, background)
3. Reason for the encounter (What your patient wants) “chief complaint”
4. Medication experience
5. Medication history
6. Current medication record
7. Other medical history
8. Review of systems

Assessment

Demographics

- Used to personalize and individualize interpretations of the patient's drug-related needs and drug therapy instructions
- Age, gender, race, height, weight.

Assessment

- Social history: living arrangements, occupation, special needs (e.g., physical abilities, cultural traits, drug administration devices).
- Pregnancy and Breast-Feeding

Pharmacist's Assessment

Family Background

- Family history: relevant health histories of parents and siblings.
  - "Has anyone in your family also had this?"
  - "Is anyone else at home also ill?"

Assessment

Reason for the Encounter

"chief complaint"

- **"What can I do for you today?"**
- **"How can I help you today?"**
- **"Tell me how you have been feeling since the last time we talked."**

Assessment

Medication Experience

- Preferences, attitudes, general understanding of his or her drug therapy, concerns about it, expressed expectations of desired outcomes, and the patient's medication taking behavior

Assessment

Medication History

Components of the Medication History

- Immunization status
- Social drug use
- Allergies, adverse reactions and other special needs, and
- History of relevant medication use.

Assessment

Immunization History

- Childhood immunization record
- Adult immunization record

Assessment

Social Drug Use: Smoking, alcohol, and drugs of abuse

- "Are you, or have you ever been a smoker?"
- "Describe your attempts to cut down or quit."
- "Is this something you would find difficult to give up?"

Assessment

- Allergies and Adverse Reactions
- In most cases, an allergic reaction to a drug product requires that the patient not receive that drug or related agents in the future.
- However, if your patient has experienced an undesirable adverse effect caused by a drug product that was not deemed to be allergic in nature, in future decisions that product may be considered appropriate despite

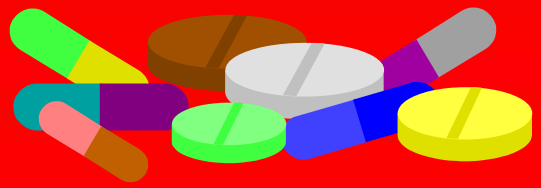
Assessment

- History of Relevant Medication Use
- For two primary reasons:
  - If the present problem has been treated before with medications and if so, what was the outcome or result.
    - If it was effective before, it is likely to be effective again
  - If the patient has experienced any treatment failures and unwanted side effects to medications used in the past

Assessment

Current Medication Record

- What medications is your patient currently taking (or supposed to be taking)?
  - Medications: Prescription, Nonprescription, Herbals
  - Indication



Current Medication Record



Include all regularly used drugs including:

- Oral contraceptives
- Vitamins & minerals
- Cough & cold preparations
- Laxatives
- Aspirin, acetaminophen, ibuprofen
- Natural and herbal preparations

Assessment

- Other Clinical Information
  - Medical History
  - Review of Systems

Assessment

Medical History

- Serious illnesses requiring drug therapy
  - Hospitalizations
  - Surgical procedures
  - Accidents and injuries
  - Pregnancies and deliveries

Assessment

Review of Systems

- To uncover significant symptoms or problems (drug-related) that have not already been revealed during the assessment interview.
- Use general questions:
  - "Are you having any trouble with your vision?"
  - "Have you ever had any stomach or bowel problems?"

Assessment

Review of Systems

- EENT
- Cardiovascular
- Pulmonary symptoms
- Gastrointestinal
- Skin
- Endocrine Systems
- Reproductive
- Urinary
- Hematopoietic
- Musculoskeletal
- Neuropsychiatric
- Infectious Disease

Drug Therapy Problems

Stated as

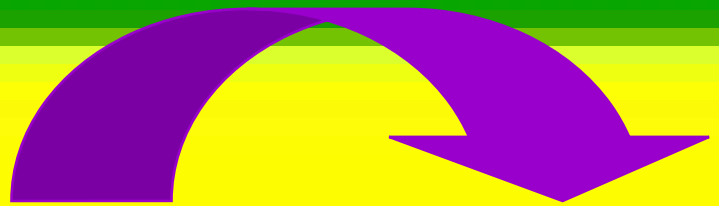
- The patient's problem
- The drug therapy involved
- The relationship (cause and effect)

Care Plan

- The purpose of the care plan is to organize all of the work agreed upon by the practitioner and the patient to achieve the **goals of therapy**.

- This requires **interventions to resolve drug therapy problems, to optimize the patient's medication** experience and prevent new drug therapy problems from developing.

Care Plan



ASSESSMENT **CARE PLAN**

- Any difficulty you have in developing a care plan, means you missed something in your assessment.

Goals of Therapy

- Curing a disease
- Address signs and/or symptoms
- Slow progression of a disease
- Prevent a disease
- Normalize laboratory values
- Assist in the diagnostic process

Goal of therapy	Medical condition
Cure a disease	Streptococcal pneumonia
	Otitis media
	Diarrhea
Reduce or eliminate signs and/or symptoms	Major depression
	Allergic rhinitis
	Common cold
Slow or halt the progression of disease	Diabetes
	Congestive heart failure
	Ischemic heart disease
Prevent a disease	Osteoporosis
	Myocardial infarction
	Pneumococcal pneumonia
Normalize laboratory values	Hypokalemia
	Anemia
Assist in the diagnostic process	Anxiety associated with MRI procedures
	Intraocular pressure tests for glaucoma

Goals of Therapy

What you are trying to accomplish with pharmacotherapy

Parameters

- Improvements in clinical signs and symptoms (**observed values**)
- Changes in laboratory test results as evidence of improvements (**measured values**)

How long it will take

Time Frame

- When to expect evidence of improvement
- Time required to achieve full therapeutic response

Care Plan

INTERVENTIONS

- **Initiate new drug therapy**
- **Increase dosages**
- **Decrease dosage**
- **Discontinue drug therapy**
- **Referrals**
- **Provide instructions for optimal use of medications**

Care Plan

- **Schedule for the next follow-up evaluation**

✓ When do you plan to see your patient again to determine the effectiveness and safety of your intervention`s?

- `

Follow-up Evaluation

- The purpose of the follow-up evaluation is to determine the actual outcomes of drug therapy for the patient, compare these results with the intended goals of therapy, and determine the effectiveness and safety of pharmacotherapy and the current status of the patient.

EVALUATION

Look for and document:

- **GOOD**: achieving goals of therapy most often improvement in the medical condition
- **BAD**: (side effects, adverse drug reaction, or toxicity resulting from drug therapies
- **NEW**: new problems, noncompliance, new medical conditions requiring drug therapy

EVALUATION: EFFECTIVENESS

Evidence:

Clinical signs and/or symptoms

(improvements in the presentation of the disease/illness)

Laboratory test results

(improvements in the indicators of the disease or illness)

EVALUATION: SAFETY

Evidence:

Clinical signs and/or symptoms

(Undesirable effects of drug therapy)

Laboratory test results

(Indicators of harmful effects of drug therapy)

EVALUATION: COMPLIANCE

“How much of your medication were you able to take?”

“How many do you take at a time?”

“When do you take them?”

“What kind of reminders do you find helpful?”

OUTCOME EVALUATIONS

1. **Resolved:** Goals achieved, therapy completed
2. **Stable**: Goals achieved, continue therapy
3. **Improved:** Progress being made, continue therapy
4. **Partial Improvement**: Progress made, minor adjustments required
5. **Unimproved**: No progress yet, continue therapy
6. **Worsened:** Decline in health, adjust therapy

REASONS TO DOCUMENT

1. Provide quality patient care
2. Manage the practice
3. Liability issues
4. Evaluate performance
5. Justify professional role
6. Reimbursement

NO DOCUMENTATION MEANS YOU DID NOT DO IT!!

Medical Terminologies

ASSEFA M | 2019

General terms

- **Hypertrophy:** increase in the size of cells
- **Hyperplasia:** increase in the number of cells
- **Atrophy:** decrease in the size of a cell
- **Hypoxia:** decreased oxygen supply to tissues
- **Ischemia:** decreased blood flow to or from an organ
- **Infarction:** an infract is an area of ischemic necrosis caused by occlusion of either the arterial supply or venous drainage in a particular tissue.
- **Inflammation :** a local response (reaction) of living vasculaized tissues to endogenous & exogenous stimuli. It is a physiologic (protective) response to injury.

General terms

- **Edema:** fluid accumulation in the body cavities in excessive amount.
  - **Hydrothorax:** fluid accumulation in pleural cavity in a pathologic amount.
  - **Hydropericardium:** pathologic amount of fluid accumulated in the pericardial cavity.
  - **Hydroperitoncum (ascites):** fluid accumulation in peritoneal cavity
  - **Anasarca** : severe & generalized edema of the body with profound subcutaneous swelling

Gastrointestinal System

- **Dysphagia**: difficulty or discomfort in swallowing.
- **Odynophagia:** pain felt during swallowing
- **Nausea**: feeling of an imminent desire to vomit, usually referred to the throat or epigastrium
- **Vomiting (emesis):** forceful oral expulsion of gastric contents.
- **Retching**: labored rhythmic contraction of respiratory and abdominal musculature that frequently precedes or accompanies vomiting
- **Regurgitation:** expulsion of food in the absence of nausea and without the abdominal and diaphragmatic muscular contraction associated with vomiting

Gastrointestinal System

- **Hematemesis**: vomiting of blood –pure or altered.
  - It heralds the possible presence of bleeding into the GIT.
  - If the rate of bleeding is fast, the color will be bright red.
  - If the rate of bleeding is slow, blood mixes with the gastric secretions and becomes altered.
- **Coffee-ground vomiting**: is the vomiting of precipitated blood clots & acid-degraded blood that produces a characteristic appearance when vomited (Dark blood or 'coffee grounds')
- **Projectile vomiting**: vomiting without antecedent nausea. It suggests the possibility of a rise in the ICP or GOO

Gastrointestinal System

- **Indigestion (Dyspepsia):** distress associated with eating.
- **Diarrhea:** an abnormal increase in stool liquidity and frequency.
- **Constipation**: defined as two or fewer bowel movements per week and/or a sensation of straining, incomplete evacuation or hard lumpy stools in most occasions
- **Hematochezia**: is the passage of bright red blood from the rectum with bowel movements (BRBPR).
- **Melena:** the presence of black tarry stools as a result of blood degraded by intestinal enzymes.
- **Icterus or jaundice**: yellowish discoloration of the skin and eyes.

Gastrointestinal System

- **Striae**: whitish or pink wrinkled marks on the abdominal skin
  - Pregnancy (Striae gravidarum)
  - Ascites
  - Acute weight loss
  - Obesity
  - Cushing syndrome
- **Caput medusae**: prominent superficial veins radiating from the umbilicus; associated with portal vein obstruction
- **Spider telangiectasia (spider angioma):** dilated small surface arteries that appear as small red spots with multiple radiating arms; associated with portal hypertension
- **Ascites**: free fluid in the peritoneal cavity
- **Hepatomegaly** is enlarged liver.

Gastrointestinal System





Ascites

Gastrointestinal System





Caput medusae

Gastrointestinal System





Spider angioma

Genitourinary system

- **Oliguria**: passage of less than 400 ml of urine per day
- **Anuria**: complete absence of urine output.
- **Polyuria**: urine output of more than 3L per day.
- **Urinary frequency**: an abnormally frequent voiding.
- **Nocturia**: the need to rise during hours of sleep to empty the bladder
- **Dysuria**: pain immediately before, during or immediately after micturation

Genitourinary system

- **Urgency**: the loss of the normal ability to postpone micturation beyond the time when the desire to pass urine is initially perceived
- **Incontinence**: refers to an involuntary loss of urine that has become a social or hygienic problem
- **Hesitancy**: difficulty initiating the process of micturation
- **Dribbling**: difficulty of completing micturation in a clean stop fashion
- **Hematuria:** the presence of red blood cells in the urine.
- **Nephrolithiasis:** a condition marked by the presence of renal calculi (stones) in the kidney or urinary system.

Respiratory system

- **Cough:** a reflex response to stimuli that irritate receptors in the larynx, trachea, or large bronchi.
- **Hemoptysis:** the expectoration of blood from the respiratory tract.
- **Dyspnea:** a non-painful but uncomfortable awareness of breathing that is inappropriate to the circumstances.
- Tachypnea is an increased respiratory rate.
- Bradypnea: abnormally slow respiratory rate with regular rhythm and normal depth of breathing.
- Chyne-Stokes breathing: a deep and fast breathing followed by diminishing respiratory effort and rate, sometimes associated with a short apnea.
- Kussmaul's respiration: deep, rapid respiration; characteristic of coma and diabetic ketoacidosis

Cardiovascular system

- **Bradycardia:** a slow (<60 beats/min) heart rate
- **Tachycardia:** a rapid (>100 beats/min) heart rate
- **Hypertension**: elevated blood pressure
- **Hypotension:** low blood pressure
- **Orthostatic hypotension**: a fall in SBP of 15 mm Hg or more when the pt assumes a more upright position
- **Pulsus alternans**: regular alteration of strong and weak pulse beats; associated with heart failure

Cardiovascular system

- S1: the first heart sound; produced by mitral & tricuspid valve closure
- S2: the second heart sound; produced by aortic & pulmonic valve closure
- S3: the third heart sound; produced by the sudden distention of the ventricular wall during ventricular filling; associated with heart failure
- S4: the fourth heart sound; produced by increased left ventricular end-diastolic pressure and loss of ventricular distensibility; associated with hypertension

Integumentary system

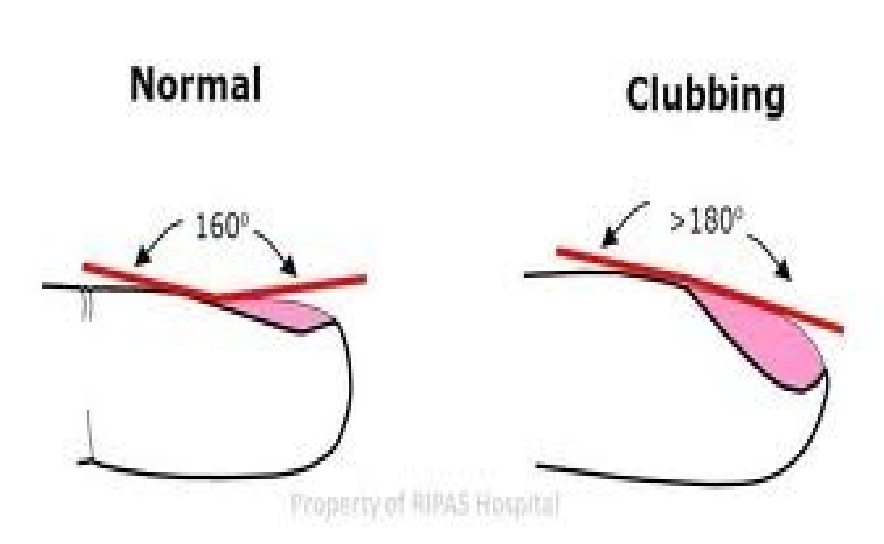
Clubbing of the nails

- Increased angle (>180 degrees) b/n the base of the nail and nail bed; associated with chronic arterial desaturation





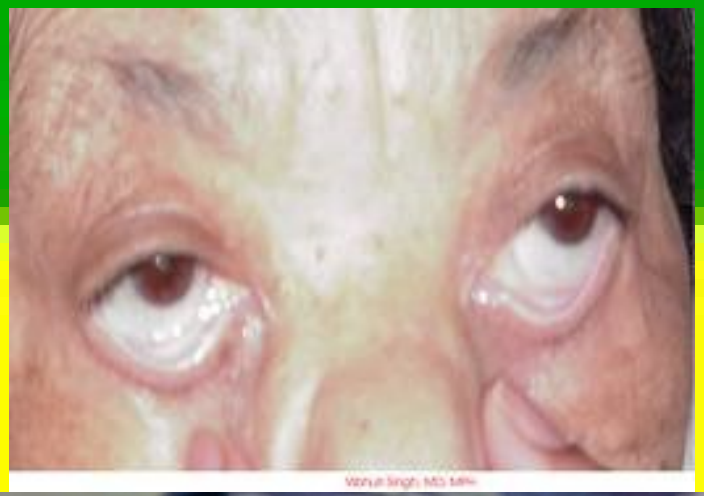
Integumentary system





Integumentary system



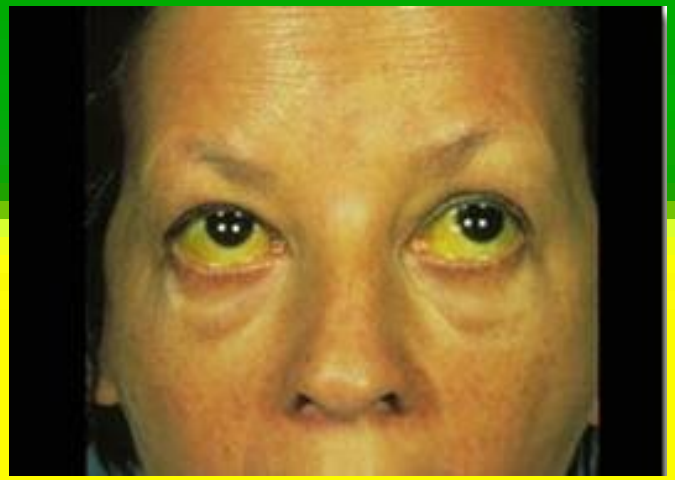






Pallor

Integumentary system







Icterus

Integumentary system







Cyanosis

CNS & Musculoskeletal

- **Affect**: the external expression of emotion
- **Aphasia**: the inability to speak
- **Asterixis**: involuntary movements characterized by nonrhythmic flapping of the extremities
- **Attention:** mental focus or concentration
- **Chorea**: involuntary movement characterized by brief, rapid, irregular, jerky motions
- **Circumstantiality**: an abnormal thought process characterized by unnecessary detail that delays reaching the point of the thought
- **Coma**: An altered state of consciousness characterized by complete loss of consciousness, unresponsiveness to stimuli, and absence of

CNS & Musculoskeletal

- **Confusion**: an abnormality of consciousness characterized by mental slowness, inattentiveness & incoherent thought patterns
- **Delirium**: an abnormality of consciousness characterized by confusion, agitation & hallucinations
- **Dementia**: acquired memory impairment
- **Dysarthria**: poorly coordinated, irregular speech
- **Dysphonia**: hoarseness
- **Dyspraxia**: difficulty coordinating body movements
- **Dystonia:** abnormal slow, twitching, irregular movements
- **Echolalia:** repetition of words or phrases spoken by others

CNS & Musculoskeletal

- **Flight of ideas**: an almost continuous flow of accelerated speech with quick changes of subject
- **Hemiplegia**: paralysis of one side of the body
- **Incoherence**: an abnormal thought process characterized by illogical connections & quick changes of subject
- **Judgment**: the ability to compare and evaluate alternatives
- **Loose association**: abnormal thought process characterized by repeated shifting to unrelated subjects

- **Mood**: a sustained emotional state
- **Myoclonus:** involuntary movements characterized by sudden, brief, unpredictable jerks

CNS & Musculoskeletal

- **Paraparesis**: a slight degree of lower extremity paralysis
- **Paraplegia**: paralysis of the lower extremities and trunk
- **Quadriplegia**: paralysis of the upper and lower extremities
- **Stupor**: an abnormal state of consciousness characterized by reduced mental and physical activity and reduced response to stimuli

DIAGNOSTIC TESTS

Chapter Two

Assefa M, 2019

1. INTRODUCTION

- Laboratory testing is used to detect disease, guide treatment, monitor response to treatment, and monitor disease progression.
- However, it is an imperfect science.
  - Laboratory testing may fail to
    - Identify abnormalities that are present (false negatives [FNs]) or
    - Identify abnormalities that are not present (false positives [FPs]).

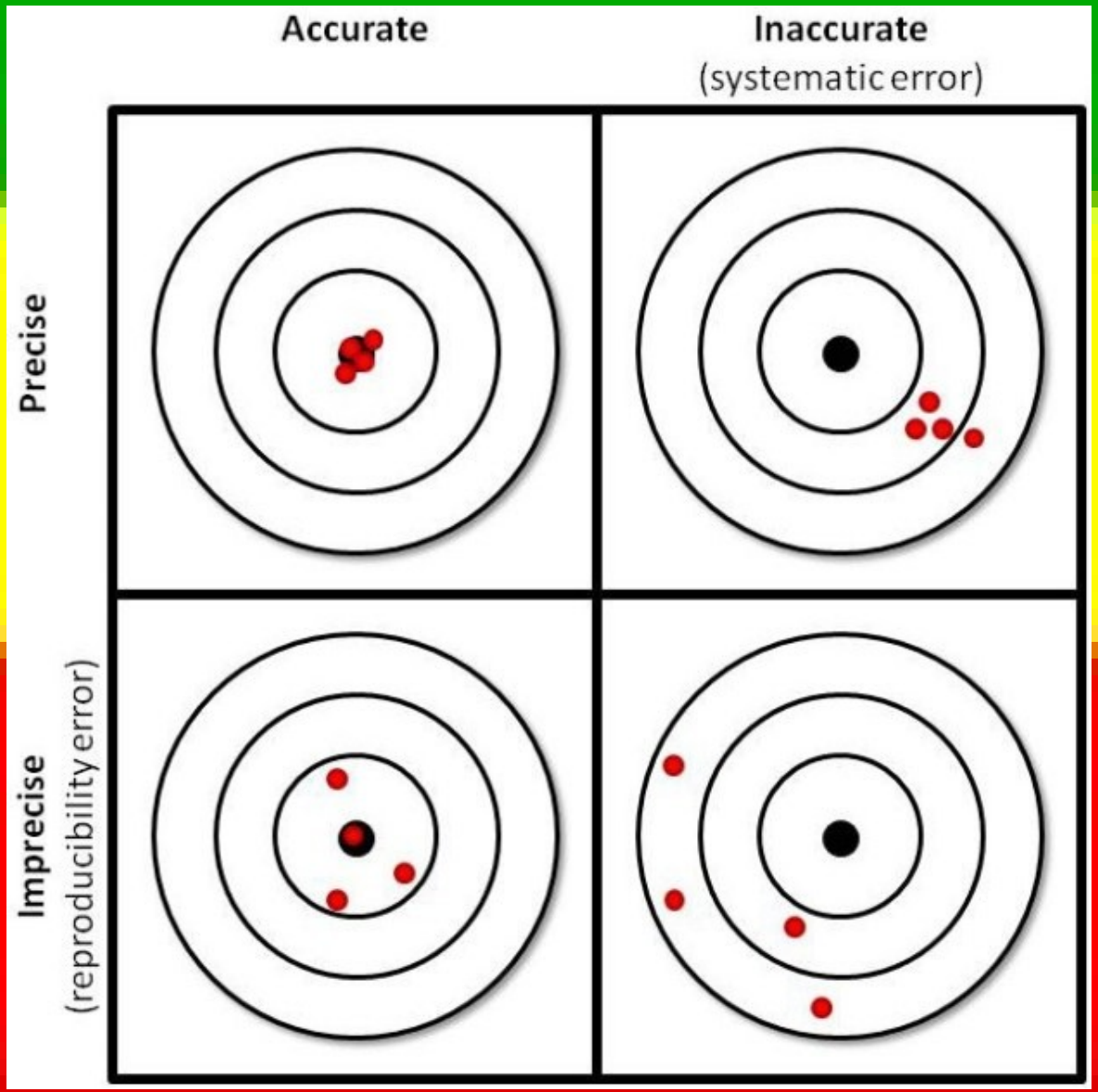
Accuracy and Precision

- ***Accuracy*** is defined as the extent to which the mean measurement is close to the true value
  - A highly accurate assay means that the repeated analyses produce a mean value that is the same as or very close to the known spiked quantity.
  - Accuracy of a qualitative assay is calculated as the sum of the true positives (TPs) and true negatives (TNs) divided by the number of samples tested
    - Accuracy = [(TP + TN)/number of samples tested] × 100%.

Accuracy and Precision

- *Precision* refers to assay reproducibility (i.e., the agreement of results when the specimen is assayed many times).
  - An assay with high precision means the methodology is **consistently** able to produce results in close agreement.
  - The accuracy of those results is a separate issue

Accuracy and Precision



Biomarker

- A ***biomarker*** (biological marker) is a marker (not necessarily a quantifiable laboratory parameter) defined as “a characteristic that is **objectively measured** and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to
a therapeutic intervention.”
- Biomarkers are used to
  - Diagnose and stage disease (i.e., determine the extent of disease),
  - Assess disease progression, and
  - Predict or assess response to therapeutic interventions
  - Example: Tumor markers, HbA1c

Noninvasive Versus Invasive Tests

- A *noninvasive test* is a procedure that examines fluids or other substances (e.g., urine and exhaled air) obtained without using a needle, tube, device, or scope to penetrate the skin or enter the body.
- An *invasive test* is a procedure that examines fluids or tissues (e.g., venous blood and skin biopsy) obtained by using a needle, tube, device, or scope to penetrate the skin or enter the body.
  - Invasive tests pose variable risk depending on the method of specimen collection (e.g., **pain** and **bruising** associated with venipuncture) and are less convenient than noninvasive tests.

Qualitative Tests

- A *qualitative test* is a test whose results are reported as either positive or negative without further characterization of the degree of positivity or negativity. For example,
  - a serum or urine pregnancy test is reported as either positive or negative;
  - a bacterial wound culture is reported as either positive for one or more specific microorganisms or reported as no growth;
  - a urine toxicology drug screen is reported as either positive or negative for specific drugs;
  - a hepatitis C viral ribonucleic acid (RNA) test is reported as positive or negative for hepatitis C viral RNA;
  - an acid fast stain for *Mycobacterium* is reported as either positive or negative

Quantitative Tests

- A *quantitative test* is a test whose results are reported as an exact numeric measurement (usually a specific mass per unit measurement) and assessed in the context of a reference range of values.
- For example,
  - Serum potassium is reported in meq/L,
  - CrCl is reported in mL/minute, and
  - LDH is reported in units/liter.

Reference Range

- The *reference range* (also known as the *reference interval* or the *reference value*) is a statistically derived numerical range obtained by testing a sample of individuals assumed to be healthy.
- The upper and lower limits of the range are not absolute (i.e., normal versus abnormal) but rather points beyond which the probability of clinical significance begins to increase.
- The term *reference range* is preferred over the term *normal range*
- Qualitative laboratory tests are either negative or positive and without a reference range; any positivity is considered abnormal

Reference Range

- *Factors that Influence the Reference Range*
  - Reference ranges may differ between labs depending on analytical technique, reagent, and equipment.
  - The initial assumption that the sample population is normal may be false.
  - Failure to control for physiologic variables (e.g., age, gender, ethnicity, body mass, diet, posture, and time of day) introduces many unrelated factors and may result in an inaccurate reference range.
  - Reference ranges calculated from nonrandomly distributed test results or from a small number of samples may not be accurate.
  - Reference ranges may change as new information relating to disease and treatments becomes available.

Reference Range

- *Critical Value*
  - The term *critical value* refers to a result that is far enough outside the reference range that it indicates impending morbidity (e.g., potassium < 2.8 mEq/L).

Semiquantitative Tests

- A *semiquantitative test* is a test whose results are reported as either negative or with varying degrees of positivity but without exact quantification.
- For example, urine glucose and urine ketones are reported as negative or 1+, 2+, 3+;
  - The higher numbers represent a greater amount of the measured substance in the urine but not a specific concentration.

Sensitivity

- The *sensitivity* of a test refers to the ability of the test to identify positive results in patients who actually have the disease (TP rate).
- Sensitivity assesses the proportion of TPs disclosed by the test.
- A test is completely sensitive (100% sensitivity) if it is positive in every patient who actually has the disease.
- The higher the test sensitivity, the lower the chance of a false negative result; the lower the test sensitivity, the higher the chance of a false negative result.
- However, a highly sensitive test is not necessarily a highly specific test

Sensitivity

- Highly sensitive tests are preferred when the consequences of not identifying the disease are serious; less sensitive tests may be acceptable if the consequence of an FN is less significant or if low sensitivity tests are combined with other tests
- The prostate specific antigen (PSA) test, a test commonly used to screen men for prostate cancer, is highly specific but has low sensitivity, especially at low PSA cutoff values of 4–10 ng/mL
  - Thus, PSA cannot be relied on as the sole prostate cancer screening method.
- Sensitivity also refers to the range over which a quantitative assay can accurately measure the analyte.
- In this context, a sensitive test is one that can measure low levels of the substance; an insensitive test cannot measure low levels of the substance accurately

Specificity

- *Specificity* refers to the percent of negative results in people without the disease (TN rate)
- Specificity assesses the proportion of TNs disclosed by the test
- The lower the specificity, the higher the chance of a false positive result.
- A test with a specificity of 95% for the disease in question indicates that the disease will be detected in 5% of people without the disease.
- Tests with high specificity are best for confirming a **diagnosis** because the tests are rarely positive in the absence of the disease
- The erythrocyte sedimentation rate (ESR) is a nonspecific test; infection, inflammation, and plasma cell dyscrasias increase the ESR

Calculation of Sensitivity and Specificity

Screening Test Result	Diseased	Not Diseased	TOTAL
Positive	TP	FP	TP+FP
Negative	FN	TN	FN+TN
TOTAL	TP+FN	FP+TN	TP+FP+FN+TN

Sensitivity = [TP ÷ (TP + FN)] x 100%.

Specificity = [TN ÷ (TN + FP)] x100%

Predictive Value

- As applied to a positive test result, the predictive value indicates the percent of positives that are TPs
  - Predictive value of positive test = (TP/[TP+FP])*100
- As applied to a negative test result, the predictive value indicates the percent of negatives that are TNs
  - Predictive value of negative test = (TN/[TN+FN])*100

Mini CASE: Rapid Streptococcal Antigen Test

- In 453 patients with acute pharyngitis symptoms, detection of group A β-hemolytic streptococci with a commercial rapid antigen detection test and standard throat culture are compared. The package insert for the rapid streptococcal antigen test (RSAT) notes a sensitivity of 95% and a specificity of 98% when used according to the manufacturer instructions.
- **QUESTION:** After reviewing the following results, what conclusions can be made about the clinical performance of the RSAT

RSAT Results (n = 453):

True Positives =51 True Negatives =362

False Positives =12 False Negatives =28

Mini CASE cont'd

- **DISCUSSION:** Calculate sensitivity, specificity, predictive value of a positive test, and the predictive value of a negative test.
- **Sensitivity** = (TP ÷ [TP + fN]) × 100% = (51 ÷ [51 + 28]) × 100%= 64.6%
- **Specificity** = (TN ÷ [TN + fP]) × 100% = (362 ÷ [362 + 12]) × 100% = 96.8%
- Predictive value of positive test = (TP ÷ [TP + fP]) × 100% = (51÷ [51 + 12]) × 100% = 81%
- Predictive value of negative test = (TN ÷ [TN + fN]) × 100% = (362÷ [362 + 28]) × 100% = 92.8%

Specimen

- A *specimen* is a sample (e.g., whole blood, plasma, serum, urine, stool, sputum, sweat, gastric secretions, exhaled air, cerebrospinal fluid, or tissues) that is used for laboratory analysis.
- Plasma is the watery acellular portion of blood, that contains
  - Dissolved proteins: albumin, globulins, fibrinogen, enzymes, and hormones,
  - Electrolytes: sodium, potassium, chloride, calcium, and magnesium
  - Lipids, carbohydrates, amino acids, and other organic substances (urea, uric acid, creatinine, bilirubin, ammonium ions)
- Serum is the liquid that remains after the fibrin clot is removed from plasma.

Specimen

- Laboratory tests are performed on:
  - On plasma only: prothrombin time, activated partial thromboplastin time [aPTT], D-dimer, and fibrinogen concentrations
  - On serum only: albumin, creatinine, bilirubin, and acetaminophen concentrations
  - Either plasma or serum: glucose, cortisol, electrolytes,
    and phenytoin concentrations
  - Whole blood: blood gases, hemoglobin, hematocrit, complete blood count [CBC], and ESR

Rationale for Ordering Laboratory Tests

- Laboratory tests are performed with the expectation that the results will
  - discover occult disease
  - confirm a suspected diagnosis
  - differentiate among possible diagnoses
  - determine the stage, activity, or severity of disease
  - detect disease recurrence
  - assess the effectiveness of therapy
  - guide the course of therapy

Rationale for Ordering Laboratory Tests

- Laboratory tests are categorized as screening or diagnostic tests.
  - Screening tests, performed in individuals without signs or symptoms of disease, detect disease early when interventions (e.g., lifestyle modifications, drug therapy, and surgery) are likely to be effective.
  - Screening tests are performed on healthy individuals and are generally inexpensive, quick and easy to perform, and reliable, although they do not provide a definitive answer.
  - Screening tests require confirmation with other clinical tests
  - Diagnostic tests are performed on at risk individuals, are typically more expensive, and are associated with some degree of risk but provide a definitive answer.

Comparative features of Screening and diagnostic laboratory tests

Feature	Screening Test	Diagnostic Test
Simplicity of test	Fairly simple	More complex
Target population	Individuals without signs or symptoms of the disease	Individuals with signs or symptoms of the disease
Characteristic	High sensitivity	High specificity
Disease prevalence	Relatively common	Common or rare
Risks	Acceptable to population	Acceptable to individual

Factors that Influence Laboratory Test Results

- ***Laboratory-Specific Factors***
  - A test result that is not the true result, *laboratory error* most appropriately refers to inaccurate results that occur because of an error made by laboratory personnel or equipment.
  - Laboratory errors should be suspected for one or more of the following situations:
    - The result is inconsistent with trend in serial test results.
    - The magnitude of error is great.
    - The result is not in agreement with a confirmatory test result.
    - The result is inconsistent with clinical signs or symptoms or other patient specific information.

Factors that Influence Laboratory Test Results

- Laboratory errors are caused by one or more laboratory processing or equipment errors, such as
  - Deteriorated reagents,
  - Calibration errors,
  - Calculation errors,
  - Misreading the results,
  - Computer entry or other documentation errors, or
  - Improper sample preparation.
  - Improper specimen handling prior to or during transport to the laboratory

Factors that Influence Laboratory Test Results

- ***Patient-Specific Factors***
  - **Time course**: Incorrectly timed laboratory tests
  - **Age:** Age related changes
  - **Genetics, ethnicity, and gender.**
  - **Biologic rhythms**
  - **Pregnancy.**
  - **Organ function: Renal, hepatic, bone marrow**
  - **Diet:** Serum glucose and lipid profiles are best assessed in the fasting state.
  - **Fluid status**: hemoconcentration
  - **Altitude**

Factors that Influence Laboratory Test Results

- **Drugs.**
  - Methodological interference;
  - Drug induced, end-organ damage;
  - Direct pharmacologic effect; and
  - Miscellaneous category

Factors that Influence Laboratory Test Results

- Methodological interference;
  - Drugs that discolor the urine interfere with fluorometric, colorimetric, and photometric tests and mask abnormal urine colors.
    - For example, amitriptyline turns the urine a blue-green color and phenazopyridine and rifampicin turn the urine an orange-red color.
  - Other drugs directly interfere with the laboratory assay.
    - For example, high doses of ascorbic acid (>500 mg/day) cause false negative stool occult blood tests.

Factors that Influence Laboratory Test Results

- Direct drug induced, end organ damage (e.g., kidney, liver, and bone marrow)
  - For example, amphotericin B causes renal damage evidenced by increased SCr.
  - Bone marrow suppressants, such as doxorubicin and bleomycin, cause thrombocytopenia
- Direct pharmacologic effect.
  - Thiazide and loop diuretics increase serum uric acid by decreasing uric acid renal clearance or tubular secretion.
  - Narcotics, such as codeine and morphine sulfate, increase serum lipase by inducing spasms of the sphincter of Oddi.

2. THE HEART: LABORATORY TESTS & DIAGNOSTIC PROCEDURES



Introduction

- The heart has two basic properties: electrical and mechanical.
- The two work in harmony to propel blood, delivering oxygen and nutrients to all body tissues.
- Heart cells responsible for these properties are

(1) Pacemaker cells or the “electrical power” of the heart;

(2) Electrical conducting cells or the “hardwiring circuitry” of the heart; and

(3) Myocardial cells or the contractile units of the hear

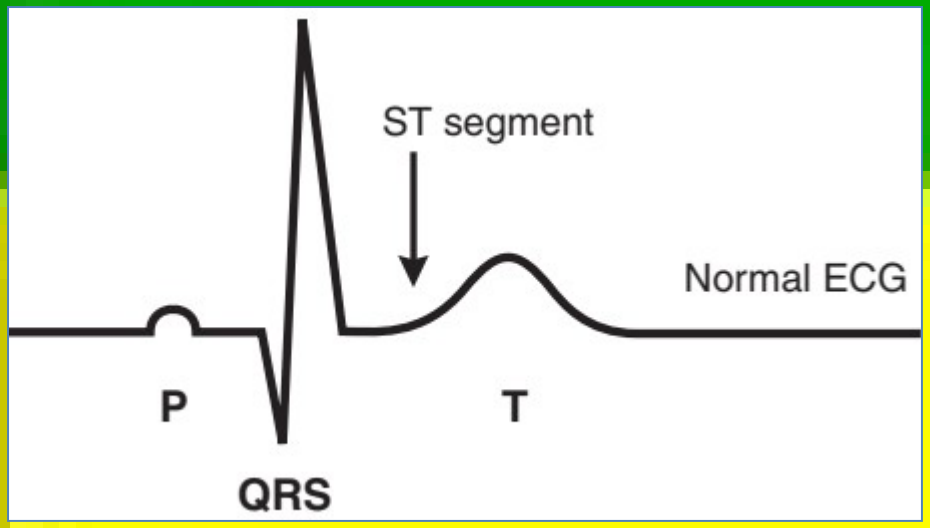
Introduction

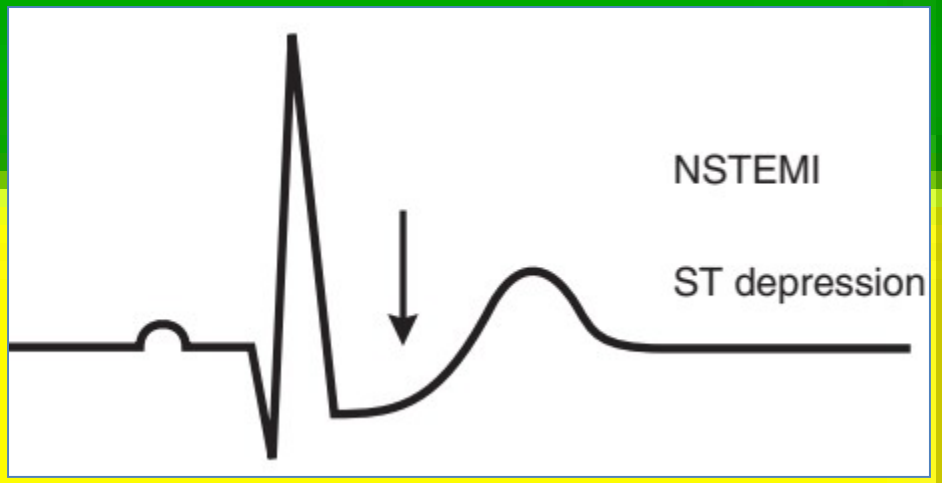
- Disturbances in the electrical system result in rhythm disorders, also known as *arrhythmias* or *dysrhythmias*.
- The pumping action is accomplished by means of striated cardiac muscle, which largely composes the myocardium.
- A number of cardiovascular diseases disrupt the mechanical function of the heart including
  - Coronary artery disease (CAD),
  - Acute coronary syndrome (ACS), and
  - Heart failure

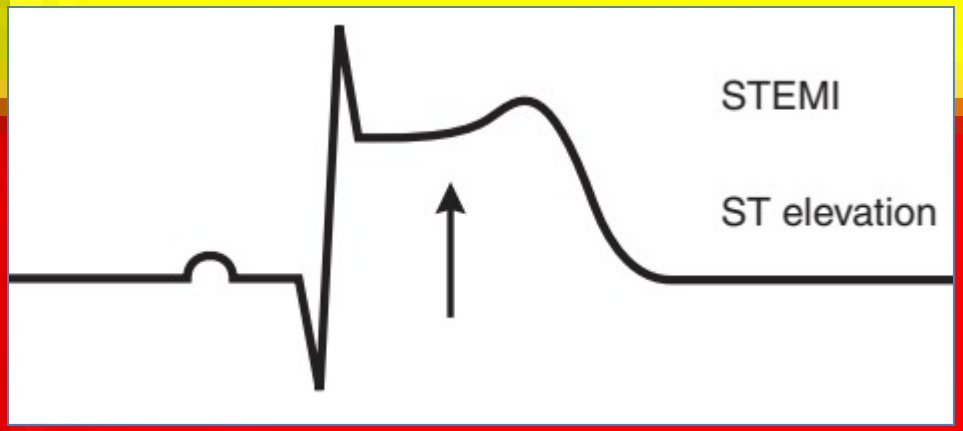
Electrocardiographic Findings in ACS

- In patients with ACS, the **ECG** is an essential tool providing immediate and invaluable data for diagnosis, determination of prognosis, and consideration of management options
- Careful reading of the ECG by an experienced clinician provides information on the presence of myocardial ischemia, injury, or infarction.
- The classic ECG changes consistent with acute presentation of myocardial ischemia or infarction are
  (1)T-wave inversion,
  (2)ST-segment elevation, and
  (3)ST-segment depression

ECG changes consistent with STEMI and NSTEMI







Laboratory Tests in ACS

- MI can be recognized by clinical presentation, ECG, elevated biochemical markers of myocardial necrosis, and imaging
- Clinical presentation does not distinguish among UA, NSTEMI, and STEMI.
- In the era of reperfusion therapy, diagnosing ACS accurately and without delay is crucial for risk stratification and appropriate, life-saving treatment implementation.
- The ECG differentiates between NSTEMI and STEMI.
- The distinction between UA and NSTEMI is ultimately made on the basis of the absence or presence, respectively, of biochemical cardiac markers in the blood.
- The release of detectable quantities of biochemical markers in the peripheral circulation indicates myocardial injury and is more consistent with MI than UA

Troponin

- *Cardiac-Specific Troponin I*
  - *Diagnostic level: ≥0.3 ng/mL (≥0.3 mcg/L)*
- *Cardiac-Specific Troponin T*
  - *Diagnostic level: ≥0.1 ng/mL (≥0.1 mcg/L)*
- Troponin is a protein complex consisting of three subunits:
  - troponin C (TnC),
  - troponin I (TnI), and
  - troponin T (TnT).

Troponin

- The TnC expressed by myocardial cells in cardiac and skeletal muscle is identical.
- In contrast, TnI and TnT expressed by cardiac cells are encoded by distinct genes different from those in skeletal muscle cells.
  - Immunoassays have been developed to detect cardiac-specific TnI (cTnI) and cardiac-specific TnT (cTnT)
- Cardiac-specific TnI and cTnT are highly specific and sensitive for MI
- Following myocardial injury, serum cTnI and cTnT begin to rise above the upper reference limit within 3–12 hours, peak in 24 hours (cTnI) or 12 hours to 2 days (cTnT), and return to normal in 5–10 days (cTnI) or 5–14 days (cTnT)

Troponin

- In contrast to cTnT, cTnI assays lack standardization among multiple commercially available assays developed by different manufacturer

Creatine Kinase

- *Normal range: males, 55–170; females, 30–135 IU/L*
- *Creatine kinase* (CK) is an enzyme that stimulates the transfer of high-energy phosphate groups, and it is found in skeletal muscle, myocardium, and the brain.
- Circulating serum CK is directly related to the individual's muscle mass.
- Serum CK concentrations rise sharply 4 – 8 hours after the onset of chest pain associated with MI, peak in 24 hours, and return to normal in three to four days
- Other causes for increased serum CK concentrations include any musculoskeletal injury or diseases, IM injections, and a number of medications like statins, amphotericin B, ethanol (binge drinking), Li, barbiturate poisoning

Creatine Kinase Isoenzyme: CK-MB

- *Normal range: CK-MB ≤6 ng/Ml*
- The enzyme CK is a dimer of two B monomers (CK-BB), two M monomers (CK-MM), or a hybrid of the two (CK-MB)
  - CK-BB is found in the brain, lungs, and intestinal tract;
  - CK-MM is found primarily in skeletal and cardiac muscle; and
  - CK-MB is found predominantly in the myocardium but also in skeletal muscle.
- Fractionation of total CK into three isoenzymes increases the diagnostic specificity of the test for MI.
- Given the availability and characteristics of cardiac troponins, CK and CK-MB measurements are no longer useful for the diagnosis of ACS

Myoglobin

- *Myoglobin* is a low-molecular-weight heme protein found in cardiac and skeletal muscle.
- Serum levels are detected within 1 to 4 hours and peak 6 to 7 hours after the onset of symptoms.
- Myoglobin is cleared rapidly by renal glomerular filtration, and levels return to the reference value 24 hours following MI.
- The fast rise and fall of myoglobin levels made it an appropriate marker for the early diagnosis of MI and detection a re-infarction if occurring 24 hours after the initial insult
- Obsolete in current practice

Laboratory Tests in Heart Failure

- **Natriuretic Peptides:** are naturally secreted hormones that are released by various cells in response to increased volume or pressure.
- A number of natriuretic peptides have been identified, including
  - Atrial natriuretic peptide (ANP),
  - B-type natriuretic peptide (BNP),
  - C-type natriuretic peptide (CNP),
  - Dendroaspis natriuretic peptide(DNP), and
  - Urodilatin

Imaging Studies

- Echocardiography,
- Cardiac catheterization,
- Perfusion imaging,
- Computed tomography (CT),
- Magnetic resonance imaging (MRI), and
- Positron emission tomography (PET)

Echocardiography

- *Echocardiography* is based on sound transmitted to and through the heart.
- Different tissues present different acoustical impedance (resistance to transmitting sound).
- Transthoracic echocardiography (TTE) involves sound waves from a transducer positioned on the anterior chest directed across cardiac tissues.
- The sound is reflected back in different frequencies, and
  images of cardiac anatomy are displayed on an oscilloscope or an electronic monitor.
- Clinical uses include anatomic assessment of the heart and functional assessment of cardiac chambers and valves.

Echocardiography

- Left ventricular ejection fraction is a valuable diagnostic and prognostic index in patients with failure
  - The fraction of end-diastolic volume ejected from the left ventricle during each systolic contraction.
- The normal range for LVEF is 55–75%.
- Patients may have heart failure due to diastolic ventricular dysfunction with a normal LVEF.
- In clinical practice, TTE is currently the modality most utilized and accepted for the evaluation of systolic and diastolic cardiac function.

Cardiac Catheterization

- *Cardiac catheterization* involves the introduction of a catheter through the femoral or radial artery, which is advanced to the heart chambers or great vessels guided by fluoroscopy.
- Measurements collected include
  - Intracardiac pressures,
  - Hemodynamic data, and
  - Blood flow in the heart chambers and coronary arteries

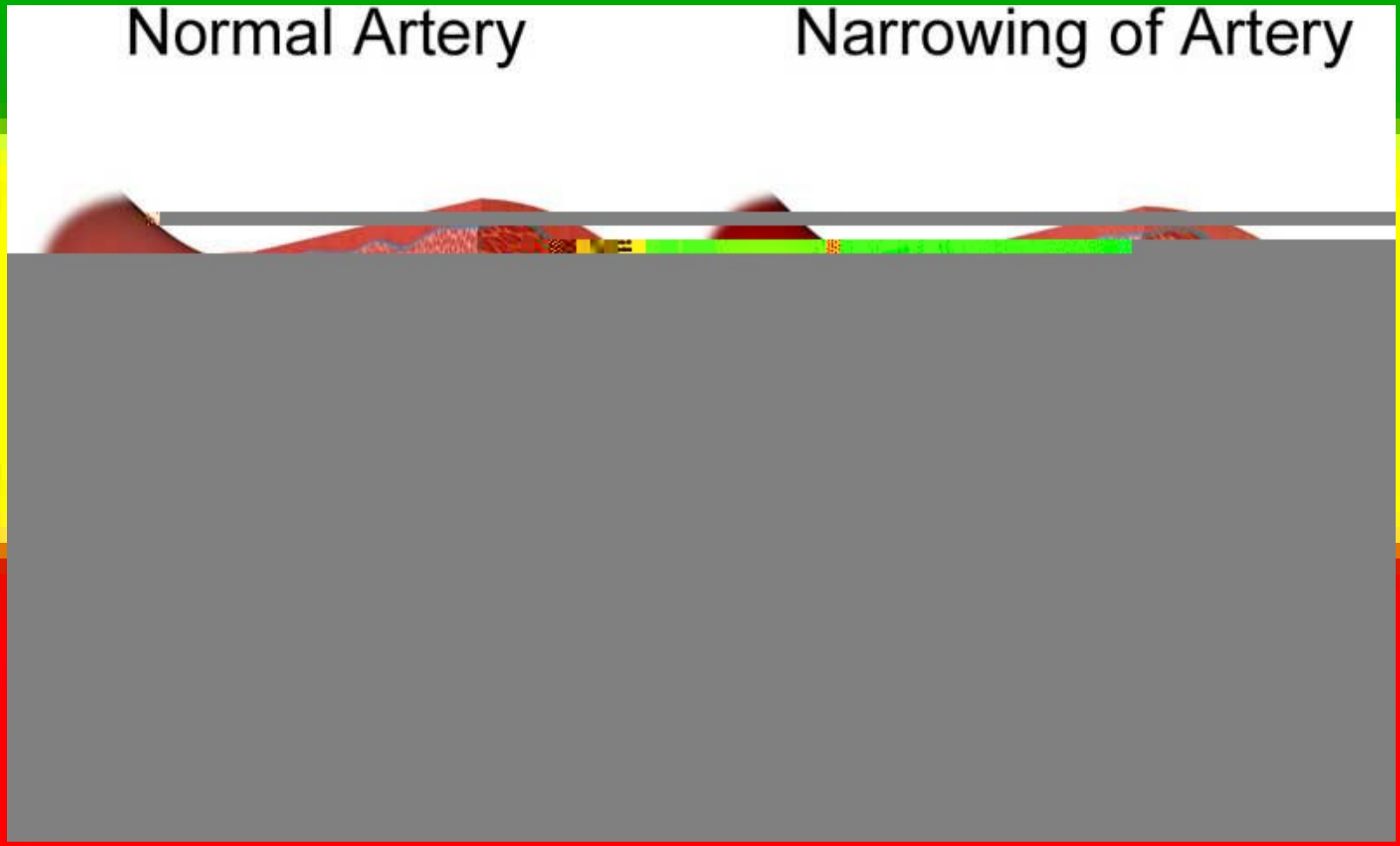
Cardiac Catheterization

- *Coronary Angiography:* also referred to as *angiocardiography* or *coronary arteriography*,
  - Is a diagnostic test in which contrast media is injected into the coronary arteries.
  - X-ray exposures of the coronary arteries are then examined to assess the location and severity of coronary atherosclerotic lesions.
  - Therapeutic interventions or PCI may be performed during the catheterization including
    - Percutaneous transluminal coronary angioplasty and
    - Bare metal or drug-eluting stent placement

Cardiac Catheterization

- *Left Ventriculography:* is the injection of contrast media into the left ventricle to assess its structure and function.
  - The test is often performed as part of a diagnostic cardiac catheterization to evaluate ventricular wall motion and measure LVEF

3. LIPID DISORDERS



Lipid Disorders

- **Dyslipidemia**, or an abnormal serum lipid profile, is a major risk factor in the development of atherosclerotic cardiovascular disease (**ASCVD**).
- Clinical manifestations of ASCVD include acute coronary syndrome (ACS), myocardial infarction (MI), angina, stroke and transient ischemic attack (TIA).
- Cardiovascular disease is a **leading cause of death** and preventative efforts are essential to decrease associated morbidity and mortality.

Lipid Metabolism

- Lipids are an essential component of several biological processes.
- The major plasma lipids are cholesterol, TGs, and phospholipids.
- Cholesterol serves as a structural component of cell wall membranes and is a precursor for the synthesis of steroid hormones and bile acids.
- TGs, the esterified form of glycerol and fatty acids, constitute the main form of lipid storage in humans and serve as a reservoir of fatty acids to be used as an energy source for the body.
- Phospholipids are lipid molecules that contain a phosphate group. Like cholesterol, phospholipids become constituents of cell wall membranes.
- Both cholesterol and TGs are hydrophobic, while phospholipids are hydrophilic

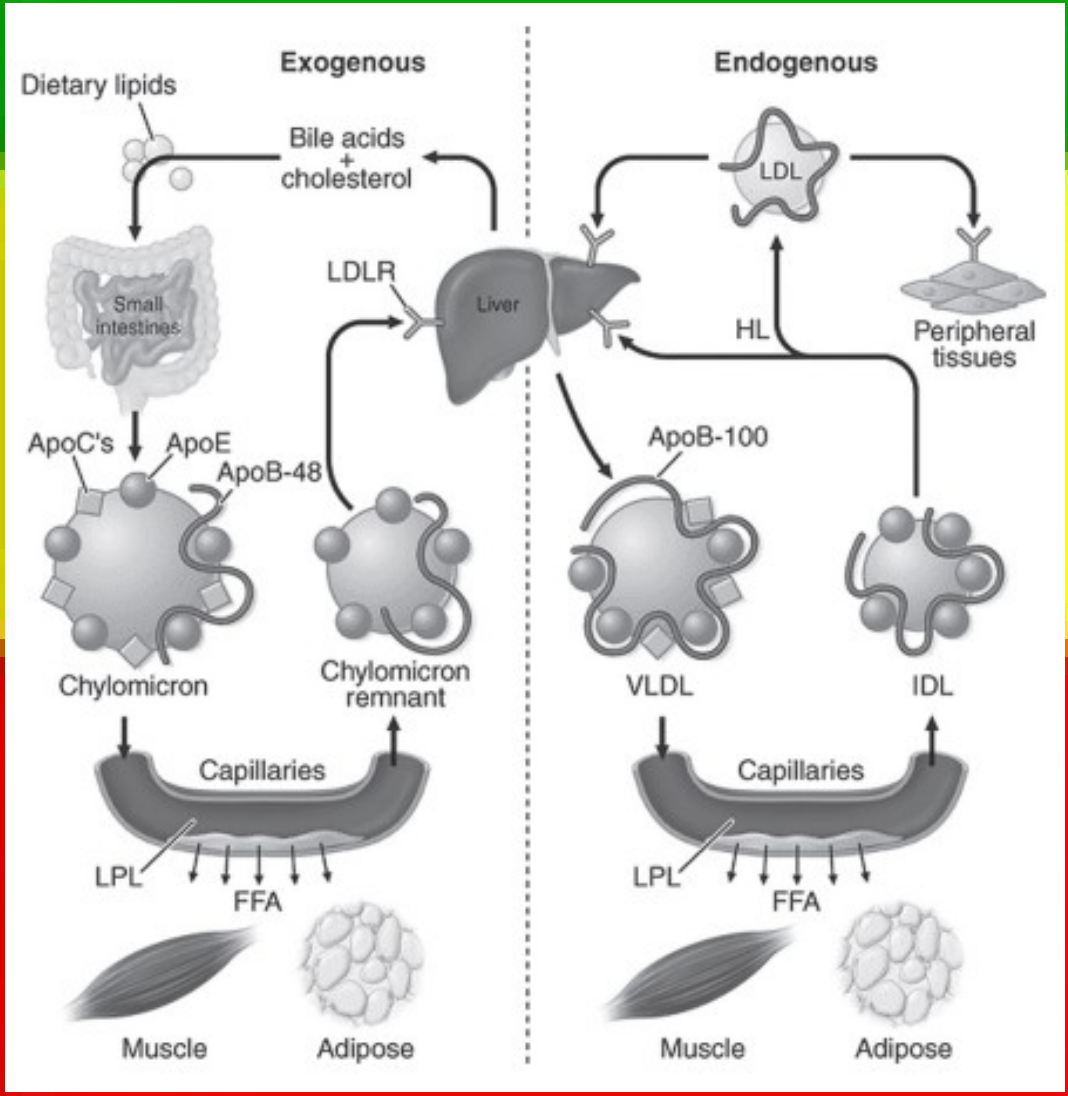
Lipid Metabolism

- Cholesterol and TGs are surrounded by proteins and phospholipids to form lipoproteins.
- These lipoproteins are more water soluble and can
  then be transported in the body
- Cholesterol and TGs can be absorbed from the diet (exogenous) or synthesized in the body (endogenous), while phospholipids are primarily synthesized in the body
- TGs are transported from the intestine to the systemic circulation via chylomicrons, which are TG rich lipoproteins.

Lipid Metabolism

- Endogenous production of cholesterol, TGs, and phospholipids primarily occurs in the liver and intestinal tract.
- The majority of serum cholesterol is derived from cholesterol synthesized in the liver.
- Intestinal cholesterol absorption, hepatic cholesterol synthesis, and excretion of cholesterol and bile acids regulate serum cholesterol concentrations
- The rate-limiting step in cholesterol synthesis is the conversion of hepatic hydroxymethylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid catalyzed by the enzyme HMG-CoA reductase

Lipid metabolism



Apo = apolipoprotein;
FFA = free fatty acid;
HL = hepatic lipase;
IDL = intermediate-density lipoprotein;
LDL = low-density lipoprotein;
LDLR = low-density lipoprotein receptor;
LPL = lipoprotein lipase;
VLDL = very low-density lipoprotein.

Lipoproteins

- Cholesterol, TGs, and phospholipid molecules complex with specialized proteins (apolipoproteins) to form **lipoproteins**
- As lipids are insoluble in aqueous plasma, they are formed into complexes with
  - An outer hydrophilic coat of phospholipids and proteins and
  - An inner core of fatty cholesterol and TGs.
- The **apolipoproteins** not only serve to support the formation of lipoproteins, but they also mediate binding to receptors and activate enzymes in lipoprotein metabolism
- Lipoproteins are classified by their density, size, and major apolipoprotein composition.

Characteristics of Lipoproteins

Lipoprotein	Size	Density	Major Apolipoprotein	Origin	Comments
Chylomicron and its reminants	Largest	Least	ApoB-48	Intestine	Primarily TG
VLDL			ApoB-100	Liver and intestine	Primarily TG
IDL or reminants			ApoB-100	Chylomicron and VLDL	Transitional form
LDL			ApoB-100	End-product of VLDL	Major carrier of cholesterol
HDL	Smallest	Most	ApoA-1	Intestine and liver	Removes cholesterol from arteries

Lipoproteins

- **Chylomicrons**,
  - Are TG-rich, deliver TGs from the gastrointestinal tract to the muscle and adipose tissue where lipoprotein lipase (LPL) releases fatty acids and glycerol.
  - After this process, the chylomicron is no longer TG rich and is referred to as a chylomicron remnant and is delivered to the liver.
  - The liver can export cholesterol and other TGs in the form of very low density lipoproteins (VLDL) into the circulation

Lipoproteins

- **VLDL**
  - Are predominantly TG rich but have a higher cholesterol composition than chylomicrons (5 mg of TGs per 1 mg of cholesterol)
  - Once in circulation, VLDL undergoes the same degradation as chylomicrons via LPL.
  - This LPL activity then converts VLDL particles to intermediate-density lipoproteins (IDL) and eventually low-density lipoproteins (LDL)

Lipoproteins

- **LDL**
  - Typically carries the largest portion of cholesterol in the body.
  - The liver degrades the majority of circulating LDL; however, other tissues can take up a small portion of LDL that provides necessary cholesterol for cell membrane and steroid synthesis.
  - It is considered to be atherogenic and has been a focus of dyslipidemia management.

Lipoproteins

- **HDL**
  - Unlike LDL, it is typically considered to be protective against atherosclerosis via reverse cholesterol transport.
  - One role of HDL is to acquire excess cholesterol from degraded VLDL and the periphery.
  - HDL undergoes an enzymatic reaction via lecithin cholesterol acyltransferase to become HDL cholesteryl ester, which is then selectively taken up by the liver and targeted for excretion via bile.
  - In addition, the cholesteryl ester transfer protein can transfer cholesteryl ester from HDL to VLDL, IDL, and LDL, which results in less dense lipoproteins that can be taken up by the liver more easily

TESTS FOR LIPIDS AND LIPOPROTEINS

- The lipid panel
  - Total cholesterol
  - Triglycerides
  - Low-Density Lipoprotein Cholesterol
  - High-Density Lipoprotein Cholesterol
  - Non-High-Density Lipoprotein Cholesterol

Total Cholesterol

- *Desirable, <200 mg/dL;*
- *Borderline high, 200–239 mg/dL;*
- *High, ≥240 mg/dL*

- Current recommendations are to use the other components of the lipid panel (e.g., LDL) instead of *total cholesterol* (TC) to guide patient care decisions.
- However, TC will still be reported as part of a lipid panel,

Triglycerides

- *Normal, <150 mg/dL;*
- *Borderline high, 150–199 mg/dL;*
- *High, 200–499 mg/dL*
- *Very high, ≥500 mg/dL*

- An overnight fast is recommended prior to measurement.
- In addition to increased risk of cardiovascular disease, very high TG concentrations (≥500 mg/dL) and especially those concentrations ≥1000 mg/dL may precipitate **pancreatitis**.

LDL Cholesterol

- Desirable, <100 mg/dL;
- Above desirable, 100–129 mg/dL;
- Borderline high, 130–159 mg/dL;
- High, 160–189 mg/dL;
- Very high, ≥190 mg/dL

- LDL cholesterol is ideally measured while the patient is in a fasting state.
- LDL can be measured directly or estimated indirectly by a method determined by Friedewald Formula
  - LDL = TC – HDL – (TG/5)
  - If a patient's serum TG concentration exceeds 400 mg/dL LDL cholesterol cannot be calculated with this formula.
  - A direct LDL measurement by laboratory would provide an LDL value (EXPENSIVE)

LDL Cholesterol

- LDL goal-centered approach is by assessing presence of clinical ASCVD (e.g., MI, TIA, or PAD) or ASCVD risk factors (e.g., premature family history, DM, current cigarette smoking, and low HDL).
- This assessment is used to categorize the patient's level of risk for ASCVD.
- The LDL goal identified for those at low, moderate, or high risk for ASCVD is <100 mg/dL, whereas the LDL goal for those at very high risk (e.g., clinical ASCVD) is <70 mg/dL

HDL-Cholesterol

- Low (men), <40 mg/dL;
- Low (women), <50 mg/dL
- *HDL cholesterol* acts as an antiatherogenic factor and is often termed “good cholesterol.”
- Higher HDL levels are protective against cardiovascular risk even in the setting of elevations in LDL.
- HDL has several antiatherogenic properties, such as
  reverse cholesterol transport and antiplatelet activity

Non-HDL Cholesterol

- *Desirable, <130 mg/dL;*
- *Above desirable, 130–159 mg/dL;*
- *Borderline high, 160–189 mg/dL;*
- *High, 190–219 mg/dL;*
- *Very high, ≥220 mg/dL*

- *Non-HDL cholesterol* (TC – HDL) provides an estimate of the sum of cholesterol carried by atherogenic particles; those that contain apo B such as LDL, VLDL, chylomicrons and Lp(a)
- Both non-HDL and apo B are better predictors of ASCVD risk than LDL cholesterol levels.
- The non-HDL cholesterol target of therapy is set at 30 mg/dL greater than the LDL goal.
  - For example, if a patient has an LDL goal of <100 mg/dL, the non-HDL goal will be set at <130 mg/dL.

4. ENDOCRINE DISORDERS

Diagnostic Laboratory Tests for DM

- ***C-Peptide***
  - *Fasting range: 0.78–1.89 ng/mL*
  - *Range one hour after a glucose load: 5–12 ng/mL during a glucose tolerance test*
  - *C-peptide* levels are used to evaluate residual β-cell function.
  - A C-peptide test distinguishes between type 1 and type 2 DM; identifies the cause of hypoglycemia; and checks that a pancreatic tumor (insulinoma) was completely removed.
  - Insulin is synthesized as the precursor, **proinsulin**, is cleaved to form C-peptide and insulin, which are both secreted in equimolar amounts into the portal circulation.

Diagnostic Laboratory Tests for DM

- High levels of C-peptide generally indicate high levels of endogenous insulin production
  - This may be a response to high levels of blood glucose caused by glucose intake and insulin resistance.
  - Also, high levels of C-peptide also are seen with insulinomas (insulin-producing tumors) and may be seen with hypokalemia, pregnancy, Cushing syndrome, and renal failure
- Low levels of C-peptide are associated with low levels of insulin production.

Diagnostic Laboratory Tests for DM

- **Diabetes-Related Autoantibody Testing**
  - Is used to distinguish between autoimmune type 1 DM and type 2 DM
  - The four most common autoantibody tests are
    - Islet cell cytoplasmic autoantibodies (ICA),
    - Glutamic acid decarboxylase autoantibodies (GADA),
    - Insulinoma-associated-2 autoantibodies (IA-2A), and
    - Insulin autoantibodies (IAA).

Lab Tests to Assess Glucose Control

- Fasting Plasma Glucose
- Glycated hemoglobin (A1c)
- Oral glucose tolerance test (OGTT)
- Fructosamine tests

Fasting Plasma Glucose

- **Normal**: FPG <100 mg/dL
- **Prediabetes**: FPG ≥100 and <126 mg/dL
  - Previously termed *impaired fasting glucose*
- **Diagnosis of diabetes**: FPG ≥126 mg/dL (on at least two occasions)
- An FPG concentration is the best indicator of glucose homeostasis.
- This test measures the ability of endogenous or exogenous insulin to prevent fasting hyperglycemia by regulating glucose anabolism and catabolism.
- The assay is performed on awakening (before breakfast).
  - This timing usually allows for an eight-hour fast.

Oral Glucose Tolerance Test (OGTT)

- Normal glucose tolerance: Two-hour postload glucose (PG), <140 mg/dL
- Prediabetes: Two-hour PG 140–199 mg/dL
  - previously termed *impaired glucose tolerance*
- Provisional diagnosis of diabetes: Two-hour PG ≥200 mg/dL
- The OGTT is used to assess patients who have signs and symptoms of DM but whose FPG is normal or suggests prediabetes (<126 mg/dL)
- The OGTT is performed by giving a standard 75-g dose of an oral glucose solution over five minutes following an overnight fast

Glycated Hemoglobin

- *Normal range: 4–5.6%*
- Is a component of the hemoglobin molecule.
- During the 120-day lifespan of an RBC, glucose is irreversibly bound to the hemoglobin moieties in proportion to the average serum glucose
- Measurement of A1c is, therefore, indicative of glucose control during the preceding two to three months.
- A fasting sample is not required

Diagnosis of Diabetes Mellitus

Level of glucose	FPG	OGTT		A1c
		30, 60, 90 Min	2hr	
Normal	<100	>200	<140	5.7%
Prediabetes	100-125	>200	140-199	5.7-6.4%
DM	≥126	>200	>200	≥6.5%
Gestational DM	>92	180 (1 hr)	>153	

Urine Glucose

- *Normal range: negative*
- Glucose “spills” into the urine when the serum glucose concentration exceeds the renal threshold for glucose reabsorption (normally 180 mg/dL).

THYROID

- The thyroid produces the hormones thyroxine (T4) and triiodothyronine (T3)
- Although T4 is produced solely by the thyroid gland, only about 20–25% of T3 is directly secreted by this gland.
- Approximately 80% of T3 is formed by hepatic and renal **deiodination** of T4.
- T4 has a longer half-life than T3, approximately seven days versus one day, respectively.
- At the cellular level, however, T3 is three to four times more active physiologically than T4

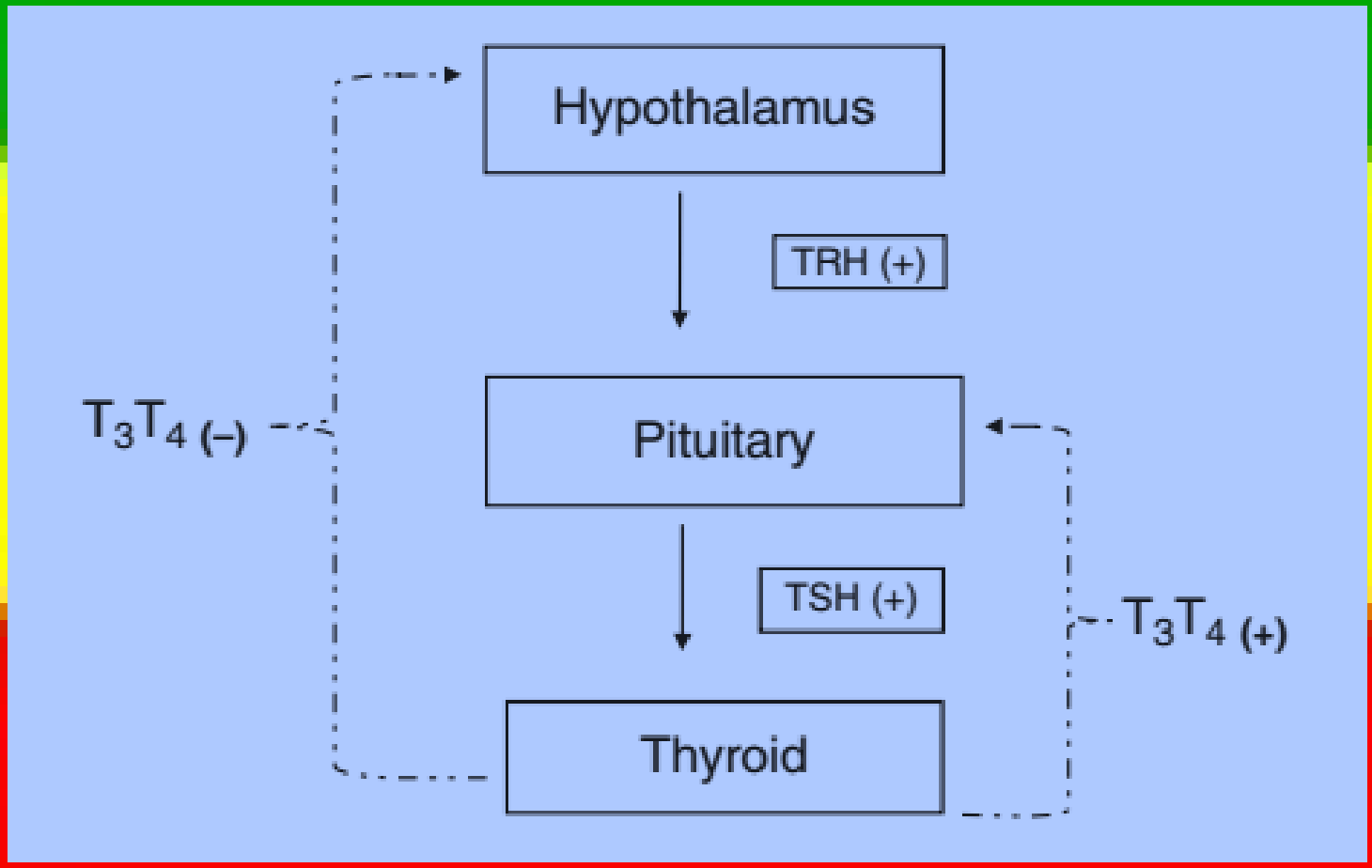
THYROID

- Both T4 and T3 circulate in human serum bound to three proteins:
  - Thyroxine-binding globulin (TBG),
  - Transthyretin, previously known as *thyroid-binding prealbumin*, and
  - Albumin.
- 80% of T4 and T3 is bound to TBG.
- Only 0.02% of T4 and 0.2% of T3 circulate unbound, free to diffuse into tissues

THYROID

- The release of T4 and T3 from the thyroid gland is regulated by *thyrotropin*, also called *thyroid-stimulating hormone* (TSH), which is secreted by the *anterior pituitary*.
- The *intrathyroidal iodine concentration* also influences thyroid gland activity, and TSH secretion primarily is regulated by a dual negative feedback mechanism:
- *Thyrotropin-releasing hormone* (**TRH**) is released by the hypothalamus, which stimulates the synthesis and release of TSH from the pituitary gland.

The hypothalamic-pituitary-thyroid axis.



Thyroid Function Tests

- Tests more specific for thyroid status or function can be categorized as:

(1) Measure the concentration of products secreted by the thyroid gland,

(2) Evaluate the integrity of the hypothalamic-pituitary-thyroid axis,

(3) Assess intrinsic thyroid gland function, and

(4) Detect antibodies to thyroid tissue.

Thyroid Function Tests

- **Free T_4**
  - *Normal range: 0.9–2.3 ng/dL*
  - This test measures the unbound T_4 in the serum and is the most accurate reflection of thyrometabolic status.

Thyroid Function Tests

- ***Total Serum T_4***
  - *Normal range: 5.5–12.5 mcg/dL*
  - Measures both bound and free T_4
  - An increased total serum T_4 may indicate
    - hyperthyroidism,
    - elevated concentrations of thyroidbinding proteins, or
    - nonthyroid illness.
  - A decreased total serum T_4 may indicate
    - hypothyroidism,
    - decreased concentrations of thyroidbinding proteins, or
    - *nonthyroid illness* (also called *euthyroid sick*

Thyroid Function Tests

- *Serum T_3 Resin Uptake*
  - *Normal range: 25–38%*
  - The *serum T_3 resin uptake* test indirectly estimates the number of binding sites on thyroid-binding protein occupied by T_3.
  - This result is also referred to as the *thyroid hormone-binding ratio*
  - The T_3 resin uptake is usually low when the concentration of thyroid-binding proteins is **high**

Thyroid Function Tests

- *Free T_4 Index*
  - *Normal range: 1–4 units*
  - The *free T_4 index* is the product of total serum T_4 multiplied by the percentage of T_3 resin uptake:
  - Free T_4 index = total serum T_4 (mcg/dL) × T_3 resin uptake (%)
- *Total Serum T_3*
  - *Normal range: 80–200 ng/dL*
  - Any alteration in thyroid-binding protein influences this measurement

Thyroid Function Tests

- *Thyroid-Stimulating Hormone*
  - *Normal range: 0.5–5.0 milliunits/L*
  - Almost all patients with symptomatic primary hypothyroidism have TSH concentrations >20 milliunits/L; those with mild signs or symptoms have TSH values of 10–20 milliunits/L
  - In patients with primary hypothyroidism, TSH concentrations are also used to adjust the dosage of levothyroxine replacement therapy.
- *Radioactive Iodine Uptake Test*
  - This test is used to detect the ability of the thyroid gland to trap
    and concentrate iodine and, thereby, produce thyroid hormone.
  - In other words, this test assesses the intrinsic function of the thyroid gland

Adrenal Disorders

- The adrenal glands are located extraperitoneally at the upper poles of each kidney.
- The **adrenal medulla**, which makes up10% of the adrenal gland, secretes catecholamines (epinephrine and norepinephrine).
- The **adrenal cortex**, which comprises 90% of the adrenal gland, is divided into three areas:
  - The *zona glomerulosa (*outer layer): makes up 15% of the adrenal gland and is responsible for production of aldosterone, a mineralocorticoid that regulates electrolyte and volume homeostasis
  - The *zona fasciculate (*center of the adrenal gland), occupies 60% of the gland and is responsible for glucocorticoid production.
    - Cortisol, a principal end product of glucocorticoid production, regulates fat, carbohydrate, and protein metabolism
  - The *zona reticularis* makes up 25% of the adrenal gland and is responsible for adrenal androgens such as testosterone and estrogens such as estradiol

Adrenal Disorders

- **Cushing Syndrome**
  - is the result of excessive concentrations of cortisol
  - **Diagnostic tests**
    - 24-hour urine-free cortisol (UFC),
    - Midnight plasma cortisol, and
    - The low-dose dexamethasone suppression test (DST) using 1 mg for the overnight test or 0.5 mg every six hours for the two-day study.

Adrenal Disorders

- **Adrenal Insufficiency (Addison Disease)**
  - *Adrenal insufficiency (Addison disease* or *primary adrenal insufficiency)* is the result of an autoimmune destruction of all regions of the adrenal cortex
  - Secondary adrenal insufficiency can result from the use of high doses of exogenous steroids, which suppress the hypothalamic-pituitary axis resulting in a decrease in the release of ACTH.
  - **Diagnostic tests.**
    - The cosyntropin stimulation test is used to diagnose patients with low cortisol levels.
    - Patients are administered 250 mcg of synthetic ACTH or cosyntropin intravenously or intramuscularly

5. THE KIDNEYS



The Kidneys

- Through the excretion of water and solutes, the kidneys are responsible in large part for maintaining homeostasis within the body.
- They also function in the activation and synthesis of many substances that affect blood pressure (BP), mineral metabolism, and red blood cell (RBC) production.
- The functional unit of the kidneys is the nephron and each of the two kidneys contains about 1 million nephrons.
- The major components of the nephron include the glomerulus, proximal tubule, loop of

Assessment of Kidney Function

- Classification of kidney disease as well as dosing of medications depends on an accurate and reliable method of assessing kidney function
- Direct measurement of GFR using markers such as inulin and iothalamate is the most accurate assessment of kidney function but is not used routinely in clinical practice due to cost and practical concerns.
- Measurements of timed 24-hour urine creatinine (UCr) collections are difficult by design, flawed by collection errors
- The estimation of creatinine clearance (CrCl) through equations such as Cockcrof-Gault has been the “gold standard” for drug dosing

Assessment of Kidney Function

- *Serum Creatinine*
  - *Normal range: adults, 0.6–1.2 mg/dL*
  - *Creatinine* and its precursor creatine are nonprotein, nitrogenous biochemicals of the blood
  - It increases with kidney dysfunction
  - Factors that affect SCr concentrations are muscle mass, sex, age, race, medications, method of laboratory analysis, and low-protein diets.

Assessment of Kidney Function

- **Urea (Blood Urea Nitrogen)**
  - *Normal range: 8–23 mg/dL*
  - Is actually the concentration of nitrogen (as urea) in the serum and not in RBCs as the name implies
  - Its serum concentration depends on urea production (which occurs in the liver), glomerular filtration, and tubular reabsorption.
  - Therefore, clinicians must consider factors other than filtration when interpreting changes in BUN

Assessment of Kidney Function

- *Elevated BUN*
  - High-protein diet (including amino acid infusions),
  - Upper gastrointestinal (GI) bleeding, and
  - Administration of corticosteroids, tetracyclines, or any other drug with antianabolic effects
- *Decreased BUN*
  - A low BUN doesn't have pathophysiological consequences.
  - BUN may be low in patients who are malnourished or have profound liver damage (due to an inability to synthesize urea).
  - Intravascular fluid overload may initially dilute BUN (causing low concentrations)

Assessment of Kidney Function

Common Causes of True BUN Elevations (Azotemia)

- **Prerenal causes**
  - Decreased renal perfusion: dehydration, blood loss, shock, severe heart failure
- **Intrarenal (intrinsic) causes**
  - Acute kidney failure: nephrotoxic drugs, severe hypertension, glomerulonephritis, tubular necrosis
  - Chronic kidney dysfunction: pyelonephritis, diabetes, glomerulonephritis, renal tubular disease, amyloidosis, arteriosclerosis, collagen vascular disease, polycystic kidney disease, overuse of NSAIDs
- **Postrenal causes**
  - Obstruction of ureter, bladder neck, or urethra

Assessment of Kidney Function

- ***BUN to SCr Ratio***
  - In acute kidney injury due to volume depletion, both BUN and SCr are elevated.
    - However, the BUN:SCr ratio is often >20:1.
  - This observation is due to the differences in the renal handling of urea and creatinine.
  - Recall that urea is reabsorbed with water, and under conditions of decreased renal perfusion both urea and water reabsorption are increased.
  - Because creatinine is not reabsorbed, it is not affected by increased water reabsorption.
  - BUN:SCr ratios >20:1 suggest prerenal causes of acute renal impairment, whereas ratios from 10:1 to 20:1 suggest intrinsic kidney damage.

Measurement of CrCl

- The most common clinical uses for CrCl are:
  - Assessing kidney function in patients with CKD
  - Monitoring the effects of drug therapy on slowing the progression of kidney disease
  - Monitoring patients on nephrotoxic drugs
  - Determining dosage adjustments for renally eliminated drugs

Measurement of CrCl

- *Calculating CrCl from Urine Collection*
  - CrCl is calculated using a 24-hour urine collection

  - Where
    - CrCl is the CrCl in mL/min/1.73 m^2
    - Cr = urine creatinine concentration (mg/dL);
    - V = volume of urine produced during the collection interval (mL);
    - SCr = serum creatinine concentration (mg/dL);
    - T = time of the collection interval (minutes), and
    - BSA = body surface area (m^2).

Measurement of CrCl

- **Estimation of CrCl**
  1. *Cockcroft-Gault Equation*
     - The patient's age, total body weight (TBW), and SCr concentration are necessary for the estimation.
  2. *Pediatric Patients*: Schwartz equation

Measurement of CrCl

3. MDRD Equation

- $CrCl = 175 \times SCr^{-1.154} \times age^{-0.203} \times 1.210$ (if African American) $\times 0.742$ (if Female)

4. CKD Epidemiology Collaboration Creatinine Equation 2009 (CKD-EPI)

- $GFR = 141 \times \min(SCr/K,1)^{alpha} \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} * Sex * Race \times 1.159$ (if African American)

  - For females, the following values are used: Sex = 1.018; alpha = -0.329; kappa = 0.7
  - For males, the following values are used: Sex = 1; alpha = -0.411; kappa = 0.9

CASE STUDY: Estimating Equations for GFR

- Patricia L., a 47-year-old female (non-African American), has a long standing history for type 1 diabetes mellitus and has been under the care of a nephrologist. Six months ago, her serum creatinine was 1.18 mg/dL. Laboratory tests today were as follows:
  - Sodium, 140 mEq/L
  - Potassium, 4.5 mEq/L
  - Chloride, 101 mEq/L
  - Carbon dioxide, 28 mEq/L
  - Magnesium, 2 mEq/L
  - Glucose, 98 mg/dL
  - BUN, 12 mg/dL
  - **SCr, 1.49 mg/dL**

CASE STUDY: Estimating Equations for GFR

- **Question:** evaluate eGFR for this patient using MDRD and CKD-EPI equations and how should these results be interpreted?

CASE STUDY: Estimating Equations for GFR

- **Discussion:**
  - Using the 2009 CKD-EPI equation, the calculated eGFR for this patient was initially 55 mL/min/1.73 m^2 and has declined to 41 mL/min/1.73 m^2, respectively
  - Using the MDRD equation, the calculated eGFR for this patient was initially 49 mL/min/1.73 m^2 and has declined to 37.5 mL/min/1.73 m^2, respectively

Urinalysis

- *Urinalysis* is a commonly used clinical tool for the evaluation of various renal and nonrenal problems (e.g., endocrine, metabolic, and genetic)
- A first-morning, midstream collection is customarily used as the specimen.
- Once voided, the urine should be brought to the laboratory as soon as possible to prevent deterioration.
- If the sample is not refrigerated, bacteria multiply and use glucose (if present) as a food source
- Subsequently, glucose concentrations decrease and ketones may evaporate with prolonged standing.
- Another problem is that formed elements begin decomposing within two hours.
- With excessive exposure to light, bilirubin and urobilinogen are oxidized

Macroscopic Analysis (General Appearance)

- The color of normal urine varies greatly – from totally clear to dark yellow or amber – depending on the concentration of solutes
- Fresh normal urine is not cloudy or hazy, but urine may become cloudy if urates (in an acid environment) or phosphates (in an alkaline environment) crystallize or precipitate out of solution.
- Turbidity may also occur when large numbers of RBCs or white blood cells (WBCs) are present.

Causes of Various Urine Coloring

Color	Cause	Possible underlining etiology
Red to orange	Myoglobin	Crush injuries, electric shock, seizures, cocaine-induced muscle damage, rhabdomyolysis
	Hemoglobin/ erythrocytes	Hemolysis (malaria, drugs, strenuous exercise), menstrual contamination; kidney stones
	Porphyrins	Porphyria, lead poisoning, liver disease
	Drugs/ chemicals	dyes: rifampin, isoniazid, riboflavin, sulfasalazine, warfarin, chlorpromazine, thioridazine, daunorubicin, doxorubicin, phenothiazines,
Blue to green	Biliverdin	Oxidation of bilirubin (poorly preserved specimen)
	Bacteria	*Pseudomonas* or *Proteus* in UTIs (rare), particularly in urine drainage bags

Causes of Various Urine Coloring

Color	Cause	Possible underlining etiology
Brown to black	Myoglobin	Crush injuries, electric shock, seizures, cocaine-induced muscle damage, rhabdomyolysis
	Bile pigments	Hemolysis, bleed into tissues, liver disease
	Melanin	Melanoma
	Methemoglobin	Methemoglobinemia from drugs, dyes
	Porphyrins	Porphyria and sickle cell crisis
	Drugs/ chemicals	Chloroquine, clofazimine, ferrous salts, metronidazole, nitrofurantoin, sulfonamides, sorbitol, α-methyldopa, HMG-CoA reductase Inhibitors, and L-dopa

Microscopic Analysis (Formed Elements)

- the three “Cs”
  - Cells,
  - Casts, and
  - Crystals.

Microscopic Analysis (Formed Elements)

- *Cells*
  - Theoretically, no cells should be seen during microscopic examination of urine.
  - In practice, however, an occasional cell or two is found.
  - These cells include microorganisms, RBCs, WBCs, and tubular epithelial cells

1) **Microorganisms (normal range: zero to trace)**
   - Contamination
   - Urinary tract infection (UTI)

2) **Red blood cells (erythrocytes) (normal range: one to three per high-power field)**
   - Hematuria
   - Vaginal blood may contaminate the urine
   - Glomerulonephritis, infection (pyelonephritis), renal infarction or papillary necrosis, tumors, stones, and coagulopathies.

Microscopic Analysis (Formed Elements)

3) **White blood cells (leukocytes) (normal range: zero to two per high-power field).**
   - Pyuri: three or more WBC
   - UTIs (upper or lower)
   - Inflammatory conditions (glomerulonephritis, interstitial nephritis)

4) **Tubular epithelial cells (normal range: zero or one per high-power field)**
   - when the tubules are damaged (acute tubular necrosis) or
   - when there is inflammation from interstitial nephritis or glomerulonephritis

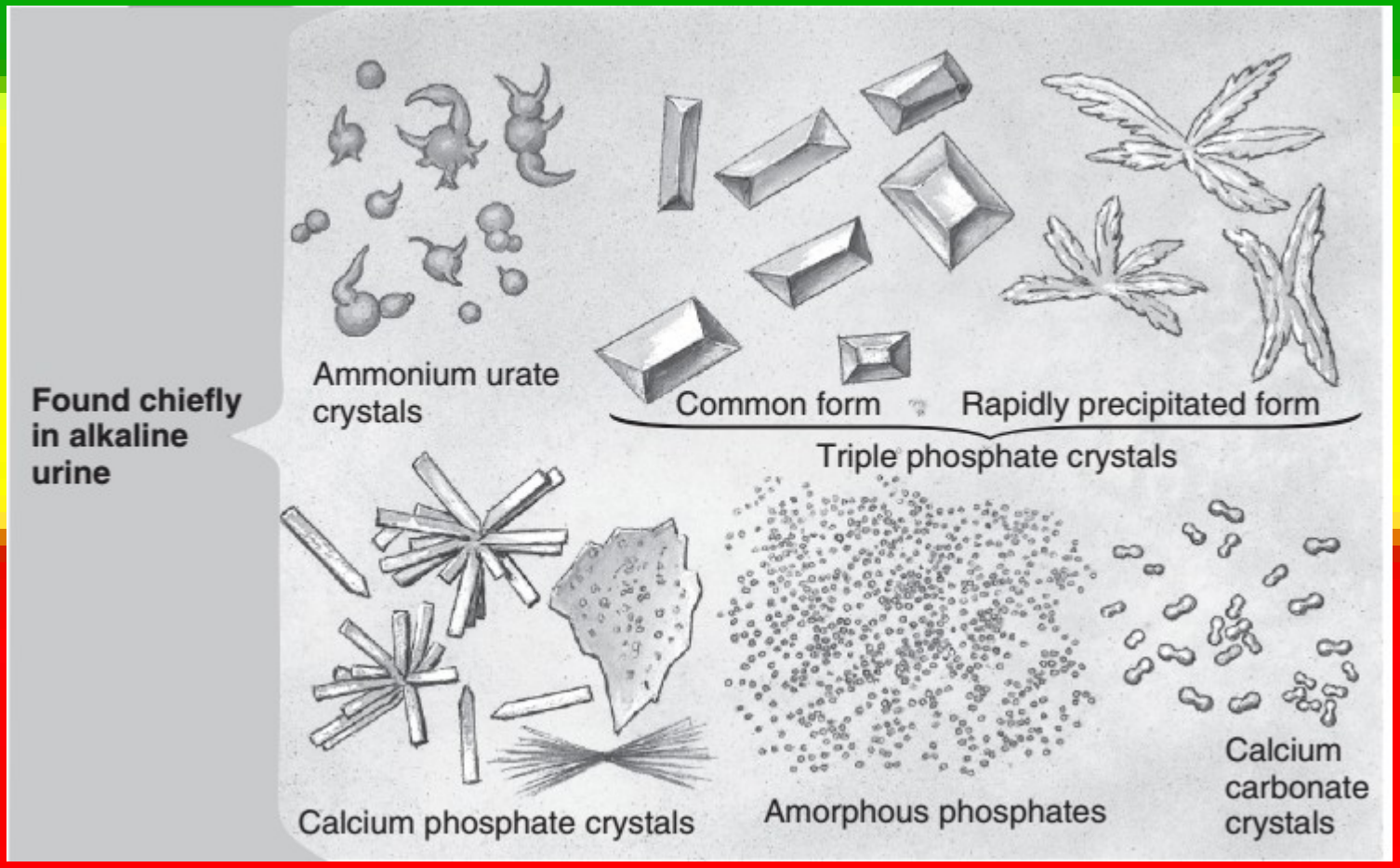
Microscopic Analysis (Formed Elements)

- *Casts*
  - *Casts* are cylindrical masses of glycoproteins that form in the tubules.
  - Casts have relatively smooth and regular margins (as opposed to clumps of cells) because they conform to the shape of the tubular lumen
  - **Cellular casts.**
    - cellular casts are seen with intrinsic renal disease.
    - They form when leukocytes, RBCs, or renal tubular epithelial cells become entrapped in the gelatinous matrix forming in the tubule

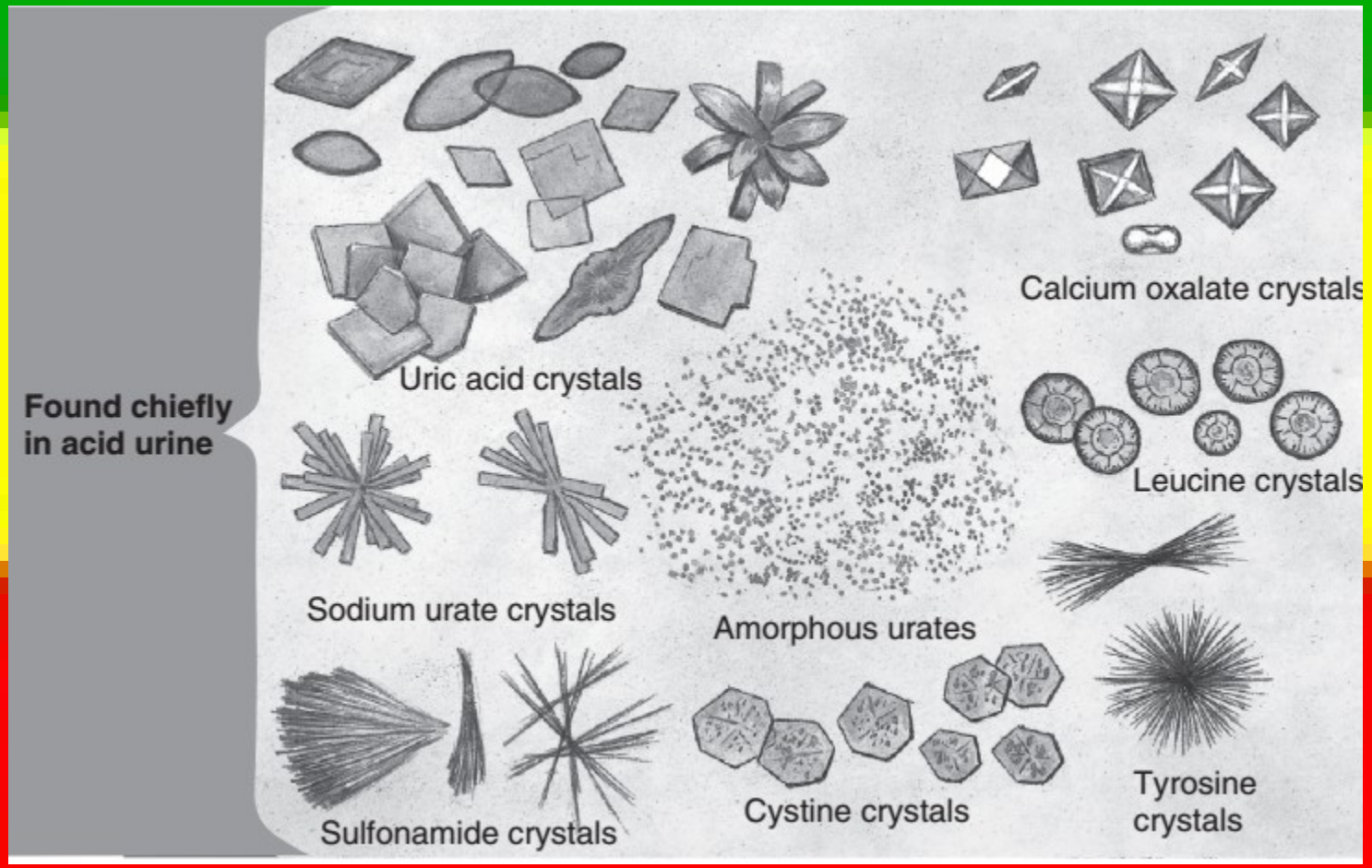
Microscopic Analysis (Formed Elements)

- *Crystals*
  - The presence of *crystals* in the urine (crystalluria) depends on urinary pH, the degree of saturation of the urine by the substance that is forming crystals, and the presence of other substances in the urine that may promote crystallization.
  - Calcium oxalate, calcium phosphate, and uric acid crystals are also suggestive of stones.

Microscopic Analysis (Formed Elements)



Microscopic Analysis (Formed Elements)



Chemical Analysis

- Semiquantitative Tests, Urine Dipstick Tests
- Biochemical analysis of urine includes protein; pH; specific gravity; bilirubin, bile, and urobilinogen; blood and hemoglobin; leukocyte esterase; nitrite; glucose; and ketones.

Chemical Analysis

- **Protein**
  - *Normal range: zero to trace on dipstick*
  - The normal urinary proteins are albumin and low molecular weight serum globulins.
  - The glomerulus is freely permeable to substances with a molecular weight of <20,000 daltons.
  - However, albumin with a molecular weight of 65,000 daltons is typically restricted from passing through the glomerulus into the urine.
  - The smaller serum globulins that are filtered in the nephron are generally reabsorbed in the proximal tubule

Chemical Analysis

- Therefore, healthy individuals excrete very small amounts of protein in the urine (about 80–100 mg of protein per day).
- In the presence of kidney damage, larger quantities of protein may be excreted.
- Increased excretion of albumin is associated with diabetic nephropathy, glomerular disease, and uncontrolled hypertension.
- ***Proteinuria*** is a general term that refers to the renal loss of protein (albumin and globulins).
- ***Albuminuria*** specifically refers to the abnormal renal excretion of albumin.
- **Clinical proteinuria** is defined as the loss of >500 mg/day of protein urine.
- Patients with **microalbuminuria** are excreting relatively small, but still pathogenic, amounts (30–300 mg/day) of albumin.

Chemical Analysis

- **pH**
  - *Normal range: 4.6–8*
  - In general, acidic (versus neutral) urine deters bacterial colonization.
  - Alkaline urine may be seen with either
    - UTIs caused by urea-splitting bacteria, such as *Proteus mirabilis* (via ammonia production), or
    - Tubular defects causing decreased net tubular hydrogen ion secretion as in renal tubular acidosis.

Chemical Analysis

- **Urobilinogen**
  - *Normal range: 0.3–1 Ehrlich unit*
  - *Urobilinogen:* formed by bacterial conversion of conjugated bilirubin in the intestine
  - is normally present in urine and increases when the turnover of heme pigments is abnormally rapid, as in hemolytic anemia, congestive heart failure with liver congestion, cirrhosis, viral hepatitis, and drug-induced hepatotoxicity.
  - Elevated urobilinogen may be premonitory of early hepatocellular injury, such as hepatitis, because it is evident in urine before serum bilirubin levels increase

Chemical Analysis

- **Bilirubin**
  - *Normal range: negative*
  - Bilirubinuria may be seen in patients with intrahepatic cholestasis or obstruction of the bile duct (stones or tumor).

Chemical Analysis

- **Glucose and Ketones**
  - *Normal range: none*
  - Although glucose is filtered in the glomerulus, it is almost completely reabsorbed in the proximal tubule so that glucose is generally absent in the urine.
  - However, at glucose concentrations >180 mg/dL, the capacity to reabsorb glucose is exceeded and glycosuria will occur.
  - Glucose in the urine is suggestive of diabetes mellitus
  - Ketones in the urine typically indicate a derangement of carbohydrate metabolism resulting in utilization of fatty acids as
    an energy source.
  - Ketonuria in association with glucose in the urine is suggestive of uncontrolled type 1 diabetes mellitus.
  - Ketonuria can also occur with pregnancy, carbohydrate-free diets, and starvation.

6. ELECTROLYTES

SODIUM (135–145 mEq/L)

- Sodium is the predominant cation of extracellular fluid (ECF).
- Along with chloride, potassium, and water, sodium is important in establishing serum osmolarity and osmotic pressure relationships between **ICF** and **ECF**.
- Dietary intake of sodium is balanced by renal excretion of sodium
- Renal excretion of sodium is regulated by
  - **Aldosterone** (enhances sodium reabsorption),
  - **Natriuretic hormone** (increases excretion of sodium),
  - **Antidiuretic hormone** (enhances reabsorption of free water).

Antidiuretic Hormone (ADH)

- Produced by hypothalamus (CNS)
- Also called **vasopressin**
- Causes of increased production
  - Hypovolumeia
  - Thirst
  - High serum osmolality.
  - Angiotensin II
- Leads to concentrated urine by increasing permeability of colleting tubules for reabsorption of water

Disorder of ADH Production

- **Syndrome of Inappropriate ADH secretion (SIADH)**
  - Inappropriately high qty of ADH
  - Excessive reabsorption of water – **hyponatremia**
- **Diabetes Insipidius (DI)**
  - DI (Center): Inadequate ADH synthesis
  - DI (Nephrogenic): kidney fails to respond to ADH (high or low) – **hypernatremia**
- **Drugs known to cause SIADH:**
  - Chlorpramide, Cyclosphosphamide, Carbamazepine, Tolbutamide, Oxytocin, and some TCAs

Aldosterone

- Mineral corticosteroid
  - Retains Na and water – more Na than water
  - Increase excretion of potassium
  - More effect on K^+ than Na
- Spironolactone – aldosterone antagonist

SODIUM

- An increase in the serum sodium concentration could suggest either impaired sodium excretion or volume contraction.
- A decrease in the serum sodium concentration to less-than-normal values could reflect hypervolemia, abnormal sodium losses, or sodium starvation.
- Patients with kidney failure, heart failure, or pulmonary disease often encounter sodium and water imbalance.
- Changes in serum sodium concentrations most often represent **water imbalances** rather than sodium imbalances.
  - ➲Serum sodium concentrations are more reflective of a patient's **fluid status** rather than sodium balance.

Hyponatremia

- Hyponatremia can result from

➲ **Dilution of the sodium concentration in serum**

- ECF compartment expands without an equivalent ↑ in Na.
- Clinical conditions (cirrhosis, congestive heart failure, renal impairment),
- Administration of osmotically active solutes (albumin, mannitol)

Hyponatremia

- **A total body depletion of sodium**
  - Low serum sodium concentration in the absence of edema
  - Caused by mineralocorticoid deficiencies, Na-wasting renal disease, or replacement of Na-containing fluid losses with nonsaline solutions.

Specific Causes

- Congestive heart failure
- Excessive antidiuretic hormone production (Excessive loss through renal excretion)
- Excessive use of diuretics (Excessive loss through renal excretion; renal absorption is blocked)
- Hepatic failure (Hemodilution related to fluid retention)

- Insufficient intake
- IV glucose infusion (hypertonic glucose draws water into extra-cellular fluid and sodium is diluted)
- Mineralocorticoid deficiency (**Addison's disease**) (inadequate production of aldosterone results in ↓ed absorption by the kidneys)
- Nephrotic syndrome (related to ↓ed ability of renal tubules to reabsorb sodium)

Hypernatremia

- Hypernatremia represents a state of relative water deficiency excessive concentrations of sodium in all body fluids (hypertonicity).
- Hypernatremia can be caused by
  - Loss of free water: diabetes insipidus
  - Loss of hypotonic fluid: Gastroenteritis
  - Excessive sodium intake: hypertonic salt solutions
  - ↑ed retention of sodium:

Specific Causes

- Burns (hemoconcentration related to excessive loss of free water)
- Cushing's disease
- Dehydration
- Diabetes (dehydration related to frequent urination)
- Diarrhea (Water loss in excess of salt loss)
- Excessive intake

Specific Causes

- Excessive saline therapy (IV fluids)
- Excessive sweating (loss of free water can cause hemoconcentration)
- Fever (loss of free water through sweating)
- **Hyperaldosteronism** (Excessive production of aldosterone increases renal absorption of sodium and increases blood levels)
- Lactic acidosis (Related to diabetes)

Specific Causes

- The primary defense against hypertonicity is thirst and subsequent fluid intake.
  - Hypernatremic syndromes usually occur in patients who are unable to drink sufficient fluids.
  - Infants

Case 1

- M.C., a 61-year-old woman with no known drug allergies (NKDA) is hospitalized with a chief complaint of increasing shortness of breath (SOB) and orthopnea over the past week.
- She has been treated previously for heart failure and has not taken any medication over the past 2 weeks.
- M.C. has severe (4+) pedal edema and

- Laboratory tests were ordered and reported back as follows: Na, 123 mEq/L (normal, 135–145); K, 4.1 mEq/L (normal, 3.5–5.0); Cl, 90 mEq/L (normal, 95–105); CO_2, 28 mEq/L (normal, 22 to 28); BUN, 30 mg/dL (normal, 8–18); SCr, 1.3 mg/dL (normal, 0.6–1.2); and fasting glucose, 100 mg/dL (normal, 70–110).
- Why should M.C. not be given sodium chloride to return her serum sodium concentration to a normal value?

Potassium (3.5–5.0 mEq/L)

- K is the major **intracellular cation** in the body.
- The potassium ion in the ECF is filtered freely at the glomerulus of the kidney, reabsorbed in the proximal tubule, and secreted into the distal segments of the nephron.
- Major role: regulate muscle and nerve excitability
- Cardiac muscle depends on K for normal contraction

Hypokalemia

- The kidneys are responsible for about 90% of daily potassium loss, and the remaining 10% is by GI system and sweating.
  - Decreased potassium intake
  - Increased loss of K
    - Thiazide or loop diuretics,
    - Excessive mineralocorticoid activity,

    Protracted vomiting

    Severe diarrhea
  - **Insulin** & **β_2-adrenergic receptor** stimulation
  - **Alkalosis**

Specific Causes

- **Alcoholism** (related to insufficient dietary intake)
- **Alkalosis** (Potassium uptake by cells is increased in response to release of hydrogen ions from cells)
- **Anorexia nervosa** (Related to significant changes in renal function that result in hypokalemia)
- **Congestive heart failure** (Related to fluid retention and hemodilution)
- **Crohn's disease** (Insufficient intestinal absorption)

Specific Causes

- **Cushing's syndrome** (Aldosterone facilitates the excretion of potassium by the kidneys)
- **Diet deficient** in meat and vegetables (insufficient dietary intake)
- **Excess insulin:** Insulin causes glucose and potassium to move into cells
- **Gastrointestinal (GI) loss** due to vomiting, diarrhea, nasogastric suction, or intestinal fistula
- **Hyperaldosteronism (**Aldosterone facilitates the excretion of potassium by the kidneys)

Specific Causes

- **Laxative abuse** (Medications cause potassium wasting)
- **Malabsorption** (Insufficient intestinal absorption)
- **Renal tubular acidosis** (Condition results in excessive loss of potassium)
- **Sweating** (Increased loss)

Hyperkalemia

- **Hyperkalemia results from**
  - **Decreased renal excretion** of potassium
  - **Excessive exogenous K administration** (especially when combined with a potassium-sparing diuretic)
  - **Excessive cellular breakdown** (hemolysis burns, crush injuries, surgery, infections)

Specific Causes

- **Acidosis** (intracellular potassium ions are expelled in exchange for hydrogen ions in order to achieve electrical neutrality)
- **Acute renal failure** (K^+ excretion is diminished and it accumulates in the blood)
- **Addison's disease** (due to lack of aldosterone, K^+ excretion is diminished and it accumulates in the blood)

Specific Causes

- **Asthma** (Related to chronic inflammation and damage to lung tissue)
- **Burns** (Related to tissue damage and release by damaged cells)
- **Chronic interstitial nephritis** (Potassium excretion is diminished and it accumulates in the blood)
- **Dehydration** (Hemoconcentration)

Specific Causes

- **Dialysis** (Dialysis treatments simulate kidney function but potassium builds up between treatments)
- **Diet** (Related to excessive intake of salt substitutes or of potassium salts in medications)
- **Exercise** (Related to tissue damage and release by damaged cells)
- **Hemolysis** (**massive**) (Potassium is the major intracellular cation)
- **Hyperventilation** (Response to respiratory alkalosis is increased blood levels of potassium in order to achieve electrical neutrality)

Specific Causes

- **Hypoaldosteronism** (Due to lack of aldosterone, potassium excretion is diminished and it accumulates in the blood)
- **Insulin deficiency** (Insulin deficiency results in movement of potassium from the cell into the extracellular fluid)
- **Ketoacidosis** (Insulin deficiency results in movement of potassium from the cell into the extracellular fluid)

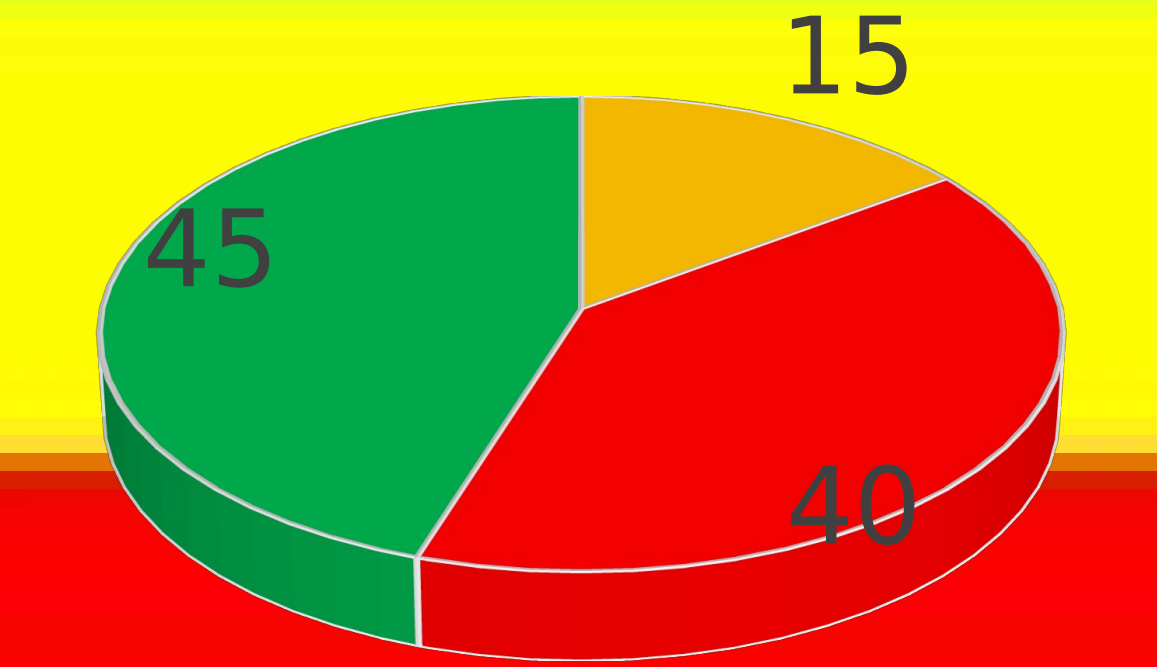
Specific Causes

- ✓ **Leukocytosis**
- ✓ **Muscle necrosis** (Related to tissue damage and release by damaged cells)
- ✓ **Pregnancy**
- ✓ **Tissue trauma** (Release by dam-aged cells)
- ✓ **Transfusion of old banked blood** (Aged cells hemolyze and release intracellular potassium)
- ✓ **Uremia**

Calcium: (8.5 – 10.8 mg/dL)

- **99%** present in skeleton (reservoir)
- Of the plasma Ca^{2+}
  - ↳**40%:** bound to plasma proteins (especially albumin)
  - ↳**15%:** complexed with phosphate, citrate or sulfate
  - ↳**45%:** unbound, ionized form.
- Functions of calcium
  - ✓Intracellular signalling
  - ✓Coagulation
  - ✓Bone mineralization
  - ✓Plasma membrane potential

Percentage of Ca2+



Major Mediators of Ca and PO_4 Balance

- Parathyroid hormone (PTH)
- Calcitriol (active form of vitamin D_3)

Role of PTH

- Stimulates renal reabsorption of calcium
- Inhibits renal reabsorption of phosphate
- Stimulates bone resorption
- Inhibits bone formation and mineralization
- Stimulates synthesis of calcitriol

Net effect of PTH → **↑ Serum calcium**
↓ Serum phosphate

Regulation of PTH

- Low serum [Ca^{+2}] → ↑ PTH secretion
- High serum [Ca^{+2}] → ↓ PTH secretion

Role of Calcitriol

- Stimulates GI absorption of both calcium and phosphate
- Stimulates renal reabsorption of both calcium and phosphate
- Stimulates bone resorption
- Reduces PTH levels

Net effect of calcitriol → **↑ Serum calcium**
↑ Serum phosphate

Hypocalcaemia

- **Deficiency** in either the production or the response to parathyroid hormone or vitamin D

Hypocalcaemia

- The abnormality in the vitamin D system
  - ↓ Nutritional intake
  - ↓ Absorption of vitamin D secondary to gastrectomy
  - Chronic pancreatitis, or small bowel disease
  - ↓ Production of 25-hydroxycholecalciferol due to liver disease
  - ↑ Metabolism of 25-hydroxycholecalciferol because of enzyme-stimulating drugs (e.g., phenobarbital, phenytoin, rifampicin); or
  - ↓ Production in 1,25-dihydroxycholecalciferol due to chronic renal disease.

Hypercalcaemia

- Malignancy or metastatic diseases: commonly
- Other causes:
  - Hyperparathyroidism: 1^0 or 2^0
  - Paget disease
  - Milk-alkali syndrome
  - Granulomatous disorders
  - Thiazide diuretics
  - Vitamin D intoxication.

Phosphate: (2.6 – 4.5 mg/dL)

- 85% present in skeleton
- Of the plasma phosphate:
  - 10% protein bound,
  - 35% complexed,
  - 55% free
- Functions:
  - Integrity of bone
  - Oxygen delivery
  - Muscle contraction

Phosphate

- Role in ATP (energy), nucleotides, NADP, cell membranes, gene transcription, cell growth
- Balance maintained primarily by kidneys
- All factors that affect Ca also affect PO_4
- Increase Ca or Al binds PO_4 leading to hypophostamia

Hypophosphatemia

- **Causes:**
  - Malnutrition
  - Excessive use of antacids (aluminum-containing antacids bind phosphorus in the GI tract),
  - Chronic alcoholics
  - Septic patients

Hyperphosphatemia

- Causes
  - Renal insufficiency
  - Increased vitamin D
  - Hypoparathyroidism
  - Advanced malignancies

Magnesium (1.6–2.4 mEq/L)

- 55% present in skeleton
- 1% of total body Mg extracellular
- Cofactor for enzymes
- Required for ATP (MgATP)
- Glycolysis
- Cell replication
- Protein biosynthesis
- PTH increases renal tubular reabs of Mg
- Homeostasis maintained - control of excretion

Hypomagnesemia

- **Causes**
  - Prolonged nasogastric suction
  - Malabsorption
  - Bowel resection
  - Diarrhoea
  - Fistulas
  - Acute pancreatitis
  - Decreased intake
  - Chronic vomiting

Hypermagnesaemia

- **Causes**
  - Excessive intake
  - Antacids
  - Enemas
  - Parenteral therapy
  - Mg administration (RF)

7. LIVER FUNCTION TESTS: LFT

LIVER FUNCTION TESTS

- The liver has two sources of blood:

1. The hepatic artery, originating from the aorta, supplies arterial blood rich in oxygen.
2. Portal veins shunt the venous blood from the intestines to the liver.
   - ✓ This transports absorbed toxins, drugs, and nutrients directly to the liver for metabolism

- The *LFT panel* or *LFTs* (liver function tests).
  - May vary slightly between hospitals and laboratories
  - Includes: aspartate and alanine aminotransferases (AST & ALT), bilirubin, alkaline phosphatase (ALP), and albumin.
  - Not all of these tests actually measure liver function (specifically, aminotransferases reflect liver injury)

Categories of Liver Tests

PROCESS	MOST CLOSELY RELATED TESTS
Protein synthesis	Albumin
	PT/INR (clotting factors)
Excretion into the bile ducts and drainage into the duodenum (cholestasis)	Bilirubin
	ALP
	GGT
Hepatocellular injury	ALT
	AST
Detoxification	Ammonia (NH3+)

Tests of Synthetic Liver Function

- One of the functions of the liver is to synthesize proteins that circulate in the blood, including albumin and clotting proteins.
- Measurement of the levels of these proteins in the blood provides a reflection of the ability of the liver to synthesize them.
- The liver has an enormous reserve function, so that it may synthesize normal amounts of proteins despite significant liver damage
- Therefore, tests of synthetic function are not sensitive to low levels of liver damage or dysfunction.
- Inadequate protein synthetic function is mainly limited to hepatic cirrhosis, scarring of the liver

Tests of Synthetic Liver Function

- **Albumin**
  - *Normal range: 4 – 5 g/dL*
  - *Albumin* is a major plasma protein that is involved in maintaining plasma oncotic pressure and the binding and transport of numerous hormones, anions, drugs, and fatty acids.
  - The normal serum half-life of albumin is about 20 days,
  - Because of albumin's long half-life, serum albumin measurements are slow to fall after the onset of hepatic dysfunction
  - For this reason, levels are often normal in acute viral hepatitis or drug-related hepatotoxicity.
  - Alternatively, albumin is commonly reduced in patients with chronic synthetic dysfunction due to cirrhosis.

Tests of Synthetic Liver Function

- Albumin levels may be low due to other abnormalities in protein synthesis, distribution, and excretion in addition to liver dysfunction.
  - Malnutrition/malabsorption,
  - Protein loss from the gut, kidney, or skin (as in nephrotic syndrome, protein-losing enteropathy, or severe burns, respectively), or
  - Increased blood volume (e.g., following administration of large volumes of IV fluids)
- At very low concentrations (<2–2.5 g/dL), patients can develop peripheral edema, ascites, or pulmonary edema.
  - Albumin normally generates oncotic pressure, which holds fluid in the vasculature

Tests of Synthetic Liver Function

- ***INR** and **PT***
  - *Normal range: INR 0.9–1.1, PT 12.7–15.4 sec*
  - These two tests measure the speed of a set of reactions in the extrinsic pathway of the coagulation cascade.
  - Decreased synthesis or impaired activation of clotting factors correlates with prolonged reaction times, and increased values of INR and PT
  - The liver is required for the synthesis of clotting factors (with the exception of factor VIII), many of which require a vitamin K cofactor for their activation).
  - Therefore, either hepatic impairment or vitamin K deficiency may lead to a deficiency in activated clotting factors with subsequent prolongation of PT/INR

Tests of Synthetic Liver Function

- The prolongation of PT/INR alone is **not specific** for liver disease.
  - Because vitamin K is a fat soluble vitamin, inadequate vitamin K in the diet or **fat malabsorption** as caused by cholestasis may cause hypovitaminosis.
  - Many broadspectrum antibiotics, including tetracyclines, may eliminate vitamin K–producing flora in the gut.
  - The anticoagulant agent warfarin interferes directly with vitamin K dependent activation of clotting factors

Tests for Excretory Liver Function and Cholestasis

- *Cholestasis* is a deficiency of the excretory function of the liver
- Bile is normally secreted by hepatocytes into bile canaliculi, where it flows into larger bile ducts, and eventually empties into the duodenum
- Excretion of bile from the liver serves multiple purposes.
  - Certain large lipophilic toxins, drugs, and endogenous substances are eliminated by secretion into the bile with eventual elimination in the feces.
  - Bile salts also play an important role in dissolving and absorbing dietary fat-soluble vitamins and nutrients within the small intestine

Tests for Excretory Liver Function and Cholestasis

- Cholestatic syndromes may be sub-classified as
  - Disorders of hepatocytes and microscopic bile ducts (*intrahepatic cholestasis*) or
  - Anatomic obstructions to macroscopic bile ducts (*extrahepatic cholestasis*).

Tests for Excretory Liver Function and Cholestasis

- ***Alkaline Phosphatase***
  - *Normal range: 33–96 units/L*
  - Is present as a number of isoenzymes and is found in the highest concentrations in **bone**, **liver**, **kidney**, **intestine** and **placenta**.
  - 80% in **liver** and **bones**
  - This **enzyme** is **secreted into the bile**, and substantially elevated ALP serum concentrations can be seen with mild intrahepatic or extrahepatic biliary obstruction.
  - Nonhepatic causes of elevated ALP include bone disorders (healing fractures, osteomalacia, Paget disease, rickets, tumors, osteoporosis, vitamin D deficiency as caused by celiac sprue), hyperthyroidism, hyperparathyroidism, sepsis, diabetes mellitus, renal failure, and neoplasms (which may synthesize ALP ectopically, outside tissues that normally contain ALP)

Tests for Excretory Liver Function and Cholestasis

- *Gamma-Glutamyl Transpeptidase (GGT)*
  - *Normal range: 9–58 units/L*
  - The enzyme GGT is found in the kidney, **liver**, and pancreas
  - To evaluate of hepatobiliary disease.
  - It is not elevated in bone disorders, adolescence, or pregnancy.
  - It is rarely elevated in conditions other than liver disease
  - Increased **ALP** in the presence of a normal GGT is more suggestive of muscular or bone-related issues.

Tests for Excretory Liver Function and Cholestasis

- ***Bilirubin***
  - *Total bilirubin: 0.3–1.3 mg/dL*
  - *Indirect (unconjugated, insoluble) bilirubin: 0.2–0.9 mg/dL*
  - *Direct (conjugated, water soluble) bilirubin: 0.1–0.4 mg/dL*
  - Bilirubin is a breakdown product of heme pigments, which are large, insoluble organic compounds.
  - Most of the body's heme pigments are located in RBCs where they are a component of hemoglobin

Tests for Excretory Liver Function and Cholestasis

- Bilirubin is primarily a breakdown product of Hgb **(Hgb → bilirubin + Iron + Globin)** in the RES

- It is then transferred into the blood, where it is almost completely bound to serum albumin.

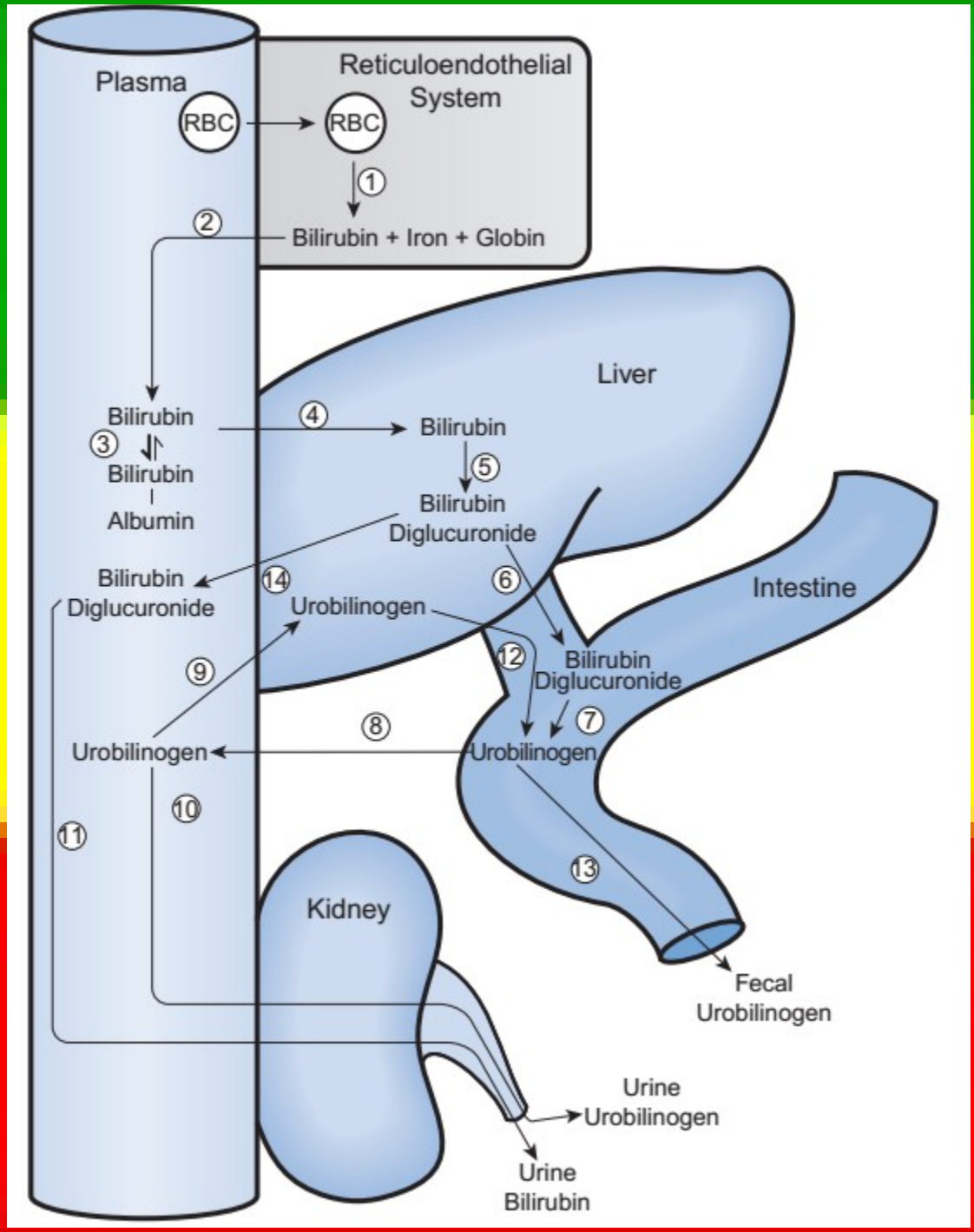
- When bilirubin arrives at the liver cells, the **free fraction** is rapidly taken up into the cell → converted to **bilirubin diglucuronide**

Tests for Excretory Liver Function and Cholestasis

- The conjugated bilirubin diglucuronide is then excreted into the bile and appears in the intestine → bacteria convert most of it to **urobilinogen**

- The majority of urobilinogen is destroyed or excreted in the feces, but a small portion is reabsorbed into the blood and either reabsorbed into the liver → excreted into the bile or excreted into the urine

❖ **Urobilinogen** is responsible for the straw color of the urine and the yellowish-brown color of the


Plasma
RBC
Reticuloendothelial System
RBC
1
2
Bilirubin + Iron + Globin
Liver
Bilirubin
3
Bilirubin
Albumin
4
Bilirubin
5
Bilirubin Diglucuronide
Bilirubin Diglucuronide
14
Urobilinogen
6
Intestine
12
Bilirubin Diglucuronide
7
9
8
Urobilinogen
Urobilinogen
10
11
13
Kidney
Fecal Urobilinogen
Urine Urobilinogen
Urine Bilirubin

Tests for Excretory Liver Function and Cholestasis

- ***Indirect Hyperbilirubinemia (unconjugated, insoluble)***
  - Bilirubinemia with >70% in the indirect fraction
  - Elevated levels may result from increased breakdown of red blood cells (hemolysis) or reduced hepatic conversion to direct bilirubin
  - Hemolysis may result from a wide variety of hematologic processes including sickle cell anemia, spherocytosis, hematomas, mismatched blood transfusions,
- ***Direct Hyperbilirubinemia (conjugated, soluble)***
  - Bilirubinemia with >50% in the direct fraction
  - Elevated direct bilirubin implies hepatic or biliary tract disease that interferes with secretion of bilirubin from the hepatocytes or clearance of bile from the liver

MINI-Case

- A.R., a 42-year-old man with a 2-year history of hypertension controlled with hydrochlorothiazide and a 1-year history of Parkinson disease controlled by carbidopa/levodopa, is hospitalized after an episode of orthostatic hypotension. Admitting laboratory results show a hematocrit (Hct) of 27% (normal, 39–49). Because A.R. had a long history of alcoholism, additional laboratory tests were obtained.

MINI-Case

- His results were as follows: **total bilirubin, 3.5 mg/dL** (normal, 0.3–1.3); **direct bilirubin, 0.5 mg/dL** (normal, <0.4); **ALP, 40 units/L** (normal, 30–120); **AST, 32 units/L** (normal, <35); and **ALT, 27 units/L** (normal, <35).
- **Question**: Based on this inform'n what might be the most logical cause of increased bilirubin in A.R.?

Hepatocellular Injury

- *Hepatitis* is a term that technically refers to a histologic pattern of inflammation of hepatocytes.
- There are multiple causes of hepatitis.
  - One common type is viral hepatitis, which is classified A, B, C, D (delta hepatitis), E, or G based on the causative virus.
  - Hepatitis may also be caused by various medications - drug-induced hepatitis
  - the most common cause of abnormal aminotransferases in ambulatory patients is fatty liver

Aminotransferases

- **Normal:**
  - **Alanine Aminotransferase (ALT): (0 – 35 IU/L)**
  - **Aspartate Aminotransferase (AST): (0 – 35 IU/L)**
- The *aminotransferases* (also known as *transaminases*) are used to assess hepatocellular injury and include:
  - AST (formerly serum glutamic-oxaloacetic transaminase or SGOT) and
  - ALT (formerly serum glutamic-pyruvic transaminase or SGPT)
- These enzymes are primarily located inside hepatocytes.
- They are released into the serum in greater quantities when there is hepatocyte damage

ALT: (0-35 IU/L)

- **ALT**) is a **cytoplasmic enzyme** in liver
- It is present in a higher concentration in the liver than in other tissues

  ↳**More specific for liver damage.**

- Formerly called “**serum glutamic pyruvic transaminase, SGPT**”

ALT: Interpretation

- **ALT** is more specific for liver disease than **AST**
- In acute **viral hepatitis** without extensive necrosis, **ALT exceeds AST**, whereas **AST exceeds ALT** in **alcoholic hepatitis** owing to release of mitochondrial AST
- Elevation lasting 6 months or more indicate chronic active or persistent hepatitis

AST (0 to 35 units/L)

- **Mitochondrial** and **cytoplasmic enzyme** in liver
- Formerly called "**serum glutamic oxaloacetic transaminase**, **SGOT**"
- Is abundant in **heart** and **liver** tissue and moderately present in skeletal muscle, the kidney, and the pancreas
- In cases of acute cellular injury to the heart or liver, the enzyme is released into the blood from the damaged cells.

AST

- Measuring AST activity is useful for identifying inflammation and necrosis of the liver
- **Ethanol** induces liver cell mitochondrial necrosis, result in the release of AST.
- Viral hepatitis usually causes release of only microsomal enzyme, but **fulminant viral hepatitis** also may cause hepatic cell mitochondrial necrosis similar to alcoholic hepatitis
- Increase ratio **AST/ALT** may be useful in **alcoholic liver** disease

AST: Interpretation

- An abnormal serum AST result is associated with an acute abnormality of the heart, liver, or skeletal muscle
- **In viral hepatitis**, serum AST activity is typically 10-20 times the upper limit of the reference range, ALT still greater than AST
- In contrast to viral hepatitis, serum AST exceeds ALT in extensive necrotic injury such as occurs in **alcoholic hepatitis**

MINI CASE

- Ms Bethi., a 36-year-old broker, is attending a referral hospital for her routine check-up. Her physician finds an elevated AST of 180 IU/L on screening. Bethi. has no symptoms; her physical examination has been normal, without any signs of liver disease or hepatomegaly. Additional studies show an ALT of 60 IU/L, a markedly elevated GGT of 380 IU/L, and a minimally elevated ALP of 91 IU/L. Her WBC count is elevated at 20 × 10^3 cells/mm^3. After much discussion, she reveals that she has been drinking 1 pint of vodka a day.
- Bethi is enrolled in Alcoholics Rehabilitation Center and stops drinking. Three months later, all of her tests are normal: ALT 28 IU/L, GGT 54 IU/L, and ALP 54 IU/L

MINI CASE

- **QUESTIONS:**
  - What findings suggest alcoholic liver disease?
  - Why did all of Bethi.’s laboratory test results return to **normal**?
  - Women vs men???

Tests Associated with Detoxification

- ***Hepatic encephalopathy*** refers to a diffuse metabolic dysfunction of the brain that may occur in acute or chronic liver failure.
- The majority of serum ammonia enters the blood from the intestines, where it is formed by:
  - Bacterial catabolism of protein within the gut lumen and
  - Conversion of serum glutamine into ammonia by enterocytes of the small intestine
- Normally, the liver removes >90% of this ammonia via first-pass metabolism
- *Ammonia*
  - *Normal range: 19–60 mcg/dL*

9. PANCREATIC TESTS

- **Amylase and Lipase**
  - **Normal**
    - **Amylase** (35–120 units/L) and
    - **Lipase** (0–160 units/L)
  - Produced in the pancreas and secreted into the duodenum to assist in the digestive process

Pancreatic tests

- **Amylase**
  - Is responsible for breaking down complex carbohydrates into simple sugars and is also found in the **saliva**.
  - Significant elevations in serum amylase are observed in patients with acute **pancreatitis** or **pancreatic duct obstruction**.
  - Amylase levels tend to rise **6 to 48 hours** after onset of the disease and usually return to normal **3 days** after the acute event.
  - In chronic pancreatitis or obstruction, amylase levels may remain elevated for longer periods.

Pancreatic tests

- **Lipase**
  - Is responsible for breaking down triglycerides into fatty acids.
  - Elevated serum lipase levels are also suggestive of pancreatic disease and tend to be **more specific for pancreatic disease than amylase**.
  - The onset of lipase elevation is similar to amylase; however, lipase typically remains elevated for 5 to 7 days and can be useful in diagnosing patients in later stages of pancreatic disease.
  - Narcotics (e.g., morphine) can constrict the sphincter of Oddi and increase serum concentrations of amylase and lipase.

10. HEMATOLOGIC TESTS

- The cellular components of blood are derived from pluripotential stem cells located in the bone marrow that can differentiate into
  - Red blood cells (RBCs),
  - White blood cells (WBCs), and
  - Platelets
- *Bone marrow* is a highly structured and metabolically active organ, which normally produces 2.5 billion RBCs, 1 billion granulocytes, and 2.5 billion platelets/kg of body weight daily

Complete Blood Count

- It supplies useful information regarding the concentration of the different cellular and noncellular elements of blood and applies to multiple disorders.
- CBC is a misnomer because concentrations of cells/µL, not counts, are measured and reported.
- Numerous measured and calculated values are included in a CBC
  - Erythrocyte (RBC) count
  - Leukocyte (WBC) count and diffrential
  - Hemoglobin (Hgb)
  - Hematocrit (Hct)
  - RBC indices: (MCV, MCH, MCHC, and RDW)
  - Platelet count and mean platelet volume
  - Reticulocyte count
  - Erythrocyte sedimentation rate (ESR

Red Blood Cell Count

- *Normal*
  - *Males 4.5–5.9 × 10^6 cells/mL*
  - *Females 4.1–5.1 × 10^6 cells/mL*
- The *red blood cell (RBC) count* is the number of red corpuscles in a given volume of blood
- After puberty, females have slightly lower counts (and Hgb) than men, partly because of
  - Their menstrual blood loss and
  - Higher concentrations of androgen (an erythropoietic stimulant) in men.
- The RBC count in all anemias is by definition below the normal range.

Hemoglobin

- *Normal range:*
  - *Males 14–17.5 g/dL*
  - *Females 12.3–15.3 g/dL*
- The *hemoglobin* (Hgb) value is the amount of this metalloporphyrin-protein contained in a given volume (100 mL) of whole blood.
- The Hgb concentration provides a direct indication of the oxygen-transport capacity of the blood.
- As the major content of the RBCs, Hgb is proportionately low in patients with anemia

Hematocrit



- *Normal range:*
  - *Males 42–50% (0.42–0.5);*
  - *Females 36–45% (0.36–0.45)*
- The *hematocrit* (Hct) is the percen
  volume of blood that is composed
  erythrocytes.
  - It is also known as the **packed cell volume**.
- To manually perform the Hct test, a blood-filled capillary tube is centrifuged to settle the erythrocytes.
  - Then, the percentage volume of the tube that is composed of erythrocytes is calculated.
- Like Hgb, Hct is low in patients with anemia

The RULE of Three

- Applies to normocytic, normochromic erythrocytes only
- Useful to detect laboratory error in measuring the Hb, HCT, and RBC count
  - 3 times the RBC count should = Hgb
  - 3 times Hgb should = Hct
  - The Hct plus 6 should approximate the first two figures of the RBC count within 3
- Example: Hct is **40%;** therefore 40 + 6 = 46, and the RBC count should be 4.6 or in the range of 4.3 to 4.9

Red Blood Cell Indices

- These indices are useful in the evaluation of anemias, polycythemia, and nutritional disorders.
- Essentially, they assess the size and Hgb content of the RBC.
- The MCV is measured directly, while the MCHC and MCH are calculated from the Hgb, MCV, and
RBC count using predetermined formulas.

Red Blood Cell Indices

- ***Mean Corpuscular Volume***
  - *Normal range: 80–96 fL/cell (80–96 mm^3/cell)*
  - MCV is an estimate of the average volume of RBCs and is the most clinically useful of the RBC indices.
  - It can be calculated by dividing the Hct by the RBC count
  - Abnormally large cells have an increased MCV and are called *macrocytic*.
    - Vitamin B12 and folate deficiency cause the formation of macrocytic erythrocytes
  - Abnormally small cells (with a decreased MCV) are called *microcytic*.
  - A decrease in the MCV implies some abnormality in Hgb synthesis.
    - The most common cause of microcytic erythrocytes is iron deficiency.

Red Blood Cell Indices

- ***Mean Corpuscular Hemoglobin***
  - *Normal range: 27–31 pg/cell*
  - MCH) is a measure of the oxygen-carrying capacity (i.e., Hgb) of each cell.
  - It is calculated as the quotient of Hgb/RBC.
  - The presence of Hgb adds color to the erythrocyte and also picks up the dyes of RBC stains for microscopic viewing.
    - Cells that have decreased amounts of Hgb are referred to as being *hypochromic*, such as in iron deficiency

Red Blood Cell Indices

- ***Mean Corpuscular Hemoglobin Concentration***
  - *Normal range: 33.4–35.5 g/dL*
  - MCHC is the Hgb divided by the Hct
  - The weight of Hgb per volume of cells is the mean cell Hgb concentration (MCHC).
  - Because MCHC is independent of cell size, it is more useful than MCH in distinguishing between microcytosis and hypochromia.
  - Iron deficiency is the only anemia in which the MCHC is routinely low,

Red Blood Cell Indices

- ***Red Blood Cell Distribution Width***
  - *Normal range: 11.5–14.5% (0.115–0.145)*
  - RDW is an indication of the variation in RBC size, termed *anisocytosis*.
  - The RDW is reported as the coefficient of variation of the MCV (standard deviation/mean value).
  - This value is used primarily with other tests to differentiate iron deficiency anemia from thalassemias.
  - The RDW increases in macrocytic anemias and in early iron deficiency, often before other tests show signs of this kind of anemia.

Reticulocyte Count

- *Normal range: 0.5–2.5% of RBCs (0.005–0.025)*
- In anemia, the *reticulocyte count* or *reticulocyte index* (RI) reflects not only the level of bone marrow production but also a decline in the total number of mature erythrocytes that normally dilute the reticulocytes.
  - Therefore, the reticulocyte count would double in a person whose bone marrow production is unchanged, but whose Hct has fallen from 46% to 23%
- In anemia secondary to acute blood loss or hemolysis, the reticulocyte count is increased
  - This increase reflects an attempt by the bone marrow to compensate for the lack of circulating erythrocytes.

Erythrocyte Sedimentation Rate

- *Normal range:*
  - *Males 1–15 mm/hr;*
  - *Females 1–20 mm/hr (increases with age)*
- Erythrocytes normally settle slowly in plasma but settle rapidly when they aggregate because of electrostatic forces.
- Each cell normally has a net negative charge and repels other erythrocytes because like charges repel each other.
- Many plasma proteins are positively charged and are attracted to the surface charge of one or more erythrocytes, thereby promoting RBC aggregation
- Nonmicrocytic anemia, pregnancy, multiple myeloma, and various inflammatory diseases (including infections) can **increase the ESR**
- Sickle cell disease, high doses of corticosteroids, liver disease, microcytosis, carcinomas, and CHF can **decrease the ESR**

Case Study

- Azeb B., a 45-year-old female alcoholic, is admitted to the hospital because of pneumonia. Her physical exam reveals an emaciated patient with ascites, dyspnea, fever, cough, and weakness. No cyanosis, jaundice, or peripheral edema is evident. Her peripheral neurologic exam is within normal limits as is her serum electrolytes, urea nitrogen, creatinine, and glucose.

Case Study

The following CBC is obtained:

Test name	Result	Reference range
RBC	3×10^6 cells/μL	$4.1–5.1 \times 10^6$ cells/μL for females
WBC	4.6×10^3 cells/μL	$4.4–11.3 \times 10^3$ cells/μL
Hgb	10.3 g/dL	12.3–15.3 g/dL for females
Hct	30.9%	36–45% for females
MCV	110.8 fL/cell	80–96 fL/cell
RWD	15.4%	11.5–14.5%
Platelet	174,000 cells/μL	150,000–450,000 cells/count μL
Neutrophils	68%	45–73%
Bands	6%	3–5%
Monocytes	11%	2–8%
Eosinophils	2%	0–4%
Basophils	2%	0–1%

Case Study

- **QUESTION:** What abnormalities are present? What is the likely cause?

WBC Count and Differential

- *Normal range: 4.4–11.3 × 103 cells/mL*
- The *white blood cell (WBC) count* is an actual count of the number of leukocytes in a given volume of blood.
- Unlike RBCs, leukocytes have a nucleus and normally represent five different mature cell types.
- The various percentages of the five mature and WBC types comprise the **WBC differential**
- When a WBC count and differential is ordered for a patient,
  the resulting laboratory report is a tally of the total WBCs in a given volume of blood plus the relative percentages each cell type that contribute to the total.
- Therefore, the percentages of the WBC subtypes must add up to 100%

WBC Count and Differential

- A convenient mnemonic for remembering the various types of WBCs is **“Never Let Monkeys Eat Bananas”**
  - N = neutrophils;
  - L = lymphocytes;
  - M = monocytes;
  - E = eosinophils; and
  - B = basophils.

Granulocytes

- *Granulocytes* are phagocytes (eating cells) and derive their name from the presence of granules within the cytoplasm.
- The granules store lysozymes and other chemicals needed to oxidize and enzymatically destroy foreign cells.
  - Neutrophils
  - Eosinophils
  - Basophils

Granulocytes

- ***Neutrophils***
  - *Normal range: PMN leukocytes 45–73% or 0.45–0.73 bands 3–5% or 0.03–0.05*
  - *Neutrophils* are also termed *segmented neutrophils* (or “segs”) or *polymorphonuclear cells* (PMNs or “polys”).
  - The less mature form of the neutrophil with a crescent-shaped nucleus is a band or stab cell
  - The **absolute segmented neutrophil count** is the percentage of neutrophils and bands multiplied by the WBC count.
  - ANC of <1000/ µL represent neutropenia, with counts of <500/µL and 100/µL considered severe and absolute neutropenia, respectively.
  - Because of the risk of rapidly progressing, life-threatening infection, prophylactic antibiotics are typically started after cytotoxic chemotherapy if the ANC is expected to be <1000/µL for more than seven days

Granulocytes

- ***Neutrophils***
  - During an **acute infection** there is an increase in the percentage of neutrophils as they are released from the bone marrow and demarginate from the endothelium.
  - Less mature band forms may also be released, but these immature neutrophils are still considered to be active.
  - The appearance of band cells in infections is termed a *left shift*

Granulocytes

- ***Eosinophils and Basophils***
  - *Normal range: eosinophils 0–4%; basophils 0–1%*
  - Eosinophils are present in large numbers in the intestinal mucosa and lungs, two locations where foreign proteins enter the body.
    - They can phagocytize, kill, and digest bacteria and yeast.
    - Elevations of eosinophils counts are highly suggestive of parasitic infections
  - Basophils contain heparin, histamine, and leukotriene B4.
    - Many signs and symptoms of allergic responses can be attributed to specific mast cell and basophil products.
    - Basophils are probably involved in immediate hypersensitivity reactions (e.g., extrinsic, or allergic, and asthma)

Monocytes/Macrophages

- *Normal range: monocytes 2–8% or 0.02–0.08*
  - *Macrophages* are present in lymph nodes, alveoli of the lungs, spleen, liver, and bone marrow
  - Participate in the removal of foreign substances from the body.
  - In addition to attacking foreign cells, they are involved in the destruction of old erythrocytes, denatured plasma proteins, and plasma lipids

Lymphocytes and Plasma Cells

- *Normal range: lymphocytes 20–40% or 0.2–0.4*
- *Lymphocytes* make up the second major group of leukocytes.
- These cells give specificity and memory to the body's defense against foreign invaders.
- There are three subgroups of lymphocytes:
  1. T lymphocytes (T cells)
  2. B lymphocytes (B cells)
  3. Natural killer cells (NK cells)

BLOOD COAGULATION TETS

- Normal hemostasis involves a complex interaction among
  - Vascular subendothelium,
  - Platelets,
  - Coagulation factors, and
  - Proteins that promote clot formation, clot degradation and inhibitors of these substances
- Disruption in normal hemostasis can result in bleeding or excessive clotting.
  - **Bleeding**: trauma or damage to vessels, acquired or inherited deficiencies of coagulation factors, or physiological disorders of platelets,
  - **Excessive clotting**: abnormalities of the vascular endothelium, alterations in blood flow, or deficiencies in clotting inhibitors

Clot formation

- The primary function of platelets is to regulate hemostasis, but platelets also play a prominent role in the pathological formation of arterial thrombi.
- Three processes (platelet adhesion, activation, and aggregation) are essential for arterial thrombus formation.
- Endothelial injury to the vasculature, caused by flow abnormalities, trauma, or the rupture of atherosclerotic plaque in the vessel wall, starts the process of platelet plug formation
- Platelet adhesion is enhanced by substances such as epinephrine, thrombin, adenosine diphosphate (ADP), serotonin, collagen, and von Willebrand factor (vWF)
- Circulating vWF acts as a binding ligand between the subendothelium and glycoprotein Ib receptors on the platelet surface

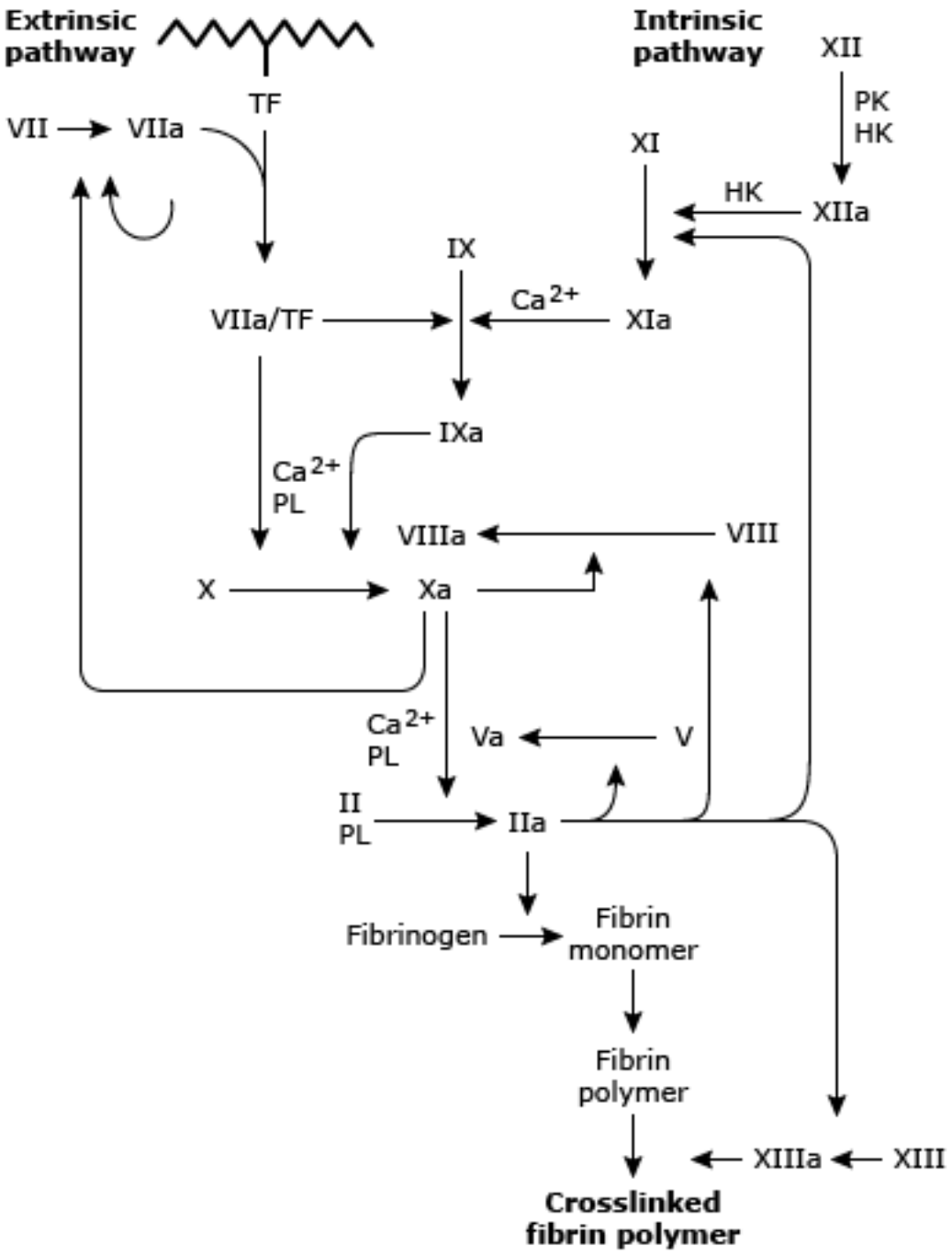
Clot formation

- Once adhesion occurs, platelets change shape and activation occurs.
- Activated platelets release their contents – including nucleotides, adhesive proteins, growth factors, and procoagulants – which promotes platelet aggregation and completes the formation of the hemostatic plug.
- This process is mediated by glycoprotein IIb/IIIa receptors on the platelet surface with fibrinogen acting as the primary binding ligand bridging between platelets.
- Thromboxane A2, a potent stimulator of platelet aggregation and vasoconstriction, is formed in platelets.
- In contrast, prostacyclin (PG2), produced by endothelial cells lining the vessel luminal surface, is a potent inhibitor of platelet aggregation and a potent vasodilator that limits excessive platelet aggregation.

Clot formation

- *Coagulation Cascade*
  - The ultimate goal of the *coagulation cascade* is to generate fibrin from thrombin.
  - Fibrin forms an insoluble mesh surrounding the platelet plug. Platelets concentrate activated clotting factors at the site of vascular injury
  - The coagulation cascade is typically divided into the intrinsic, extrinsic, and common pathways
  - The intrinsic and extrinsic pathways provide different routes to generate factor X, while the common pathway results in thrombin formation.

Factors	Name	Approximate half-life (Hrs)
I	Fibrinogen	100 - 150
II	Prothrombin	50 – 80
III	Thromboplastin, tissue extract	
IV	Calcium	
V	Proaccelerin, labile factor, accelerator globulin	12 – 36
VI	Activated factor V; this numeral is no longer used	n/a
VII	Proconvertin, serum prothrombin conversion accelerator, stable factor, autoprothrombin I	4 – 66
VIII	Antihemophilic factor, antihemophilic globulin, platelet cofactor I, antihemophilic factor A	12 – 15
IX	Plasma thromboplastin component, Christmas factor, antihemophilic factor B, platelet cofactor II, autoprothrombin II	18 – 30
X	Stuart-Prower factor	25 - 60
XI	Plasmin thromboplastin antecedent	40 – 80
XII	Hageman factor	50 – 70



HK: high-molecular-weight kininogen;
PK: prekallikrein;
PL: phospholipid.

Inhibition of Coagulation

- Mechanisms that limit *coagulation* include the natural inhibitors such as
  - antithrombin (AT) and the vitamin K dependent proteins C and S,
  - tissue factor pathway inhibitor (TFPI), and
  - the fibrinolytic system.

Clot Degradation

- Fibrinolysis is the mechanism by which formed thrombi are lysed to prevent excessive clot formation and vascular occlusion.
- Tissue plasminogen activator (tPA) and urokinase plasminogen activator activate plasminogen, which generates plasmin.
  - Plasmin is the enzyme that eventually breaks down fibrin into fibrin degradation products (FDPs).

Thrombocytes

- *Platelet Count*
  - *Normal range: 150,000–450,000/µL*
  - **Thrombocythemia**, also known as *thrombocytosis* or *elevated platelet count,* may be caused by the following factor
  - Caused by:
    - Myeloproliferative neoplasms,
    - Essential thrombocythemia,
    - Polycythemia vera,
    - Chronic myelogenous leukemia, or
    - Idiopathic myelofibrosis.
  - Clinical consequences of thrombocythemia include thrombosis, hemorrhage, and microcirculatory disturbances.

Thrombocytes

- Decrease in platelet counts or **thrombocytopenia** may lead to petechiae, ecchymosis, and spontaneous hemorrhage.
- Thrombocytopenia is defined as a platelet count <150,000/microL
- **Causes include:**
  - ✓ Decreased platelet production: infections, chemotherapy, radiation therapy, bone marrow aplasia or hypoplasia, direct alcohol toxicity.
  - ✓ Accelerated destruction: Idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), disseminated intravascular coagulation (DIC)
  - ✓ Loss from excessive bleeding/trauma
  - ✓ Dilution of blood samples secondary to blood transfusion
  - ✓ Sequestration secondary to hypersplenism

Coagulation Studies

- The control of bleeding depends on the formation of a platelet plug and the formation of a stable fibrin clot
  - The prothrombin time (PT),
  - International normalized ratio (INR), and
  - Activated partial thromboplastin time (aPTT)
- These tests are used to
  - Diagnose coagulation abnormalities or
  - Monitor the effectiveness of patients receiving anticoagulation therapy.

Prothrombin Time

- Prothrombin is a plasma protein, it is present in normal plasma in a concentration of about 15mg/dl
- Prothrombin is synthesized in the liver and is converted to thrombin during the blood clotting process.
- If the liver fails to produce prothrombin its concentration in the plasma falls too low to provide normal blood coagulation.
- **Vitamin K** is required by the liver for normal formation of prothrombin as well as for formation of a few other clotting factors (Factor VII, Factor IX, Factor X, and protein C & S).
- Therefore, either lack of vitamin K or the presence of liver disease can decrease the prothrombin level so low that a bleeding tendency results.

Prothrombin Time

- Prothrombin time (PT) is a coagulation test performed to measure the time it takes for a firm fibrin clot to form after tissue thromboplastin (factor III) and calcium are added to the sample.
- Normal: 10 to 13 sec
- It is used to evaluate the extrinsic pathway of the coagulation sequence
- Blood removed from the patient is immediately oxalated so that none of the prothrombin can change into thrombin.

Prothrombin Time

- Excess of calcium ion and tissue factor is quickly mixed with the oxalated blood.
- The excess calcium nullifies the effect of the oxalate, and the tissue factor activates the prothrombin-to-thrombin reaction by means of the extrinsic clotting pathway
- The time required for coagulation to take place is known as the **prothrombin time**.

Prothrombin Time

- Increased in:
  - Biliary obstruction
  - Disseminated intravascular coagulation
  - Hereditary deficiencies of factors II, V, VII, & X
  - Liver disease (cirrhosis)
  - Poor fat absorption
  - Presence of circulating anticoagulant

International Normalized Ratio

- The INR is calculated using:

$$INR = [PT(patient)/PT\ (normal\ average)]^{ISI} = PTR^{ISI}$$

- Commercial manufacturers quantify the ISI for the specific thromboplastin reagent used in each lot and report this information in the product package insert.
- The INR, which compensates for differences in sensitivity of various PT reagents
- Less than 2.0, for patients not receiving anticoagulation therapy
- 2.0 to 3.0 for patients receiving treatment for venous thrombosis, pulmonary embolism, and valvular heart disease

Activated Partial Thromboplastin Time

- aPTT measures the **intrinsic clotting system**, which depends on factors VIII, IX, XI, and XII and the factors involved in the final common pathway of the clotting cascade (factors II, X, and V).
- The test is performed by recalcifying citrated plasma in the presence of a thromboplastic material that **does not have tissue factor** activity (hence the term partial thromboplastin) and a **negatively charged substance**, which results in contact factor activation, thereby initiating coagulation via the intrinsic clotting pathway

Activated Partial Thromboplastin Time

- The typical control ranges from 35 to 45 seconds.
- aPTT is commonly used to monitor unfractionated heparin therapy.
- A normal aPTT with a prolonged PT can occur only with factor **VII** deficiency.
- A prolonged aPTT with a normal PT could indicate a deficiency in factors XII, XI, IX, and VIII

Coagulation Studies

Test Result		Cause of test result pattern
PT	aPTT	
Prolonged	Normal	**Inherited:** ✓ Factor VII deficiency
		Acquired: ✓ Factor VII deficiency (acquired) ✓ Vit K deficiency ✓ Liver disease ✓ Coumadin administration ✓ Inhibitor of factor VII

Coagulation Studies

Test Result		Cause of test result pattern
PT	aPTT	
Normal	**Prolonged**	**Inherited:** ✓ Deficiency of factor VIII, IX, XI, or XII ✓ Von Willebrand
		Acquired: ✓ Deficiency of factor VIII, IX, XI, or XII ✓ Acquired Von Willebrand disease

Coagulation Studies

Test Result		Cause of test result pattern
PT	aPTT	
Prolonged	**Prolonged**	**Inherited:** ✓ Deficiency of prothrombin, fibrinogen or factor V and X ✓ Combined factor deficiencies
		Acquired: ✓ DIC ✓ Supratherapeutic dose of Heparin ✓ Supratherapeutic dose of coumadin ✓ Combined heparin and coumadin administration

DRUG THERPY IN SPECIFIC PATIENT GROUPS

Chapter Three

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AAU

DRUG THERPY IN SPECIFIC PATIENT GROUPS

- Pregnancy and lactation
- Geriatrics
- Pediatrics

PREGNANCY AND LACTATION

Therapeutic Considerations



Objectives

Upon completion of the session, you will be able to:

1. Explain the principles of embryology and teratology.
2. Identify known teratogens and drugs of concerns during lactation.
3. Evaluate the risks of a drug when taken during pregnancy or lactation.
4. Counsel patients on the use of drugs during pregnancy and lactation.
5. Describe physiologic changes during pregnancy and their impact on pharmacokinetics.

Introduction

- Medication use during pregnancy and lactation is a challenge for health professionals, as pregnant and breast-feeding women are usually **excluded from clinical trials**.
- Since approximately one-half of pregnancies are **unplanned**, many women are exposed to medications before being aware of their pregnancy
- The most popular medications are:
  - Vitamins and minerals,
  - Analgesics, antibiotics
  - Antacids, antiemetics, laxatives,
  - Asthma medication, cold and flu medications, and
  - Medications for topical administration (e.g., antifungals, antibiotics, corticosteroids)

Introduction

- It is the clinician's responsibility to ensure safe and effective therapy
  - Before conception,
  - During pregnancy, and
  - After delivery.

PHYSIOLOGY OF PREGNANCY

- **Fertilization** occurs when a sperm attaches to a receptor on the outer protein layer of the egg, the **zona pellucida.**
- Fertilization usually occurs in the fallopian tube.
- Cell division continues for the first 2 days while the fertilized egg travels down the fallopian tube, reaching the uterine cavity on the third day.
- Cell division continues for another 2 to 3 days in the uterine cavity before implantation begins.

PHYSIOLOGY OF PREGNANCY

- Approximately 6 days after fertilization, the cell mass is termed a **blastocyst.**
- **Human chorionic gonadotropin** now is produced in amounts that may be detected by commercial laboratories.
- The blastocyst sloughs the zona pellucida and rests directly on the endometrium and begins to grow into the endometrial wall.
- After 6 days of this growth, the blastocyst lies **implanted** under the surface of the endometrium and begins to receive nutrition from maternal blood.
  - ➲Now it is called an **embryo**

PHYSIOLOGY OF PREGNANCY

- The **embryonic period** lasts from approximately 2 weeks after fertilization until 8 weeks after fertilization, when the conceptus is renamed a **fetus**
- Most body structures are formed during the embryonic period, and they continue to grow and mature during the fetal period
- The **fetal period** continues until the pregnancy reaches **term**, approximately **40 weeks** after the last menstrual period.

Parity and Gravida

- **Parity** and **gravida** are terms used to describe a pregnant woman.
- **Parity** is the number of deliveries after 20 weeks' gestation.
- A delivery before the completion of 20 weeks' gestation is considered an **abortion** and can be either **elective** or **spontaneous**.
- Parity is independent of **the number of fetuses delivered** (**live** or **stillborn**, **single fetus**, or **twins**) or **the method of delivery**.

Parity and Gravida

- **Gravida** refers to the number of pregnancies a woman has had regardless of the outcome.
- A **multiple birth** is counted as a single pregnancy.
- Example: a woman who is currently pregnant and has previously delivered one set of twins and had two spontaneous abortions is described as a gravida 4 para 1 **(G_4P_1).**

Pregnancy Dating

- Approximately 280 days (about 40 weeks or 9 months) constitute the **duration of a pregnancy**; this time period extends from the first day of the last menstrual period (LMP) to birth.
- Pregnancy is typically divided into three **trimesters,** approximately 13 to 14 weeks each.
- The time between the end of the 22nd week of gestation and the end of the 28th day after birth is considered the **perinatal period.**

Date of Confinement (Due Date)

- The assessment of gestational age is important to determine the
  - Expected date of confinement (EDC),
  - Schedule a cesarean section, or
  - Determine when it is safe to end a pregnancy prematurely
- Gestational age can be determined by several methods, including
  - The 1st day of the LMP,
  - Pelvic examination,
  - Uterine size, and
  - Measurement of fetal parameters by ultrasound.

Date of Confinement (Due Date)

First day of the LMP

- The EDC is generally determined by adding 7 days to the first day of the LMP, counting back 3 months, and adding 1 year (Nagele rule).
- Limitation:
  - For a woman who doesn’t know her first day of LMP
  - Women with irregular or prolonged menstrual cycles

Case: Due Date

- S.S., a 29-year-old, G_1P_1 woman, who has not started her menstrual period since she had unprotected intercourse, come to your pharmacy today, on October 30, 2017. She is worried that she may be pregnant. S.S.'s first day of her LMP was estimated to be on July 01, 2017. Her pregnancy test is positive. When will be her due date?

Delivery

- Depending on the gestational age at the time of delivery, the result can be an abortion, preterm, term, or post-term birth.
- **An abortion** (spontaneous or terminal) is a delivery before 20 weeks' gestation.
- **A term infant** is a fetus delivered between 37 and 42 weeks gestation.
- **A preterm birth** is one occurring between 20 and 37 weeks' gestation, and a **post-term** (postmaturity) birth occurs after the beginning of 43 weeks' gestation.
- **Parturition** refers to labor, and the **puerperium** is the 6 to 8 weeks after delivery.

Pregnancy Signs and Symptoms

- **Early symptoms**: **fatigue** and **increased frequency of urination.**
- At 6 weeks' gestation: **nausea and vomiting** (morning sickness) but can occur at any time of the day.
  - Nausea and vomiting usually resolve at 12 to 18 weeks' gestation.
- **Fetal movement** is detected in the woman's lower abdomen at 16 to 20 weeks of gestation.
- **Signs of pregnancy**: sudden cessation of menses, changes in consistency of the cervical mucus, bluish discoloration of the vaginal mucosa, increased skin pigmentation, and anatomic breast changes

Transplacental Drug Transfer

- Most drugs move from the maternal circulation to the fetal circulation by diffusion.
- Certain chemical properties influence the rate of transfer across the placenta, such as:
  - Lipid solubility,
  - Electrical charge,
  - Molecular weight, and
  - Degree of protein binding of medications.

Transplacental Drug Transfer

- Drugs with molecular weights less than 500 Da **readily** cross the placenta,
- Whereas larger molecules (600–1,000 Da) cross more **slowly.**
- Drugs with molecular weights greater than 1,000 Da, such as insulin and heparin, **do not cross** the placenta in significant amounts.

Transplacental Drug Transfer

- **Lipophilic** drugs, such as opiates and antibiotics, cross the placenta more easily than do water-soluble drugs.
- **Maternal plasma albumin** progressively decreases while fetal albumin increases during the course of pregnancy, which may result in higher concentrations of certain **protein-bound** drugs in the fetus.

Transplacental Drug Transfer

- Fetal pH is slightly more acidic than maternal pH, permitting **weak bases** to more easily cross the placenta.
- Once in the fetal circulation, however, the molecule becomes more ionized and less likely to diffuse back into the maternal circulation.
  - **Ion trapping**

Teratogens

- A teratogen is an exogenous agent that can modify normal embryonic or fetal development.
- Teratogenicity can manifest as:
  - Structural anomalies,
  - Functional deficit,
  - Cancer,
  - Growth retardation, and
  - Death (spontaneous abortion, stillbirth)

Phase of Development and Potential Teratogenic Effect

- Pregnancy is usually divided into three trimesters of 13 weeks.
- However, it can be divided more precisely into three phases:
  - Implantation and pre-differentiation,
  - Organogenesis (or embryogenesis), and
  - Fetogenesis
- The risk of birth defects is most often higher during **organogenesis**

Phase of Development and Potential Teratogenic Effect

- **Implantation and pre-differentiation**
  - All-or-none period
    - Cells are fragile at this moment. If too many are killed, a miscarriage will occur before the pregnancy is detected
  - Very little contact between the blastocyst and the mother's blood
  - Cells are pluripotent, capacity to repair a damage remains
  - Stage of Pregnancy
    - 0 –14 days after conception (14–28 days after LMP)
  - Potential Teratogenic Effect
    - Spontaneous abortion or miscarriage

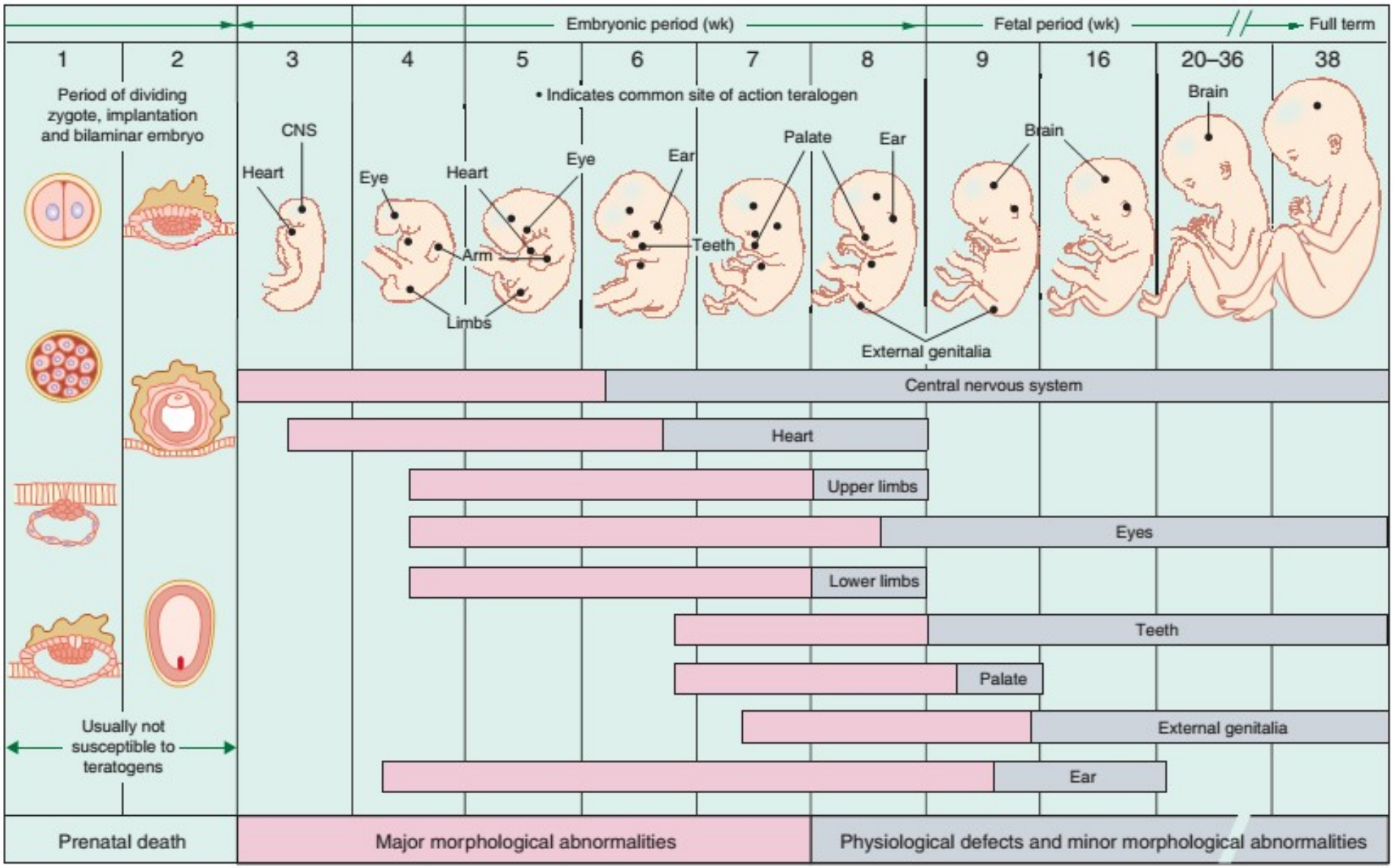
Phase of Development and Potential Teratogenic Effect

- **Organogenesis (embryogenesis)**
  - Organs are formed; **most critical period** for structural anomalies
  - Organs are formed at different times; period of sensitivity for a potential teratogen could be different for each organ
  - Stage of Pregnancy
    - From day 14 until the 9th week after conception (From day 28 until the 11th week after LMP)
  - Potential Teratogenic Effect
    - Major or minor structural anomalies

Phase of Development and Potential Teratogenic Effect

- **Fetogenesis**
  - The fetus grows and organs begin to function (e.g., kidneys are formed during organogenesis, but glomerular filtration begins during fetogenesis)
  - Active cell growth, proliferation, and migration (eg., CNS)
  - Stage of Pregnancy
    - After the organogenesis and until birth
  - Potential Teratogenic Effect
    - Fetal growth retardation
    - Functional deficit (e.g., renal insufficiency, pulmonary hypertension, neurologic impairment)

Embryonic and fetal development. The horizontal bars represent potential sensitivity to teratogens. The colored areas represent the more critical times



Drug Ratings in Pregnancy (US FDA)

Category	Interpretation
A	**Controlled human studies show no risk**
	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	**No evidence of risk in studies**
	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was

Drug Ratings in Pregnancy (US FDA)

	Risk cannot be ruled out
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
	Positive evidence of risk
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
	Contraindicated in pregnancy
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The

Medications with Proven Teratogenic Effects in Humans

Drug/ Drug Class	Teratogenic Effects	Critical Period
Alkylating agents	Malformations of many different organs	Organogenesis
Amiodarone	Transitory hypothyroidism (17%, goiter in 18% of these cases) or hyperthyroidism (3%)	From 10th week after conception
Androgens (danazol, Testosterone)	Masculinization of genital organs in female fetus	Danazol: from 6th week after conception Testosterone: not defined
ACEI, ARBs	Renal failure, anuria, oligohydramnios, pulmonary	After the first trimester

Medications with Proven Teratogenic Effects Cont'd

Drug or Drug Class	Teratogenic Effects	Critical Period
Anticonvulsants • Carbamazepine • Phenytoin • Phenobarbital • Valproic acid	NTDs (for carbamazepine and valproic acid); oral cleft, skeletal, urogenital, craniofacial, digital, and cardiac malformations; microcephalia Risk of major malformations estimated at 5–10% depending on the agent used (about 5% for carbamazepine, 10–14% for valproic acid). Valproic acid: abnormal neurologic development	7–14 weeks (gestational age); higher risk between 8 and 11 weeks. Neurologic development: not established
Systemic corticosteroids	Oral cleft (risk of 3–4/1,000 versus 1/1,000 in general population)	Organogenesis
Diethylstilbestrol	Girls: Cervical or vaginal adenocarcinoma, incidence of less than 1.4/1,000 exposures. Structural genital anomalies	First and second trimesters

Medications with Proven Teratogenic Effects Cont'd

Drug	Teratogenic Effects	Critical Period
Fluconazole high doses	Skeletal and craniofacial malformations, cleft palate (with chronic dose more than 400 mg/day; not reported with 150 mg single dose)	Not defined, but cases are reported where exposure was for most parts of pregnancy
Radioactive iodine (I^{131})	Thyroid suppression (goiter)	From 10th week after conception (consider the dosage and time to eliminate the product on a case-by-case basis)
Isotretinoin, acitretin, etretinate, and vitamin A (more than 10,000 IU/day)	CNS, skull, eyes and ears malformations, oral cleft, cardiac malformations, thymus anomalies, mental retardation: estimated at 25–30% (may be higher for neurologic development impairment) Contraindicated throughout	Organogenesis (risk of teratogenic effect after organogenesis not excluded)

Medications with Proven Teratogenic Effects Cont'd

Drug	Teratogenic Effects	Critical Period
Lithium	Cardiac malformations: risk of 0.9–6.8% (higher risks from small studies that included also minor cardiac anomalies) (general population risk: approximately 1%)	Cardiac organogenesis
Methimazole / propylthiouracil	Methimazole: aplasia cutis, syndrome including choanal atresia, esophageal atresia, facial anomalies, developmental delay; risk probably low	Organogenesis
	Methimazole/PTU: fetal hypothyroidism in 2–10% of infants whose mothers were treated for Graves disease or goiter	Second and third trimesters
Methotrexate	CNS and cranial malformations, oral cleft, skeletal and limb malformations	Organogenesis

Medications with Proven Teratogenic Effects Cont'd

Drug	Teratogenic Effects	Critical Period
Misoprostol	Moebius syndrome± limb anomalies ± CNS anomalies	Organogenesis
NSADs	In utero closure of ductus arteriosus (constriction is rare before 25 weeks, 50–70% at 30 weeks and 100% at 32 weeks (gestational age) and pulmonary hypertension	Third trimester
Penicillamine	Cutis laxa	Not defined
Tetracyclines	Teeth discoloration	14 weeks postconceptional
Thalidomide	Limb anomalies Cardiac, urogenital, GI, and ear malformations	20–36 days after conception
Trimethoprim	Cardiac and urogenital malformations, neural tube defects, oral cleft	Organogenesis

Pharmacokinetic Changes During Pregnancy

Absorption

- **Decreased gastrointestinal transit** can result in a delay in drug peak effect, prolonging the time of contact of drugs with the intestinal mucosa, and possibly enhancing absorption of certain drugs.
- The **higher gastric pH** may affect the absorption of weak bases or acids.
- Skin, tissue, and lung **absorption** might also be increased by physiologic changes during pregnancy

Pharmacokinetic Changes During Pregnancy

Distribution

- The **volume of distribution increases** for most drugs during pregnancy due to plasma volume expansion and the presence of amniotic fluid, the placenta, and the fetus.
  - ➲This results in a decrease in maximal concentrations of drugs and in their half-life.
- In addition, **hypoalbuminemia** and decreased protein binding of drugs increases free fraction of some medication

Pharmacokinetic Changes During Pregnancy

Metabolism

- During pregnancy the activity of some isoenzymes is ↑**ed** (e.g., CYP3A4, CYP2A6, CYP2D6, CYP2C9), and the activity of others is ↓**ed** (e.g., CYP1A2, CYP2C19).
- It is difficult to predict the **net impact** on drug effect since there is a wide inter-individual variability and since some drugs are metabolized by several isoenzymes.

Renal Elimination

- Renal blood flow and glomerular filtration are increased significantly during pregnancy.
- The impact of this increase is more important for drugs that are eliminated in the urine

Medication and Lactation

- Mothers should breastfeed exclusively for 6 months.
- Most drugs are safe during breast-feeding
- One should also consider the additive side effects of medication for the baby when the mother is taking a combination of medications.
- If clinical data are **not available** on drug transfer into breast milk, choose drugs that:
  - Are highly protein bound,
  - Have a high molecular weight,
  - Have a short half-life,
  - Have no active metabolites, and
  - Are well tolerated by children

Drugs of Concern During Breast-Feeding

Drugs that can decrease the breast milk production	
Clomiphene	Has been used to suppress lactation
Ergot derivatives • Bromocriptine, • Cabergoline, • Ergotamine	Have been used to suppress lactation
Estrogens	Hormonal contraceptives with ethinylestradiol should be delayed for 4–6 weeks following delivery.
Pseudoephedrine	Do not use in women with low milk production; a few doses will probably not have significant clinical effect

Drugs of Concern During Breast-Feeding

Drugs which may expose the neonate to a significant quantity and may necessitate a strict follow-up	
β-blocking agents • Acebutolol, • Atenolol, • Sotalol	Neonatal β-blockade reported Concern for acebutolol, atenolol and sotalol, but some other β-blocking agents are safe to use
Amiodarone	May accumulate because of long hal-flife; possible neonatal thyroid and cardiovascular toxicity
Antineoplastics	Neonatal myelosuppression possible
Chloramphenicol	Severe side effects reported when used to treat babies (blood dyscrasia, grey baby syndrome)
Ergotamine	Symptoms of ergotism (vomiting and diarrhea) reported
Illicit drugs	Unknown contents and effects

Drugs of Concern During Breast-Feeding

Drugs which may expose the neonate to a significant quantity and may necessitate a strict follow-up	
Lithium	Up to 50% of maternal serum levels have been measured in infants; cases of infant toxicity have been reported
Phenobarbital	Drowsiness and reduced weight gain reported. Up to 25 % of a pediatric dose can be ingested via breast milk
Radioactive iodine-131	Long radioactive half-life (21–42 days)
Tetracyclines	Chronic use may lead to dental staining or decreased epiphyseal bone growth

PEDIATRICS

Therapeutic Considerations

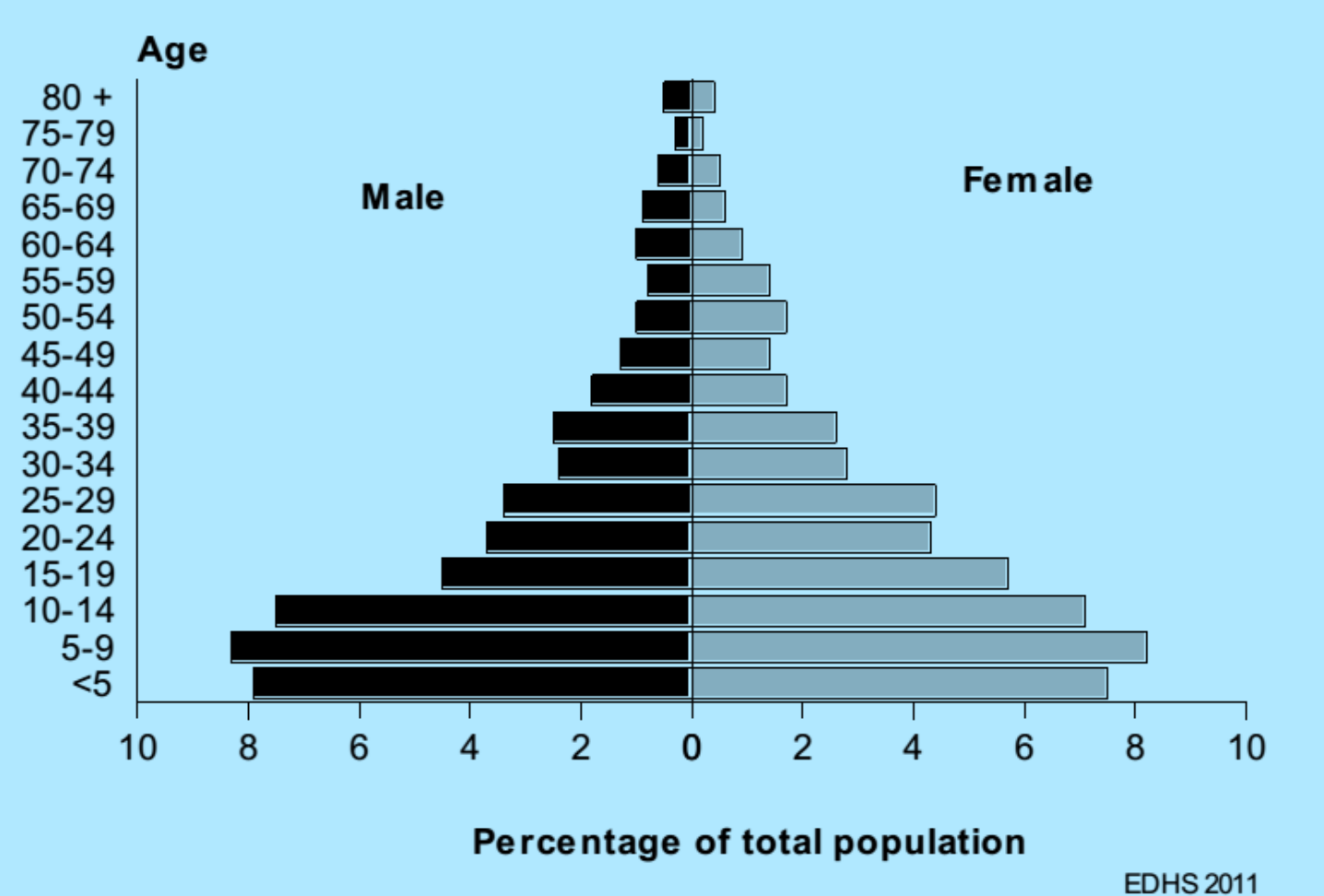
Objectives

Upon completion of the session, you will be able to:

1. Define different age groups within the pediatric population.
2. Explain general pk and pd differences in pediatric versus adult patients.
3. Identify factors that affect selection of safe and effective drug therapy in pediatric patients.
4. Identify strategies for appropriate medication administration to infants and young children.
5. Apply pediatric pharmacotherapy concepts to make drug therapy recommendations, assess outcomes, and effectively communicate with patients and caregivers.

Introduction

- Children under age 15 account for nearly half (47 percent) of the total po



Introduction

- Pediatric clinical practice involves the care of **infants**, **children**, and **adolescents** with the goal of optimizing their health, growth, and development toward adulthood
- Despite the common misconception of pediatric patients as "**smaller adults**" where doses are scaled only for their smaller size, there are multiple factors to consider when selecting and providing drug therapy for patients in this specific population.
- Pediatric patients significantly differ within their age groups and from adults regarding drug administration, psychosocial development, and organ function development, which affect the efficacy and safety of pharmacotherapy.

Classification of Pediatric Patients

ediatric Age Groups

Age Group	Age
Neonate	≤28 days (4 weeks) of life
Infant	29 days to <12 months
Child	1–12 years
Adolescent	13–17 years

Classification of Pediatric Patients

Age Terminology	Definition
Gestational age (GA)	Age from date of mother's first day of last menstrual period to date of birth
Full term	Describes infants born at ≥ 37-weeks gestation
Premature	Describes infants born before 37-week gestation
Chronological or postnatal age	Age from **birth** to present, measured in days, weeks, months, or years
Corrected or adjusted age	Used to describe the age of a premature child up to 3 years of age: Corrected age = Chronological age in months – [(40 – GA at birth in weeks) + 4 weeks]

Classification of Pediatric Patients

Weight Classification

Classification	Definition
LBW infant	Premature infant with birth weight between 1,500 and 2,500 g
VLBW infant	Premature infant with birth weight 1,000 g to less than 1,500 g
ELBW infant	Premature infant with birth weight less than 1,000 g

Differences in Vital Signs

- Normal values for **heart rate** and **respiratory rate** vary based on their **age**.
- Normal values for **blood pressure** vary based on **gender** and **age** for all pediatric patients, and also height percentile for patients older than 1 year
- In general, blood pressure increases with age,
  - With average blood pressures of **70/50** in neonates, increasing throughout childhood to **110/65** in adolescents

Differences in Vital Signs

- **Heart rates** are highest in neonates and infants, ranging from 85 to 205 beats per minute (bpm) and decrease with age, reaching adult rates (60 to 100 bpm) around 10 years of age.
- **Respiratory rates** are also higher in neonates and infants (30 to 60 breaths/minute), decreasing with age to adult rates around 15 years of age (12 to 16 breaths/minute).

Differences in Vital Signs

- Another vital sign commonly monitored in children by their caregivers is **body temperature**, especially when they seem "warm to the touch."
- The American Academy of Pediatrics (AAP) recommends **rectal temperature** measurement in children less than 4 years of age, using a digital thermometer.
- Generally, **rectal** temperature is greater than **oral** temperature by 0.6°C (1°F), and **oral** temperature is 0.6°C (1°F) higher than **axillary** temperatures

Differences in Vital Signs

- Low-grade fevers are considered those ranging from 37.8° to 39°C (100° to 102°F),
- Antipyretic treatment (e.g., acetaminophen) considered in cases of temperature greater than 38.3°C (101°F, any measurement route) accompanied by patient discomfort.

Differences in Vital Signs

- Considered as the fifth vital sign, **pain** assessment is more challenging in neonates, infants, and young children due to their inability to communicate symptoms.
- Indicators of possible pain include physiological changes such as
  - Increased heart rate, respiratory rate, and BP,
  - Decreased oxygen saturation,
  - Behavior changes such as prolonged, higher pitch crying and facial expressions.

Fluid Requirements

- Fluid requirement and balance are important to monitor in pediatric patients, especially in premature neonates and infants.
- Maintenance fluid requirement can be calculated based on **body surface area** for patients greater than **10 kg** with a range of 1,500 to 2,000 mL/m^2 per day.
- However, a weight-based method of determining normal maintenance fluid requirement for children is often used

Fluid Requirements

Patient Body Weight	Maintenance Fluid Requirement
Less than10 kg	100 mL/kg/day
11–20 kg	1,000 mL + 50 mL/kg over 10 kg
More than 20 kg	1,500 mL + 20 mL/kg over 20 kg

Case study, MM

- MM is a 36-week GA **premature** baby boy weighing 2,250 g, length 47 cm, born to a 21-year-old woman this morning. He requires maintenance IV fluids until his further assessment for total parenteral nutrition is complete

a) What is MM's weight classification as a neonate?

b) Calculate MM's corrected age for MM 6 months from today.

c) How much maintenance fluid would you recommend for MM at birth?

PHARMACOKINETIC AND PHARMACODYNAMIC DIFFERENCES

- Equations to calculate pediatric doses based on adjusted age or weight such as the Clark's, Fried's, or Young's rule should not be routinely used to calculate pediatric doses because:
  - They account for only one factor of difference, age or weight, and
  - Lack integration of the effect of growth and development on drug PK and PD in this population.
- For off-label medication dosing when no alternative treatment is available and limited dosage guidelines have been published, clinicians may choose to estimate a pediatric dose based on body surface area ratio.

Pediatric dose = Adult dose × [BSA (in m^2)÷ 1.73 m^2]

PD: Efficacy and Toxicity

- Pathophysiologic and pharmacodynamic differences are numerous.
- Clinical presentation of chronic asthma differs in children and adults.
- Children present almost exclusively with a reversible extrinsic type of asthma, whereas adults have nonspecific, nonatopic bronchial irritability.

PD: Efficacy and Toxicity

- The maintenance dose of digoxin is substantially higher in infants than in adults.
- This is explained by a **lower binding affinity of receptors** in the myocardium for digoxin and increased digoxin-binding sites on **neonatal erythrocytes** compared with adult erythrocytes.
- **Insulin** requirements are highest during adolescence because of the individual's rapid growth.
- **Growth hormone** therapy has allowed children with growth hormone deficiency to attain greater adult height.

PD: Efficacy and Toxicity

- Certain adverse effects of drugs are most commonly seen in the newborn period
- **Promethazine** now is contraindicated for use in children younger than 2 years because of the risk of severe respiratory depression.
- **Chloramphenicol** toxicity is increased in newborns because of immature metabolism and enhanced bioavailability.
- Similarly, **propylene glycol**, which is added to many injectable drugs, including phenytoin, phenobarbital, digoxin, lorazepam, vitamin D, and hydralazine, to increase their stability, can cause **hyperosmolality** in infants

PD: Efficacy and Toxicity

- The common cold occurs frequently in infants and children and is often treated with **antihistamines**, **decongestants**, **antitussives**, and **expectorants**.
- Given the lack of evidence for their efficacy and serious toxicities associated with overdoses, the FDA recommended that these drugs not be used in children younger than 2 years of age
- **Tetracyclines** are contraindicated for use in pregnant women, nursing mothers, and children younger than 8 years because these drugs can cause dental staining and defects in enamelization of deciduous and permanent teeth, as well as a decrease in bone growth

PD: Efficacy and Toxicity

- Some drugs may be less toxic in pediatric patients than in adults.
- **Aminoglycosides** appear to be less toxic in infants than in adults.
- In adults, aminoglycoside toxicity is related to both peripheral compartment accumulation and the individual patient's inherent sensitivity to these tissue concentrations
  - Newborn infants have less inherent tissue sensitivity for toxicity than do adults.

PK: Absorption

- Oral absorption may be different in premature infants and neonates due to differences in **gastric acid** secretion and **pancreatic** and **biliary** function.
- Full-term neonates have a gastric pH of 6 to 8 at birth and pH 1 to 3 by 48 hours of age.
- Gastric pH remains elevated in premature infants because of immature acid secretion.
- Low gastric acid secretion can result in
  - Increased serum concentrations of acid-labile medications, such as penicillin, ampicillin and naficillin
  - Decreased serum concentrations of weak acid medications, such as phenobarbital, due to increased ionization

PK: Absorption

- **Gastric emptying time** and **intestinal transit time** are delayed in premature infants, increasing drug contact time with the GI mucosa and drug absorption.
- Diseases such as gastroesophageal reflux, respiratory distress syndrome, and congenital heart disease may **delay gastric emptying time.**
- **Pancreatic exocrine** and **biliary** function are also reduced in newborns, with about 50% less secretion of amylase and lipase than adults, reaching adult values as early as the end of the first year and as late as 5 years of age.
- Deficiency in pancreatic secretions and bile salts in newborns can result in decreased bioavailability of **prodrug esters**, such as **erythromycin**, which requires solubilization or intraluminal hydrolysis

PK: Absorption

- **Topical** or **percutaneous absorption** in neonates and infants is increased due to:
  - A thinner stratum corneum,
  - Increased cutaneous perfusion, and
  - Greater body surface-to-weight ratio.
  - ➲ Hence, application of topical medications should be limited to the smallest amount possible.
- Increased percutaneous absorption can lead to high serum concentrations of topically applied drugs such as corticosteroids, lidocaine, or chlorhexidine, as well as inactive additives such as **propylene glycol**, potentially causing adverse effects.

PK: Absorption

- **Intramuscular absorption** in premature and full-term infants can be erratic due to
  - Variable perfusion,
  - Poor muscle contraction, and
  - Decreased muscle mass compared with older patients.
- Use of IM route of administration can be painful and is usually reserved when other routes are not accessible,
  - e.g., for initial IV doses of ampicillin and gentamicin for neonatal sepsis.

PK: Volume of Distribution

- **Total body water**, as a percentage of total body weight, has been estimated to be 94% in fetuses, 85% in premature infants, 78% in full-term infants, and 60% in adults
- Extracellular fluid and total body water per kilogram of body weight are increased in neonates and infants, resulting in **higher Vd for water-soluble drugs** such as aminoglycosides and decreases with age.
- This conforms to the observed **gentamicin** distribution volumes of 0.48 L/kg in neonates and 0.20 L/kg in adults

PK: Volume of Distribution

- Binding of drugs to plasma proteins is decreased in newborn infants because of:
  - Decreased plasma protein **concentration**,
  - Lower binding **capacity** of protein,
  - Decreased **affinity** of proteins for drug binding, and
  - **Competition** for certain binding sites by endogenous compounds such as bilirubin
- Neonates and infants have a lower normal range for serum albumin (2 to 4 g/dL), reaching adult levels after 1 year of age.
- This affects highly protein-bound drugs such as **phenobarbital**, **salicylates** and **phenytoin**, resulting in lower total serum concentrations needed to achieve therapeutic unbound serum concentrations

PK: Volume of Distribution

- Pharmacologic and toxic effects are related directly to the concentration of free drug in the body.
- Increases in **free** drug concentrations may result directly from decreases in plasma protein binding or indirectly from, for example, drug displacement from binding sites.
- Increased mortality from the development of **kernicterus** secondary to displacement of **bilirubin** from albumin and other serum proteins by sulfisoxazole in neonates is well documented

PK: Volume of Distribution

- The amount of body fat is substantially lower in neonates than in adults, which may affect drug therapy.
- Certain highly lipid-soluble drugs are distributed less widely in infants than in adults.
- The apparent volume of distribution of diazepam has ranged from 1.4 to 1.8 L/kg in neonates and from 2.2 to 2.6 L/kg in adults

PK: Metabolism

- Drug metabolism is slower at birth in full-term infants compared with adolescents and adults, with further delay in premature neonates.
- Phase 1reactions and enzymes, such as oxidation and alcohol dehydrogenase, are impaired in premature neonates and infants and do not fully develop until later childhood or adolescence.
  - The use of products containing ethanol or propylene glycol can result in increased toxicities, including respiratory depression, hyperosmolarity, metabolic acidosis, and seizures, and they should be avoided in neonates and infants.
- Cytochrome P450 isoenzymes (e.g., CYP2C9, CYP1A2) develop at various ages, ranging from a few months to 3 years of age, with delayed development in premature infants

PK: Metabolism

- Among phase 2 reactions, sulfate conjugation by sulfotransferases is well developed at birth in term infants.
- Glucuronidation by the uridine diphosphate **glucuronosyltransferases**, in contrast, is immature in neonates and infants, requiring at least several months to develop to adult values at approximately 4 years of age.
- In neonates, this deficiency results in adverse effects including cyanosis, ash gray color of the skin, limp body tone, and hypotension, also known as “gray baby syndrome” with use of chloramphenicol

PK: Metabolism

- Products containing benzyl alcohol or benzoic acid should be avoided in neonates due to immature glycine conjugation, resulting in accumulation of benzoic acid.
- This accumulation can lead to “gasping syndrome,” which includes respiratory depression, metabolic acidosis, hypotension, seizures or convulsions, and gasping respirations.

PK: Metabolism

- Interestingly, higher serum concentrations of morphine are required to achieve efficacy in premature infants than in adults,
  - Because infants are not able to metabolize morphine adequately to its 6-glucuronide metabolite (20 times more active than morphine).
  - This **is** balanced to some degree by the fact that the clearance of morphine quadruples between 27 and 40 weeks of postconceptional age

PK: Metabolism

- Conversely, hepatic enzyme activity increases to nearly twice as much as adults at 6 months of age and may continue to be high through **puberty**, around 9 to 12 years of age.
- These children may require higher doses per kilogram of body weight for hepatically metabolized drugs.
- Common examples include antiepileptic medications such as phenytoin, carbamazepine, and valproic acid.
- This increase in metabolism slows to adult levels as the child goes through puberty into adulthood

PK: Excretion

- Renal drug clearance is reduced in infants and slowest in premature neonates, due to immature renal function, resulting in the need for longer dosing intervals for renally cleared medications, such as vancomycin, to prevent accumulation.
- Glomerular filtration rate (GFR) is lowest in premature neonates, increasing with age and peaking at 3 to 12 years of age, after which there is a gradual decline to approximate adult value.
- For example, vancomycin is often given:
  - Every 18 to 24 hours in a low birth weight (LBW) premature neonate,
  - Every 6 hours in children with normal renal function, and
  - Every 8 to 12 hours in adult patients with normal renal function.

PK: Excretion

- The use of the Cockroft-Gault equations for estimating CrCl (an estimation of GFR) in adults should not be used for evaluating patients younger than 18 years
- **Schwartz's** equation is a common method of estimating pediatric CrCl for LBW infants up to 21 years of age
- This equation uses patient length (cm), serum creatinine (mg/dL), and a constant, k, which depends on age for all patients and also gender for those older than 2 years.
- Urine output is also a parameter used to assess renal function in pediatric patients, with a urine output more than 1 to 2 mL/kg/h considered normal.

PK: Excretion

$$CrCl = \frac{kL}{SCr}$$

k = Proportionality constant
L = Length in cm
SCr = Serum creatinine in mg/dL
CrCl = Creatinine clearance in mL/min/1.73 m^2

Age	k
Low birth weight less than 1yr	0.33
Full term less than 1 yr	0.45
1–12 yr	0.55
13–21 yr (male)	0.55
13–21 yr (female)	0.70

Case study, MM

MM is now 7 weeks old (weight: 4.5 kg; length: 60 cm) and presents to the community pharmacy with a 2-day history of lethargy, poor oral intake, and fever.

- The pharmacist refers the child to seek medical attention at the emergency department.
- MM is admitted to the general pediatric ward for further assessment including a neonatal sepsis and meningitis rule-out.
- Blood samples, cerebral spinal fluid, and urine were collected for Gram stain and culture, still pending results.

Case study, MM

- History of present illness reveals that his aunt who had a considerable flare-up of cold sores was babysitting him for the past week.
- He was empirically started on ampicillin 225 mg (50 mg/kg/dose) IV q 6 h, cefuroxime 225 mg IV q 6 h (50 mg/kg/dose), and acyclovir 90 mg IV q 8 h (20 mg/kg/dose).
- Given his poor oral intake on admission, the team requests addition of maintenance IV fluids and a nutrition consultation

Case study, MM

Lab tests	Result	Normal ranges
WBC	18 × 10^3/μL	6–17 × 10^3/mm^3
Bands	7%	4–12%
Segs	36%	13–33%
Lymphs	51%	41–71%
Monocytes	6%	4–7%
Serum creatinine	0.5 mg/dL	≤0.6 mg/dL

Case study, MM

Questions

- How much maintenance fluid would you recommend for MM now?
- Using the most appropriate method, calculate a creatinine clearance for MM.

Issues in Pediatric Drug Therapy

Alteration of Dosage Forms

- Many drugs used in pediatric patients are not available in suitable dosage forms.
- This necessitates dilution of high concentrations of drugs intended for adult patients.
  - Can be associated with large errors in measurements
- Administration of oral drugs continues to challenge parents and nurses.
- Alteration of these drugs by crushing or mixing, refusal of patients to accept the medication, and loss of drug during administration are some factors that can affect pediatric therapy.
- A common practice is to mix medications in applesauce, syrup, ice cream, or other vehicles just before administration to make the drugs palatable

Issues in Pediatric Drug Therapy

Medication Adherence

- The issue of medication adherence is more complex in pediatric patients than in adults.
- Among the factors that can negatively affect adherence are:
  - Poor communication between the physician and patient or parent,
  - Insufficient prescribing information,
  - Lack of understanding about the severity of illness by the patient or parent,
  - Lack of interest (e.g., among adolescents),
  - Fear of side effects,
  - Failure of the patient or parent to remember to administer the drugs,
  - Inconvenient dosage forms or dosing schedules involving administration of three or more doses daily, and
  - Unpalatability of drug products

Issues in Pediatric Drug Therapy

Dose Requirements

- Medication doses often are based on the body weight of neonates, infants, and children (e.g., milligrams per kilogram of body weight per day to be given in one or more portions daily).
- However, certain drugs, including antineoplastic agents, may be given based on **BSA** (e.g., milligrams per square meter in one or more doses daily).
- An additional challenge in managing pediatric drug therapy is understanding the effects of obesity on a population that relies on weight-based dosing

Issues in Pediatric Drug Therapy

Drug Interactions

- Drug interaction studies in pediatric age groups generally are lacking.
- The data often are extrapolated from studies in adult populations.
- Special attention should be given to adolescents, who may concurrently use
  - Alcohol,
  - Recreational or illicit drugs, or
  - Other prescription or nonprescription medications

Issues in Pediatric Drug Therapy

Complementary and Alternative Therapy

- Little is known about the efficacy of herbal products in infants, children, and adolescents.
- Healthcare professionals must ask caregivers specifically about the use of complementary and alternative treatments to minimize the adverse effects and costs associated with ineffective therapies

Issues in Pediatric Drug Therapy

Medication Safety

- Pediatric medication errors commonly occur at the medication-ordering step
  - Because of the multiple calculations required for weight-based dosing and the adjustments needed for providing therapy to the developing pediatric patient
- The medication-preparation step is also a high-hazard point owing to the need for dilution or manipulation of commercially available products only available in adult doses
- Among drug administration–related errors, wrong dose, wrong technique, and wrong drug are the three most common errors and may be related to an inability to access pediatric drug information.

Issues in Pediatric Drug Therapy

- Risk-reduction strategies include:
  - Placing a clinical pharmacist on pediatric wards in hospitals,
  - Simplifying the medication-use system,
  - Ordering standardized concentrations and doses,
  - Implementing computerized physician order-entry systems with dose range checking,
  - Dispensing pharmacy-prepared or ready-to-administer doses,
  - Standardizing infusion equipment,
  - Using smart infusion pumps,
  - Using bar-coded medications and bar-coding systems that check the medication at the point of care, and
  - Implementing computerized adverse event detection systems

GERIATRICS

Therapeutic Considerations

Objectives

Upon completion of the session, the you will be able to:

1. Explain the physiologic changes with aging
2. Discuss age-related pharmacokinetic and pharmacodynamic changes.
3. Identify drug-related problems and associated morbidities commonly experienced by older adults.

Introduction

- Pharmacotherapy for older adults can cure or palliate disease as well as enhance health-related quality of life (HRQOL).
- HRQOL considerations for older adults include focusing on improvements in:
  - Physical functioning (e.g., activities of daily living),
  - Psychological functioning (e.g., cognition, depression),
  - Social functioning (e.g., social activities, support systems), and
  - Overall health (e.g., general health perception).
- Despite the benefits of pharmacotherapy, HRQOL can be compromised by **drug-related problems**.
- Prevention of drug-related adverse consequences in older adults requires that health professionals become knowledgeable about a number of age-specific issues.

Introduction

- The proportion of the population age 65 and older is increasing.
- In 2013, persons age 60 and older accounted for 5% of the total Ethiopian population
- By 2040, 25% of the population will purchase 50% of all prescription drugs

Physiologic Changes with Aging

- Clinical manifestations of normal aging include
  - Changes in the biochemical makeup of tissues,
  - Reduced capacity of body systems,
  - Reduced ability to adapt to physiologic stress, and
  - Increased vulnerability to disease.
- Interindividual variability in physiology increases with age because individuals experience aging at different rates along

Physiologic Changes with Aging

Organ System	Manifestation
Balance and gait	• ↓ Stride length and slower gait • ↓ Arm swing • ↑ Body sway when standing
Body composition	• ↓ Total body water • ↓ Lean body mass • ↑ Body fat • ↔ or ↓ Serum albumin • ↑ α_1-Acid glycoprotein (↔ or ↑ by several disease states)

Physiologic Changes with Aging

Organ System	Manifestation
CVS	• ↓ Cardiovascular response to stress • ↓ Baroreceptor activity leading to ↑ orthostatic hypotension • ↓ Cardiac output • ↑ Systemic vascular resistance with loss of arterial **elasticity** and dysfunction of systems maintaining vascular tone • ↓ Resting and maximal heart rate
CNS	• ↓ Size of the hippocampus and frontal and temporal lobes • ↓ Number of receptors of all types and ↑ sensitivity of remaining receptors • ↓ Short-term memory, coding and retrieval, and executive function

Physiologic Changes with Aging

Endocrine	• ↓ Estrogen, testosterone, TSH, and DHEA-S levels • Altered insulin signaling
Gastrointestinal	• ↓ Motility of the large intestine • ↓ Vitamin absorption by active transport mechanisms • ↓ Splanchnic blood flow • ↓ Bowel surface area
Genitourinary	• Atrophy of the vagina with decreased estrogen • Prostatic hypertrophy with androgenic hormonal changes • Detrusor hyperactivity may predispose to incontinence
Hepatic	• ↓ Hepatic size • ↓ Hepatic blood flow

Physiologic Changes with Aging

Immune	↓ Antibody production in response to antigen ↑ Autoimmunity
Oral	Altered dentition ↓ Ability to taste salt, bitter, sweet, and sour
Pulmonary	↓ Respiratory muscle strength ↓ Chest wall compliance ↓ Arterial oxygenation and impaired CO_2 elimination ↓ Vital capacity ↓ Maximal breathing capacity ↑ Residual volume
Renal	↓ GFR ↓ Renal blood flow ↓ Filtration fraction ↓ Tubular secretory function ↓ Renal mass

Physiologic Changes with Aging

Sensory	• Presbyopia (diminished ability to focus on near objects) • ↓ Night vision • Presbycusis (high-pitch, high-frequency hearing loss) • ↓ Sensation of smell and taste
Skeletal	• ↓ Skeletal bone mass (osteopenia) • Joint stiffening caused by reduced water content in tendons, ligaments, and cartilage
Skin/hair	• Thinning of stratum corneum • ↓ Langerhans cells, melanocytes, and mast cells • ↓ Depth and extent of the subcutaneous fat layer

Altered Pharmacokinetics

PK Phase	Pharmacokinetic Parameters
Gastrointestinal absorption	• Unchanged passive diffusion and no change in bioavailability for most drugs • ↓ Active transport and ↓ bioavailability for some drugs • ↓ First-pass metabolism, ↑ bioavailability for some drugs, and ↓ bioavailability for some prodrugs
Distribution	• ↓ Volume of distribution and ↑ plasma concentration of water-soluble drugs • ↑ Volume of distribution and ↑ terminal disposition half-life ($t_{1/2}$) for lipid-soluble drugs
Hepatic metabolism	• ↓ Clearance and ↑ $t_{1/2}$ for some drugs with poor hepatic extraction; phase I metabolism may be affected more than phase II • ↓ Clearance and ↑ $t_{1/2}$ for drugs with high hepatic extraction ratios (flow-limited metabolism)
Renal excretion	• ↓ Clearance and ↑ $t_{1/2}$ for renally eliminated drugs and active metabolites

Clinical Geriatrics

- Maintenance of independence and prevention of disability are primary goals in the clinical care of persons 65 years of age and older.
- Functional status is a proxy measure of a patient's ability to live independently
  - Determined by inquiring about an older person's ability to perform specific tasks.
- To fully assess functional status, the patient's psychological state, financial resources, physical function, and social circumstances also must be considered.

Clinical Geriatrics

- Problems found more commonly in older persons sometimes are referred to as the "*I*s of geriatrics"
- These problems are often the result of underlying disease processes that may or may not be diagnosed.
- Examples of diseases and syndromes that can present as common problems in older adults include:
  - Parkinson's disease,
  - Falls,
  - Hip fractures,
  - Benign prostatic hypertrophy,
  - Dementia,
  - Glaucoma, and
  - Postherpetic neuralgia.

Clinical Geriatrics

The *I's* of Geriatrics: Common Problems in Older Adults	
• Immobility	• Instability
• Isolation	• Intellectual impairment
• Incontinence	• Impotence
• Infection	• Immunodeficiency
• Inanition (malnutrition)	• Insomnia

Drug-Related Problems in Older Adults

- Three important and potentially preventable negative outcomes caused by drug-related problems are

(a) **Adverse drug withdrawal events** (ADWEs), which are clinically significant sets of symptoms or signs caused by the removal of a drug;

(b) **Therapeutic failure** (inadequate or inappropriate drug therapy and not related to the natural progression of disease); and

(c) **Adverse drug reactions** (ADRs), defined as reactions that are noxious and unintended and occur at dosages normally used in humans for prophylaxis, diagnosis, or therapy

Drug-Related Problems in Older Adults

- **Risk Factors**
  - Polypharmacy
  - Inappropriate Prescribing
  - Underuse
  - Medication Nonadherence

Assessing and Monitoring Drug Therapy

- Match the medical problem list with the drug list.
  - Determine whether the patient has a chronic condition and is taking a medication that has been shown to improve the management of a particular condition
- Examine laboratory test results and vital signs that can be used to monitor the efficacy and toxicity of each medication

Monitoring Medication Use

Drug	Monitoring	Interval (in months)
Acetaminophen (>4 g/d)	Hepatic function tests	
Amiodarone	Hepatic function tests, TSH level	6
Antiepileptic agents (carbamazepine, phenobarbital, phenytoin, primidone, valproate)	Drug levels	3 – 6
ACEIs or ARBs	Potassium levels	6
Antipsychotic agents	Extrapyramidal side effects, fasting serum glucose, serum lipid panel	6
Digoxin	Serum blood urea nitrogen, creatinine, trough drug	6

Monitoring Medication Use

Erythropoiesis stimulants	Blood pressure, iron and ferritin levels, CBC	1
Fibrates	Hepatic function test, CBC	6
Hypoglycemic agents	Fasting serum glucose level or glycated hemoglobin level	6
Iron	Iron and ferritin levels, CBC	
Lithium	Trough serum drug levels	3
Metformin	Serum blood urea nitrogen, creatinine levels	

Monitoring Medication Use

Niacin	Blood sugar levels, hepatic function tests	6
Statins	Hepatic function tests	6
Theophylline	Trough serum drug levels	3
Thyroid replacement	TSH level on tests	6
Warfarin	Prothrombin time or international normalized ratio	1

GI PHARMACOTHERAPY

Assefa M. (MSc, Clinical Pharmacist, AAU)

CHAPTER FOUR

GI PHARMACOTHERAPY

- Gastroesophageal Reflex Disease
- Peptic Ulcer Disease
- Inflammatory Bowel Disease
- Viral Hepatitis
- Portal Hypertension and Cirrhosis
- Pancreatitis

Gastroesophageal Reflux Disease: GERD

Objectives

At the end of this session, you will be able to:

- Define GERD, describe its pathophysiology, and epidemiology
- Describe the clinical features of GERD
- Describe the consequence of GERD
- Describe the diagnostic work up of GERD
- Explain the general principle of GERD treatment

Definition and epidemiology

- Back flow of the acid gastric contents up in to the esophagus
- GERD: troublesome symptoms and/or complications caused by refluxing the stomach contents into the esophagus.
- Incompetent LES
- One of the most common GI diseases
- About 15% of individuals have heartburn and/or regurgitation at least once a week, and 7% have symptoms daily

Definition and epidemiology

- GERD syndromes can be divided into two distinct categories:

(a)Symptomatic esophageal syndromes with **normal endoscopic** findings and

(b)Syndromes associated with **esophageal tissue injury** including:

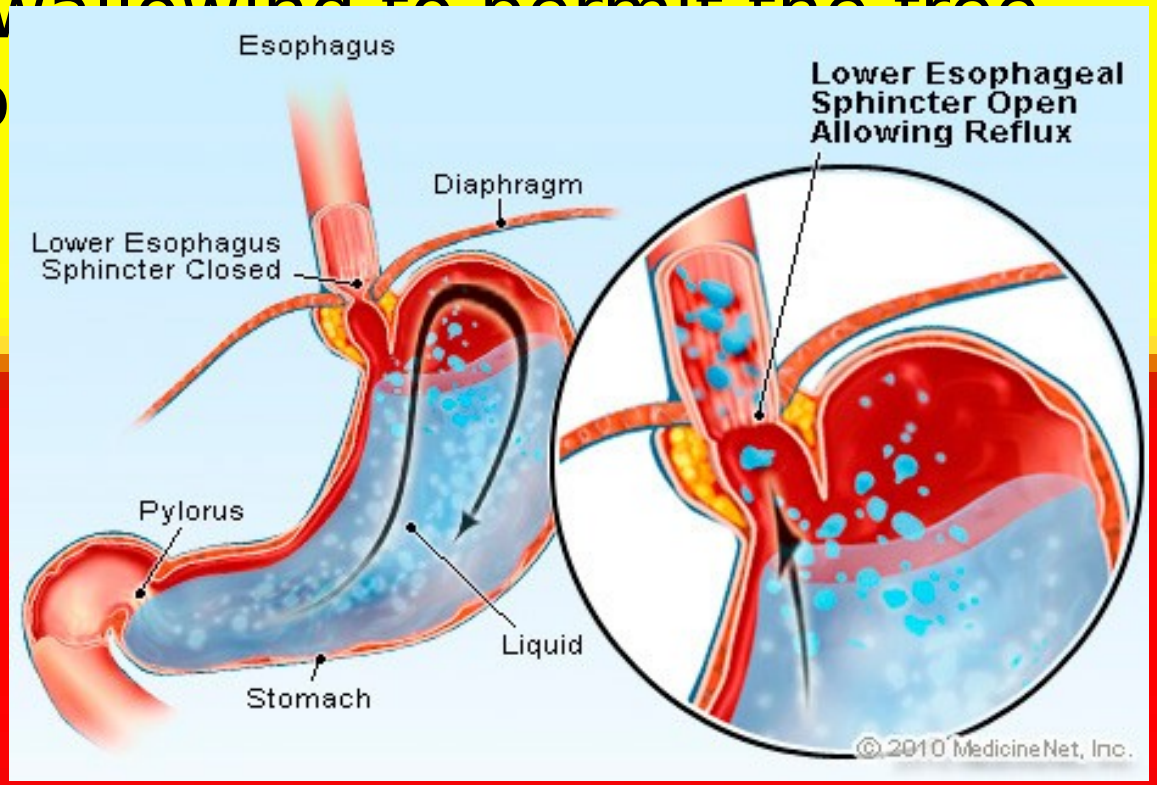
- Erosive esophagitis,
- Strictures,
- Barrett's esophagus, and
- Esophageal adenocarcinoma

PATHOPHYSIOLOGY

- Major factor in the development of GERD:
  - Defective lower esophageal sphincter (LES) pressure or function
  - Anatomic factors,
  - Esophageal clearance,
  - Mucosal resistance,
  - Gastric emptying,
  - Epidermal growth factor, and
  - Salivary buffering

Lower Esophageal Sphincter (LES) Pressure

- The sphincter is normally in a tonic, contracted state, preventing the reflux of gastric material from the stomach.
- It relaxes on sw
passage of foo



LES Pressure

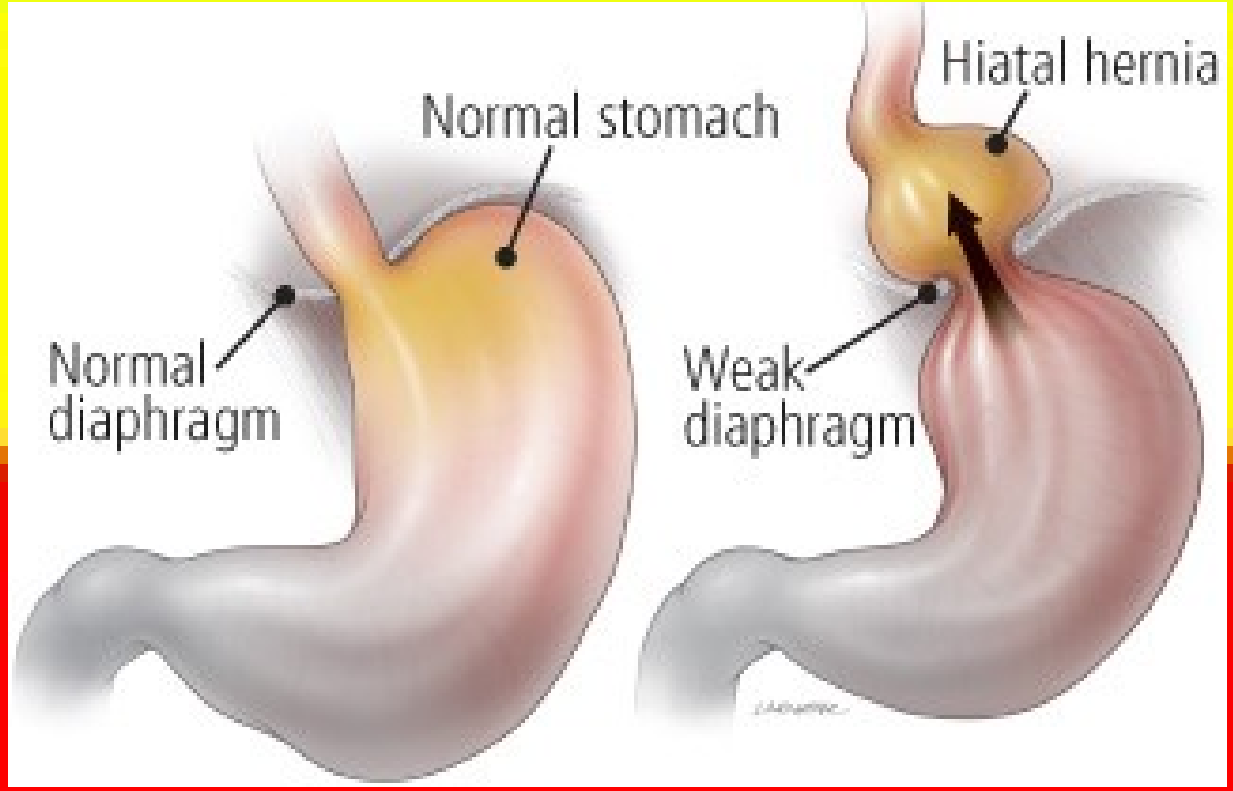
- Mechanisms by which defective LES pressure may cause gastroesophageal reflux:
  - **Spontaneous transient LES relaxations** that are not associated with swallowing.
    - Due to: esophageal distention, vomiting, belching, and retching
  - Transient **increases in intraabdominal pressure** (stress reflux).
    - Due to: straining, bending over, or a Valsalva maneuver
  - **Atonic LES**, thus permitting free reflux

Foods and Medications that may Decreased LES Pressure

Foods	Medications	
Fatty meal/fried foods	Anticholinergics	Ethanol
Carminatives (e.g., peppermint)	Barbiturates	Isoproterenol
Chocolate	Benzodiazepines	Narcotics (e.g., morphine)
Coffee, caffeinated drinks	Caffeine	Nicotine
Garlic	Dihydropyridine CCBs	Nitrates
Onions	Dopamine	Progesterone

Anatomic Factors

- Disruption of the normal anatomic barriers by a **hiatal hernia**



Esophageal Clearance

- Acid produced may spend too much time in contact with the esophageal mucosa.
- The contact time depends on the rate at which the esophagus clears the noxious material, as well as the frequency of reflux.
- The esophagus is cleared by primary peristalsis in response to **swallowing** or by secondary peristalsis in response to esophageal distention & gravitational effects.

Esophageal Clearance

- Swallowing contributes to esophageal clearance by increasing **salivary** flow.
- Saliva contains **bicarbonate** that buffers the residual gastric material on the surface of the esophagus.
- The production of saliva decreases with **increasing age**, making it more difficult to maintain a neutral intraesophageal pH.
- Therefore, esophageal damage due to reflux occurs more often in the **elderly** and patients with **Sjögren's syndrome** or **xerostomia**.
- Swallowing is also decreased during **sleep**, which contributes to nocturnal GERD in some patients

Mucosal Resistance

- The esophageal mucosa and submucosa consist of mucus secreting glands that contain **bicarbonate**.
- Bicarbonate moving from the blood to the lumen can neutralize acidic refluxate in the esophagus.
- A decrease in this normal defense mechanism can potentially lead to erosions in the esophagus.

Direct Irritants to the Esophageal Mucosa

Medications	Foods
Bisphosphonates	Spicy foods
Aspirin	Tomatoes
Iron	Citrus fruits,
NSAID	Coffee,
Quinidine	Orange juice
Potassium chloride	Carbonated beverages

Gastric Emptying and Increased Abdominal Pressure

- **Gastric volume** is related to the amount of **material ingested**, **rate of gastric secretion**, **rate of gastric emptying**, and amount and frequency of **duodenal reflux** into the stomach.
- Delayed gastric emptying can lead to increased gastric volume and can contribute to reflux by increasing intragastric pressure.
- Factors that increase gastric volume and/or decrease gastric emptying, such as **smoking** and **high-fat meals**, are often associated with gastroesophageal reflux.
- **Obesity** has been linked to GERD because of increased abdominal pressure.
- Morbidly obese patients may also have more transient LES relaxations, incompetent LES, and impaired esophageal motility

Clinical presentation

- Heart burn: substernal
- Sore throat
- Bad metal like taste
- Hoarseness
- Cough and
- Wheezing

Complicated Symptoms

- ♣Continual pain,
- ♣Dysphagia
- ♣Odynophagia
- ♣Bleeding,
- ♣Unexplained weight loss,
- ♣Unexplained anemia, and
- ♣Choking

Complications

- Peptic stricture:
  - In the distal esophagus and
  - Are generally 1 to 2 cm in length
- Barrett's esophagus
- Esophageal bleeding, anemia
- Adenocarcinoma
- Ulcer
- Extraintestinal: bronchitis, laryngitis, trachitis, pneumonia, exacerbation of bronchial asthma, pulmonary fibrosis

Diagnosis

- Most cases are diagnosed by history
- Additional studies might not be necessary if characteristic presentation
- Therapeutic trial provides support

Additional diagnostic approach

- Documentation of mucosal injury
  - Esophagoscopy
  - Mucosal biopsy
  - Barium swallow
  - The Bernstein test

NB: Normal esophagoscopy doesn't rule out GERD

Treatment

Goals:

- Alleviate symptoms,
- Decrease the frequency of recurrent disease
- Promote healing of mucosal injury, and
- Prevent complications.

General Approach to Treatment

- The treatment of GERD is categorized into one of the following modalities:

(a) Lifestyle modifications and patient-directed therapy with antacids, nonprescription H_2-receptor antagonists, and/or nonprescription PPIs;

(b) Pharmacologic intervention with prescription-strength acid suppression therapy;

(c) Interventional therapies (antireflux surgery or endoscopic therapies)

General Approach to Treatment

1. Intermittent, mild heartburn

- Individualized lifestyle modifications, PLUS
- Antacids, AND/OR
- Patient-directed therapy
  - OTC H2RAs, OR
  - OTC PPI

2. Symptomatic GERD, Moderate

- Individualized lifestyle modifications, PLUS
- Standard dose acid-suppressing therapy
  - H2RAs for 6–12 weeks, OR
  - PPIs for 4–8 weeks

3. Healing of erosive esophagitis or treatment of moderate to severe symptoms or complications

- Individualized lifestyle modifications, PLUS
- PPIs for 4–16 weeks

Nonpharmacologic Therapy

(a)Lifestyle modifications, which should be started initially and continued throughout the treatment course for GERD, and

(b)Interventional approaches

- ✓ Antireflux surgery or
- ✓ Endoscopic therapies

Lifestyle Modifications

- The most common lifestyle modifications that a patient should be educated about include
  - (a) Weight loss;
  - (b) Elevation of the head of the bed; 15-25 cm
    - ✓ Not just elevating the head with pillows
  - (c) Consumption of smaller meals and not eating 3 hours prior to sleeping;
  - (d) Avoidance of foods/medications that exacerbate GERD;
  - (e) Smoking cessation; and
  - (f) Avoidance of alcohol

PHARMACOLOGIC THERAPY

- Pharmacologic treatment consists of

(a) Patient-directed therapy with nonprescription antacids, H2-receptor antagonists, or proton pump inhibitors and

(b) Prescription-strength acid suppression therapy or promotility medications.

Patient-Directed Therapy

- Patient-directed therapy is appropriate for mild, intermittent symptoms.
- Patients with continuous symptoms lasting longer than **2 weeks** should seek medical attention.

Antacids and Antacid-Alginic Acid Products

- Magnesium/aluminum hydroxide 30 mL after meals and at bedtime as needed
- Antacid/alginic acid 2 tablets or 15 mL after meals and at bedtime
- Maintaining the intragastric pH >4 decreases the activation of pepsinogen to pepsin, a proteolytic enzyme.
- Also, neutralization of gastric fluid leads to increased LES pressure.
- An antacid product combined with alginic acid forms a highly viscous solution that floats on the surface of the gastric contents.

Antacids and Antacid-Alginic Acid Products

- Antacid or antacid combination products may cause GI adverse effects (diarrhea or constipation, depending on the product), alterations in mineral metabolism, and acid–base disturbances.
- Aluminum-containing antacids may bind to phosphate in the gut and lead to bone demineralization.
- Antacids interact with a variety of medications by altering gastric pH, increasing urinary pH, adsorbing medications to their surfaces, providing a physical barrier to absorption, or forming insoluble complexes with other medications.

Nonprescription H_2RAs and PPIs

- Nonprescription H_2-receptor antagonists are effective in lowering gastric acid when taken prior to meals and decrease GERD symptoms associated with exercise.
- Antacids may have a slightly faster onset of action, while the H_2-receptor antagonists have a much longer duration of action compared with antacids.

Nonprescription H_2RAs and PPIs

- Nonprescription H_2-receptor antagonists (taken up to twice daily)
  - ✓Cimetidine 200 mg
  - ✓Famotidine 10 mg
  - ✓Nizatidine 75 mg
  - ✓Ranitidine 75 mg
- Nonprescription proton pump inhibitor (taken once daily)
  - ✓Omeprazole 20 mg
  - ✓Lansoprazole 15 mg

Acid-Suppression Therapy

- Acid-suppression therapy with prescription-strength H_2RAs and PPIs are the mainstay of GERD treatment.

H_2-Receptor Antagonists

- For patients with mild to moderate GERD
- Symptomatic improvement is achieved in an average of **60%** of patients after 12 weeks of therapy.
- The H_2-receptor antagonists are well tolerated: the most common adverse effects are headache, somnolence, fatigue, dizziness, and either constipation or diarrhea.
- DI: **Cimetidine** may inhibit the metabolism of theophylline, warfarin, phenytoin, nifedipine, and propranolol

H_2-Receptor Antagonists

- Prescription-strength acid suppression therapy
  - H_2-receptor antagonists (for 6–12 weeks)
    - Cimetidine 400 mg twice daily
    - Famotidine 20 mg twice daily
    - Nizatidine 150 mg twice daily
    - Ranitidine 150 mg twice daily

PPIs

- Proton pump inhibitors are superior to H_2-receptor antagonists in treating patients with moderate to severe GERD
- Symptomatic relief is seen in approximately 83% of patients after 8 weeks treated with a proton pump inhibitor
- The proton pump inhibitors are usually well tolerated; however, potential adverse effects include headache, dizziness, somnolence, diarrhea, constipation, nausea, and vitamin B_{12} deficiency.

PPIs

- All proton pump inhibitors can decrease the absorption of drugs such as ketoconazole or itraconazole, which require an acidic environment to be absorbed.
- Proton pump inhibitors (for 4–8 weeks); all are given **once daily**
  - ✓ Esomeprazole 20 mg
  - ✓ Lansoprazole 15 mg
  - ✓ Omeprazole 20 mg
  - ✓ Pantoprazole 40 mg
  - ✓ Rabeprazole 20 mg

Promotility Agents

- Metoclopramide (Plasil®)
  - ✓A dopamine antagonist
  - ✓Increases LES pressure in a dose-related manner, and
  - ✓Accelerates gastric emptying in GERD patients.

Maintenance Therapy

- Candidates for maintenance therapy include
  - Patients whose symptoms return once therapy is discontinued or decreased,
  - Patients with a history of esophagitis healed by PPIs,
  - Patients with complications such as Barrett's esophagus or strictures, and
  - Patients with atypical symptoms.
- PPIs (taken **once** or **twice** daily) for **4–16 weeks**
  - Dexlansoprazole 60 mg
  - Esomeprazole 20–40 mg
  - Lansoprazole 30 mg
  - Omeprazole 20 mg
  - Rabeprazole 20 mg
  - Pantoprazole 40 mg

Quiz

1. **Lifestyle modifications for the management of GERD include:**
   A. Elevating the head of the bed with three to four pillows
   B. Eating larger meals less often
   C. Increasing intake of spicy foods
   D. Elevating the head of the bed 6 to 8 inches with blocks
   E. Wearing tight closes
2. **The following type patient is more at risk for developing GERD:**
   A. A. 70-year old obese female smoker
   B. 24-year old white male
   C. 18-year old African American male athlete
   D. 35-year old male with below-the-knee amputation
   E. 5-year old female with Type I diabetes

Quiz con'd

3. **Elderly patients with GERD can have the following defect in one of their protective host defense mechanisms:**
   - **A. Decreased saliva production**
   - B. Increased bile acid production
   - C. Increased GI motility
   - D. Increased gastric emptying
   - E. Decreased acid production
4. **Which drug is more effective for Severe GERD management?**
   - **A. Pantoprazole** B. Cimetidine C. Aluminum hydroxide D. All are equally effective
5. **A patient suffering from GERD for the last one month can be effectively treated with non-prescription strength ranitidine**
   - A. True B. **False**

PUD

Objectives

At the end of this session, the student will be able to:

- Understand what PUD is
- Describe the epidemiology and etiology of PUD
- Recognize the pathophysiology of PUD
- Identify the clinical presentation of PUD
- Distinguish the diagnostic techniques of PUD

Introduction

- Peptic ulcer disease (PUD) refers to a group of **ulcerative disorders** of the upper GI tract that require acid and **pepsin** for their formation.
- **Ulcers** differ from **gastritis** and **erosions** in that they extend deeper into the muscularis mucosa.
- An **ulcer** is a break in the mucosal surface >5mm in size
- PUD is a significant cause of morbidity and is associated with substantial healthcare costs.

Epidemiology & Etiology

- **H. pylori** infection and **NSAID** use account for most cases of PUD.
- The prevalence of H. pylori in the United States and Canada is about **30%**, whereas the global prevalence is > **50%.**
- Factors that influence the incidence and prevalence of H. pylori include **age**, **ethnicity**, **sex**, **geography**, and **socioeconomic status**.
- The prevalence of H. pylori has decreased over the past few decades, probably due to improved sanitary conditions;
  - However, H. pylori infection remains a public health issue in developing countries

GU Vs DU

- In general, ulcers related to H. pylori infection more commonly affect the **duodenum**, whereas ulcers related to NSAIDs more frequently affect the **stomach**
- However, ulcers may be found in either location from either cause.
- GU may occur anywhere in the stomach; DU tends to occur most often in the **duodenal bulb**.
- The epigastric pain associated with a **DU** typically occurs during the **fasting state** or **at night** and is often **relieved by food**, whereas pain from a GU is usually aggravated by food intake.
- Malignancy is more commonly found with **GU** than **DU**

Etiologies and Risk factors

Potential Causes of Peptic Ulcer

Common causes

- Helicobacter pylori infection
- Nonsteroidal antiinflammatory drugs
- Critical illness (stress-related mucosal damage)

Uncommon causes

- Hypersecretion of gastric acid (e.g., Zollinger-Ellison’s syndrome)
- Viral infections (e.g., cytomegalovirus)
- Vascular insufficiency (crack cocaine associated)
- Radiation
- Chemotherapy (e.g., hepatic artery infusions)
- Rare genetic subtypes
- Idiopathic

Etiologies and Risk factors

Helicobacter pylori

- Helicobacter pylori causes **gastritis** in all infected patients.
- However, only a small proportion **(<10%)** of patients actually develops symptomatic **PUD**.
- In 2005, Warren and Marshall received the Nobel Prize for recognizing H. pylori eradication as a cure for PUD.
- The infection normally resides in the stomach and is transmitted via the **fecal–oral** route or through ingestion of fecal-contaminated water or food.

Etiologies and Risk factors

- Prevalence varies greatly throughout the world,
  - Increasing with **older age** and with **lower socioeconomic status** during childhood.
  - Infection with H. pylori is more common in **developing countries** because of the presence of contaminated food and water.

Etiologies and Risk factors

Nonsteroidal Anti-inflammatory Drugs

- Chronic NSAID ingestion leads to symptoms of **nausea** and **dyspepsia** in nearly **half of patients**.
- **Peptic ulceration** occurs in up to **30%** of patients who use NSAIDs (including aspirin) chronically,
- **GI bleeding** or **perforation** occurring in **1.5%** of patients who develop an ulcer.

Etiologies and Risk factors

Risk factors for NSAID-induced peptic ulcers and complications

- Age over 60 years
- Concomitant anticoagulant use
- Preexisting coagulopathy (elevated INR or thrombocytopenia)
- Concomitant corticosteroid or SSRIs therapy
- Previous PUD or PUD complications (bleeding/perforation)
- CV disease and other comorbid conditions
- Multiple NSAID use (e.g., low-dose aspirin in conjunction with another NSAID)
- Duration of NSAID use (greater than 1 month)
- High-dose NSAID use
- NSAID-related dyspepsia

Risk Group	Drug	Relative Risk
Low	Ibuprofen	2.0
	Diclofenac	4.2
Medium	Naproxen	9.1
	Indomethacin	11.3
	Piroxicam	13.7
High	Ketoprofen	23.7
	Azapropazone	31.5

Etiologies and Risk factors

Stress-Related Mucosal Damage

- SRMD occurs most frequently in critically ill patients and is due to compromised mesenteric perfusion resulting in mucosal defects
- SRMD usually develops within the first few hours after a major trauma or serious illness.
- Physiologically stressful situations that lead to SRMD include **sepsis**, **organ failure**, prolonged **mechanical ventilation**, **thermal injury**, **trauma**, and **surgery**.

Etiologies and Risk factors

ASHP Guidelines on Appropriate Indications for SUP in ICU patients

- Coagulopathy or hepatic failure (platelet count less than 50 $\times 10^3/mm^3$, INR greater than 1.5, or aPTT less than two times control)
- History of GI ulceration or bleeding within 1 year of admission
- Head trauma or Glasgow Coma Score of 10 or less (or inability to obey simple commands)
- Thermal injuries to more than 35% of body surface area
- Multiple traumas (injury severity score of 16 or greater)
- Partial hepatectomy
- Transplant patients in the ICU perioperatively
- Spinal cord injuries
- Two of the following risk factors: sepsis, ICU stay for more than 1 week, occult bleeding lasting 6 or more days, and use of high-dose corticosteroids (more than 250 mg/day of hydrocortisone or equivalent)

SUP, stress ulcer prophylaxis

Etiologies and Risk factors

Cigarette Smoking

- Epidemiologic evidence links cigarette smoking to PUD
- The risk is proportional to the number of cigarettes smoked and is modest when fewer than 10 cigarettes are smoked per day.
- Death rates are higher among patients who smoke than among nonsmoking patients
- Possible mechanisms include:
  - Delayed gastric emptying of solids and liquids,
  - Inhibition of pancreatic bicarbonate secretion,
  - Promotion of duodenogastric reflux, and
  - Reduction in mucosal prostaglandin (PG) production.

Etiologies and Risk factors

Cigarette smoking

- Smoking increases gastric acid secretion, but this effect is inconsistent.
- Whether nicotine or other components of smoke are responsible for these physiologic alterations is unknown.
- Cigarette smoking may provide a favorable milieu for H. pylori infection.

Etiologies and Risk factors

Dietary Factors

- Coffee, tea, cola beverages, beer, milk, and spices may cause dyspepsia, but do not increase the risk for PUD
- In high concentrations, **alcohol ingestion** is associated with acute gastric mucosal damage and upper GI bleeding;

Etiologies and Risk factors

Zollinger – Ellison Syndrome

- ZES is caused by a gastrin producing **tumor** called a gastrinoma.
- This results in a state of **gastric acid hypersecretion** in which patients develop diarrhea & malabsorption.
- Ulcers tend to be numerous and have a high risk of perforation and bleeding

PATHOPHYSIOLOGY

- Ulcer formation is the net result of a lack of homeostasis between:
  - Factors within the GI tract responsible for the breakdown of food (e.g., **gastric acid** and **pepsin**) and
  - Factors that promote mucosal defense and repair (e.g., **bicarbonate**, **mucus secretion**, and **PGs**).

PATHOPHYSIOLOGY

Gastric Acid and Pepsin

- Three different stimuli are responsible for acid secretion through their interactions with the ***histaminic***, ***cholinergic***, and ***gastrin*** receptors on the surface of parietal cells.
  - Histamine, acetylcholine, and gastrin
- Gastric acid output occurs in two stages:

(a) Basal acid output, which reflects the baseline output of acid during the **fasting state**,

- Follows a circadian cycle and is modulated by the effects of acetylcholine and histamine acting on the parietal cell.

(b) Maximal acid output, which occurs in response to **meals**.

PATHOPHYSIOLOGY

- Food can cause gastric acid secretion in two ways.
  - In the **Cephalic phase** of acid secretion, the physical distention caused by food induces, the vagus nerve stimulates acid secretion in response to the **sight**, **smell**, or **taste** of food.
  - In both the **gastric** and **intestinal phases** of acid secretion gastrin secretion resulting in acid production.
- **Pepsinogen** released from **chief cells** in the body of the stomach is converted to pepsin in the presence of an acidic environment
  - Plays a key role in the initiation of protein digestion, proteolysis of collagen

PATHOPHYSIOLOGY

Mucosal Defense and Repair

- The mucus/phospholipid and bicarbonate barrier, through its buffering action
  - Maintain neutral pH on the epithelial lining
- PGs inhibit gastric acid secretion and have numerous mucosal protective effects,
  - Stimulation of mucus, bicarbonate, and phospholipid production.
  - Increase mucosal blood flow and stimulate epithelial cell regeneration.

PATHOPHYSIOLOGY

Helicobacter pylori

- H. pylori, a gram-negative microaerophilic S-shaped rod, is found on the surface of the gastric epithelium
- H. pylori colonization does not necessarily reflect an active infection because the organism can attach itself to the gastric epithelium without invading cells.
- The **motility** provided by the flagella allows the organism to penetrate the mucous gel barrier and cause an acute infection in the epithelial cells
- The organism is able to survive in the acidic stomach via production of **urease**, an enzyme that hydrolyzes urea (found in gastric juice) into carbon dioxide and ammonia

PATHOPHYSIOLOGY

H. pylori

- In addition to PUD, H. pylori infection may also result in
  - Gastric cancer (0.1% to 3%) and
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (less than 0.01%).

PATHOPHYSIOLOGY

Nonsteroidal Anti-inflammatory Drugs

- Nonselective NSAIDs (those that inhibit both COX-1 and COX-2) cause gastric mucosal damage by two primary mechanisms:
  - Direct or **topical irritation** of the gastric epithelium and
    - NSAIDs are weak acids.
  - Systemic inhibition of endogenous mucosal **PG synthesis**
    - PGs are important factors in gastric healing and protection.
    - Inhibition of PG production by NSAIDs compromises these important protective mechanisms.
- Finally, the **antiplatelet effects** of NSAIDs may worsen bleeding complications associated with PUD

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

- Symptoms
  - Mild epigastric pain that may be described as burning, gnawing, or aching in character.
  - Abdominal pain
    - Described as burning or a feeling of discomfort.
    - Nocturnal pain.
    - The intensity of pain can vary widely (e.g., from dull to sharp).
    - DU pain occurs 1to 3 hrs after meals and may be relieved by food ingestion.
    - GU pain occurs immediately after meals and is often aggravated by food.
  - Patients may also complain of heartburn, belching, bloating, nausea, or vomiting

CLINICAL PRESENTATION AND DIAGNOSIS

- **Signs**
  - Weight loss may be associated with nausea and vomiting.
  - Complications such as bleeding, perforation, or obstruction may occur.
- **Alarm signs and symptoms**
  - Family history of upper GI malignancy,
  - Unintentional weight loss,
  - Overt GI bleeding,
  - Iron deficiency anemia,
  - Progressive dysphagia or odynophagia,
  - Early satiety,
  - Persistent vomiting,
  - Prior history of esophagogastric malignancy, palpable mass, or lymphadenopathy.

PUD-related complications

Gastrointestinal bleeding

- GI bleeding is the most common complication observed in PUD.
- It occurs in ~15% of patients and more often in individuals >60 years of age.
  - ✡ Due to the increased use of NSAIDs in this group
- The mortality rate is as high as 5–10%.

PUD-related complications

Perforation

- The second most common ulcer-related complication
  - as many as 6–7% of PUD patients.
- DUs tend to penetrate posteriorly into the pancreas, leading to **pancreatitis**, whereas GUs tend to penetrate into the **left hepatic lobe**.
- Gastrocolic fistulas associated with GUs have also been described

PUD-related complications

Gastric outlet obstruction

- Gastric outlet obstruction is the least common ulcer related complication, occurring in 1–2% of patients.
- A patient may have relative obstruction secondary to ulcer related inflammation and edema in the peripyloric region

Diagnostic Tests

- Testing for H. pylori infection is indicated in patients with:
  - Active PUD,
  - Past history of documented PUD, or
  - Gastric MALT lymphoma
- Diagnostic tests for the presence of H. pylori can be either endoscopic or nonendoscopic
- Endoscopic diagnosis requires the extraction of gastric tissue samples that are subsequently tested for H.pylori.

Diagnostic Tests

- The urea breath test is usually the first-line test to detect active H.pylori infection because it has a sensitivity and specificity greater than 95% and a short turnaround time.
- Concomitant acid-suppressive or **antibiotic therapy** may give false-negative results.
- The urea breath test can also be used to confirm eradication of H. pylori infection.

Endoscopic Testing

Histology

- Gastric biopsy can be helpful in making the primary diagnosis of H. pylori infection.
- It also provides additional information regarding the presence of gastritis and the detection of **intestinal metaplasia** and mucosa-associated lymphoid tissue (MALT).
- Potential problems include:
  - The density of H. pylori can vary at different sites, possibly leading to sampling error
  - Interobserver variability
  - The sensitivity of histology may be decreased in patients taking antisecretory therapy
  - Costly

Endoscopic Testing

Bacterial culture and sensitivity testing

- Patients with refractory disease may benefit from culture and sensitivity testing, since the incidence of resistance is very high in this subgroup
- Concerns over metronidazole and macrolide resistance are growing and a standard definition of antibiotic resistance is being established.
  - The incidence of metronidazole resistance appears to vary with geography and is estimated to range from 80 to 90% in tropical countries
  - The incidence of primary macrolide resistance is **4 to 12%**

Noninvasive Testing

Urea breath testing

- Urea breath testing is based upon the hydrolysis of urea by H. pylori to produce **CO_2** and **ammonia**.
- False positive results are therefore uncommon.
- False negative results may be observed in patients who are taking antisecretory therapy, bismuth , or antibiotics
- To reduce false negative results, the patient should be off antibiotics for at least four weeks and off PPIs for at least two weeks

Noninvasive Testing

Serology

- Laboratory-based serologic testing using ELISA technology to detect IgG antibodies is inexpensive, noninvasive, and well suited to primary care practice
- Concerns over its accuracy have limited its use

Stool antigen assay

- The presence of H. pylori in the stool of infected patients has led to the development of fecal assays, which are widely available and require no special set-up

TREATMENT OF PUD

DESIRED OUTCOME

- Overall treatment goal
  - ✡ Relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications
- H. pylori-positive patients
  - ✡ Eradicate H. pylori, heal the ulcer, and cure the disease
- Patient with a NSAID-induced ulcer
  - ✡ To heal the ulcer

General Treatment Approach

- Drug regimens containing antimicrobials such as clarithromycin, metronidazole, amoxicillin, and bismuth salts and antisecretory drugs (PPIs or H_2RAs) relieve ulcer symptoms, heal the ulcer, and eradicate **H. pylori infection**
- PPIs are preferred to H_2RAs or sucralfate for healing **H. pylori-negative NSAID ulcers** because they accelerate ulcer healing and provide more effective relief of symptoms.
- A PPI-based H. pylori eradication regimen is recommended in **H. pylori-positive patients** with an active ulcer who are also taking an NSAID.

General Treatment Approach

- Prophylactic co-therapy with either a PPI or misoprostol decreases ulcer risk and upper GI complications in patients taking nonselective NSAIDs.
- A COX-2 inhibitor may be used as an alternative to a nonselective NSAID, but the risk of adverse CV effects must be weighted against the gastroprotective benefits in each patient.

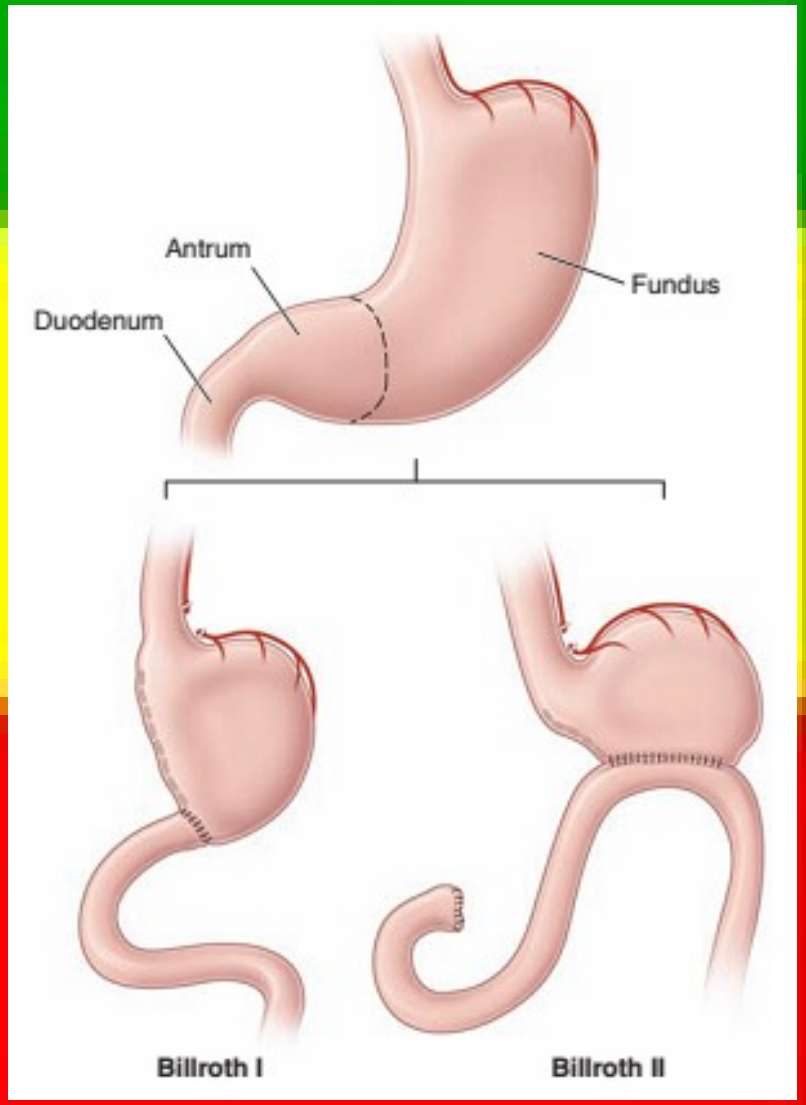
NONPHARMACOLOGIC THERAPY

- Patients with PUD should eliminate or reduce psychological stress, cigarette smoking, and the use of nonselective NSAIDs (including aspirin).
- The patient should avoid foods and beverages (e.g., spicy foods, caffeine, and alcohol) that cause dyspepsia or that exacerbate ulcer symptoms.
- If possible, alternative agents such as paracetamol, or COX-2 inhibitors should be used for relief of pain.

NONPHARMACOLOGIC THERAPY

- **Elective surgery**
  - For patients with bleeding, perforation, or obstruction.
  - Vagotomy with pyloroplasty or
  - Vagotomy with antrectomy.
- Stomach is anastomosed with the duodenum (Billroth I) or with the jejunum (Billroth II).
- Postoperative consequences associated with these procedures include postvagotomy diarrhea, anemia, and recurrent ulceration

- Gastroduodenostomy (Billroth I) or
- Gastrojejunostomy (Billroth II)



PHARMACOLOGIC THERAPY

- **Treatment of H. pylori-Associated Ulcers**
  - **First-line therapy**: PPI-based three-drug regimen for 10 to 14 days.
  - If a second course of treatment is required, the PPI-based three-drug regimen should contain different antibiotics or a four-drug regimen with bismuth subsalicylate, metronidazole, tetracycline, and a PPI should be used.

PPI-based 3-drug regimens (triple therapy)

Drug #1	Drug #2	Drug #3
Omeprazole 20 mg twice daily or lansoprazole 30 mg twice daily or pantoprazole 40 mg twice daily or esomeprazole 40 mg daily or rabeprazole 20 mg daily	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily or metronidazole 500 mg twice daily

Triple therapy

- The combination of lansoprazole-amoxicillin-clarithromycin is available in a daily dose convenience packaging, Prevpac® (TAP Pharmaceuticals, Inc).
- Metronidazole (500 mg twice daily) can be substituted for amoxicillin , but only in penicillin-allergic individuals since metronidazole resistance is common and can reduce the efficacy of treatment

Bismuth-based 4-drug regimens (quadruple therapy)

Drug #1	Drug #2	Drug #3	Drug #4
Omeprazole 40 mg BID or lansoprazole 30 mg BID or pantoprazole 40 mg BID or esomeprazole 40 mg QD or rabeprazole 20 mg QD or standard ulcer-healing dosages of an H_2RA taken for 4–6 Weeks	Bismuth subsalicylate 525 mg QID	Metronidazole 250–500 mg QID	Tetracycline 500 mg QID or amoxicillin 500 mg QID, or, clarithromycin 250–500 mg QID

Quadruple therapy

- Quadruple therapy is appropriate as **initial** therapy
  - In areas in which the prevalence of resistance to clarithromycin or metronidazole is >20 percent, or
  - In patients with recent or repeated exposure to clarithromycin or metronidazole
- A combination preparation of bismuth subcitrate-metronidazole-tetracycline is available in the United States (trade name **Pylera**)

Sequential Therapy

- Sequential triple therapy may improve eradication rates, especially with clarithromycin resistant strains.
- This 10-day regimen involves giving a PPI (twice daily) and amoxicillin (1g twice daily) **for five days**, followed by a PPI (twice daily) plus clarithromycin (500 mg twice daily) and **tinidazole** (500 mg twice daily) **for five days**.

Initial Treatment Failure

- Quadruple therapy for 14 days is generally required,
- Metronidazole or clarithromycin should be replaced by another antibiotic if either one of these agents was used in the initial regimen.
- If both clarithromycin and metronidazole were used as initial therapy, a regimen consisting of amoxicillin 1 g twice daily, levofloxacin 250 mg twice daily, and a PPI twice daily may be used for 14 days
- Sequential therapy is a possible alternative 10-day regimen that may also be used to treat H. pylori infection

Treatment of NSAID-Induced Ulcers

- Patients with NSAID-induced ulcers should be tested to determine their H. pylori status.
- If H. pylori-positive: a PPI-based three-drug eradication regimen.
- If H. pylori-negative, the NSAID should be discontinued and the patient treated with a PPI, H_2RA, or sucralfate.
- If the NSAID must be continued,
  - ✡ If H. pylori-negative: PPI
  - ✡ If H. pylori-positive: PPI-based three-drug eradication regimen.

Prophylaxis for patients on NSAIDs

- For patients at risk of developing ulcer-related upper GI complications
  - ✡ Prophylactic cotherapy with a PPI or misoprostol or
  - ✡ Switching to a selective COX-2 inhibitor (if available)
- **Misoprostol Co-therapy**
  - ✓ Misoprostol, 200 mcg orally four times per day,
  - ✓ Reduces the risk of NSAID-induced gastric and duodenal ulcer, and ulcer-related GI complications,
  - ✓ But diarrhea and abdominal cramping limit its use
  - ✓ A fixed combination of misoprostol 200 mcg and diclofenac (50 mg or 75 mg)
- **PPI Cotherapy**
  - ✓ Proton pump inhibitor cotherapy reduces the risk of nonselective NSAID-related gastric and duodenal ulcer
  - ✓ Superior to the H_2RAs

Treatment During Pregnancy And Lactation

- Acid Suppression
  - All of the PPIs are considered low risk in pregnancy, whereas **misoprostol** is contraindicated in pregnancy.
- If *H. pylori* is present, treatment is typically deferred until after delivery.
  - However, with the exception of bismuth and tetracycline , the other medications used for H. pylori eradication are low risk in pregnancy, especially after 14 weeks.
  - H. pylori can cause severe nausea/vomiting in pregnancy, including hyperemesis gravidarum
- Some of the medications typically used for the treatment of *H. pylori* are considered possibly unsafe for nursing infants (eg, bismuth, metronidazole)

OUTCOME EVALUATION

- Obtain a baseline complete blood count (CBC).
  - Recheck the CBC if the patient exhibits alarm signs or symptoms.
- Obtain a history of symptoms from the patient. Monitor for improvements in pain symptoms (e.g., epigastric or abdominal pain) daily.
- Monitor the patient for the development of any alarm signs and symptoms
- Recommend a follow-up visit if signs and symptoms worsen at any time or do not improve within the defined treatment period.
- Assess for potential drug interactions whenever there is a change in the patient’s medications.

OUTCOME EVALUATION

- Educate the patient on the importance of adhering to the H.pylori eradication regimen.
- Monitor the patient for complications related to antibiotic therapy (e.g., diarrhea or oral thrush) during and after completion of H.pylori eradication therapy.
- Recommend follow-up care if the patient’s signs and symptoms do not improve after completion of H.pylori eradication therapy.

VIRAL HEPATITIS

OBJECTIVES

At the end of this session, students will be able to:

1. Differentiate the five types of viral hepatitides by their epidemiology, etiology, pathophysiology, and clinical presentation.
2. Identify modes of transmission and risk factors among the major types of viral hepatitis.
3. Evaluate hepatic serologies to understand how the type of hepatitis is diagnosed.
4. Recommend appropriate pharmacotherapy for prevention of viral hepatitis.
5. Develop a pharmaceutical care plan for treatment of chronic viral hepatitis.
6. Identify monitoring parameters for CHB and CHC

INTRODUCTION

- The most common types of viral hepatitis include hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV).
- **Acute hepatitis** may be associated with all five types of hepatitis and does **not exceed 6 months** in duration.
- **Chronic hepatitis** (disease lasting longer than 6 months) is usually associated with hepatitis B, **C**, & **D**.

INTRODUCTION

- Viral hepatitis may occur at any age and is the most common cause of liver disease in the world
- **Chronic viral hepatitis** may lead to the development of cirrhosis and may result in end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC).
- Complications of ESLD include ascites, edema, hepatic encephalopathy, infections, hepatorenal syndrome, and esophageal varices.
- Therefore, prevention and treatment of viral hepatitis may prevent ESLD and HCC.

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis A

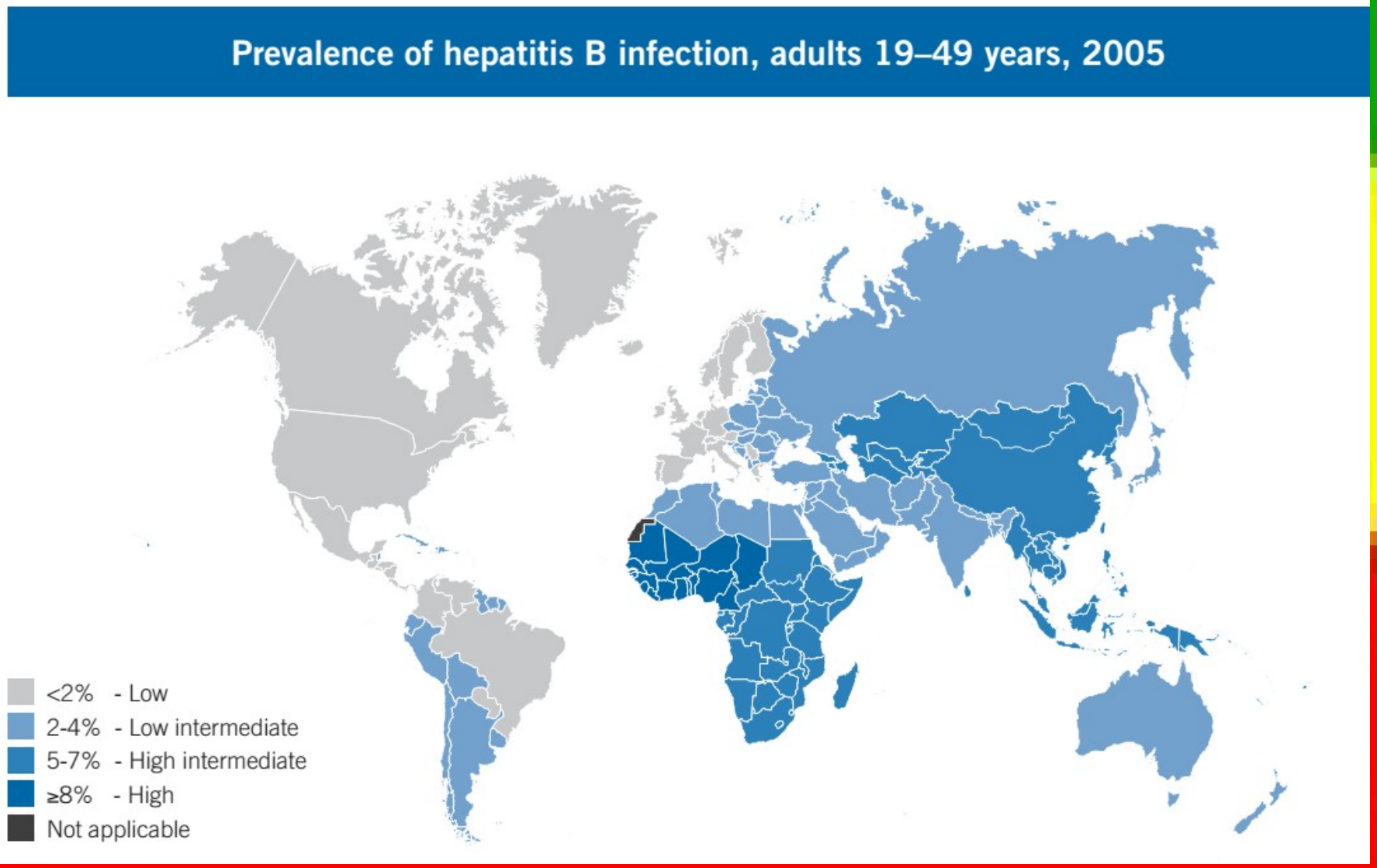
- Hepatitis A (HAV) affects **1.4 million** people yearly world wide.
- The prevalence is highest in developing countries including Africa, parts of South America, the Middle East, and Southeast Asia.
- HAV is primarily detected in contaminated feces and infects people via the fecal–oral route.
- There are no documented cases of chronic hepatitis A

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis B

- Hepatitis B is a blood-borne infection affecting approximately **2 billion** people worldwide.
- About **350 million** people have CHB infection that may lead to cirrhosis and complications of ESLD.
- Annually, an estimated **1million** deaths are associated with hepatitis B.
- The primary modes of transmission are either by blood or body fluids through perinatal, sexual, or percutaneous exposure

EPIDEMIOLOGY AND ETIOLOGY



EPIDEMIOLOGY AND ETIOLOGY

Hepatitis C

- More than **170 million** people are infected with hepatitis C worldwide
- **IV drug users** using contaminated material are responsible for about **60%** of HCV transmissions

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis D

- Hepatitis D affects approximately **15 million** people worldwide.
- The most likely modes of transmitting HDV are similar to those of HBV, including IV drug use with unsterilized needles and administration of contaminated blood products
- Sexual and perinatal transmissions are rare for HDV

Hepatitis E

- Hepatitis E is found worldwide, but acute cases occur primarily in Central and Southeast Asia, the Middle East, North Africa, and Mexico
- The HEV is primarily transmitted by the fecal–oral route via fecally contaminated water.

Risk Factors

Hepatitis A, E

- International travelers
- Sexual contact with infected persons (e.g., MSM)
- Shellfish infected with HAV, HEV
- Daycare centers or household contacts with people infected with HAV, HEV
- Healthcare workers
- IV drug users using unsterilized needles
- Workers involved with nonhuman primates
- Food service handlers

Hepatitis B, C and D

- Men having sex with other men
- Individuals with multiple heterosexual partners
- IV drug users using unsterilized needles
- Recipients of blood products
- Household contacts with acute hepatitis B, C & D with open cuts
- Healthcare providers in contact with contaminated needles
- Patients undergoing dialysis
- Perinatal transmission

PATHOPHYSIOLOGY

Hepatitis A

- Hepatitis A is a nonenveloped single stranded RNA virus classified as the Hepatovirus genus.
- The primary host for the HAV is humans, with hepatic cells as the main site for viral replication.
- As part of the viral degradation process, the HAV is released into the biliary system causing elevated concentrations of the virus in the feces.
- Hepatitis A infections are usually self limiting and do not lead to chronic disease; they may rarely result in fulminant hepatitis.

PATHOPHYSIOLOGY

Hepatitis B

- The hepatitis B virus belongs to the Hepadnaviridae family.
- It is a double stranded DNA virus with a **phospholipid layer** containing **hepatitis B surface antigen (HBsAg)** that surrounds the nucleocapsid.
- The nucleocapsid contains the core protein that produces **hepatitis B core antigen (HBcAg)**, which is undetectable in the serum.
- Hepatocellular injury from HBV is thought to be due to a **cytotoxic immune reaction** that occurs when HBcAg is expressed on the surface of the hepatic cells.

PATHOPHYSIOLOGY

Hepatitis B

- Antibodies against hepatitis B core antigen (anti-HBc) are measurable in the blood, where
  - Anti-HBc to immunoglobulin M (IgM) indicates **active infection** and
  - Anti-HBc to IgG relates to either **chronic infection** or possible **immunity** against HBV.
- **Viral replication** occurs when the **HBeAg** is present and circulating in the blood.
- Once the hepatitis B infection **resolves**, antibodies against the hepatitis B envelope (anti-HBe) and antibodies against hepatitis B surface antigen (anti-HBs) develop, and HBV DNA levels become undetectable.

PATHOPHYSIOLOGY

Hepatitis B

- If anti-HBe and anti-HBs antibodies do not develop, the likelihood of developing **CHB** increases
- This depends primarily on the host's immune system at the time of the infection.
- In immunocompetent individuals, the disease resolves spontaneously and does not lead to further complications.
- In immunocompromised persons, the HBV is less likely to be eradicated, thus causing persistent infection.
- This often leads to hepatic cell damage and inflammation that may lead to cirrhosis and hepatocellular carcinoma

PATHOPHYSIOLOGY

Hepatitis B

- Chronic HBV occurs in less than **5%** of those who are older than 5 years, whereas the rate is more than **90%** in infants born to mothers infected with HBV.
- Approximately **90%** of adults infected with the HBV develop anti-HBs, which results in lifelong immunity.
- Cirrhosis and HCC are the two major complications associated with CHB hepatitis B infections.

PATHOPHYSIOLOGY

Hepatitis C

- Hepatitis C, first known as non-A, non-B hepatitis (NANB), is a bloodborne infection caused by a single stranded **RNA virus**.
- There are **11 genotypes** (numbered 1 to 11) and more than 90 subtypes (genotypes 1a, 1b, 2a, 3b, etc.) that are unique to hepatitis C.
- Antibodies against HCV (anti-HCV) in the blood indicate infection.
- If the infection persists for more than 6 months and viral replication is confirmed by HCV RNA levels, the person has chronic hepatitis C

PATHOPHYSIOLOGY

Hepatitis C

- In more than **70%** of cases, hepatitis C develops into a **chronic disease** that is asymptomatic in about 60% to 80% of patients.
- Cirrhosis and its complications occur in **15% to 20%** of patients infected with HCV
- Chronic disease may be due to an ineffective host immune system, with cytotoxic T lymphocytes being unable to eradicate the HCV, thereby allowing persistent damage to hepatic cells.
- Risk factors for developing hepatic fibrosis include
  - **Obesity, diabetes, heavy alcohol use, male sex, and acquiring HCV when older than 40 years.**

PATHOPHYSIOLOGY

Hepatitis D

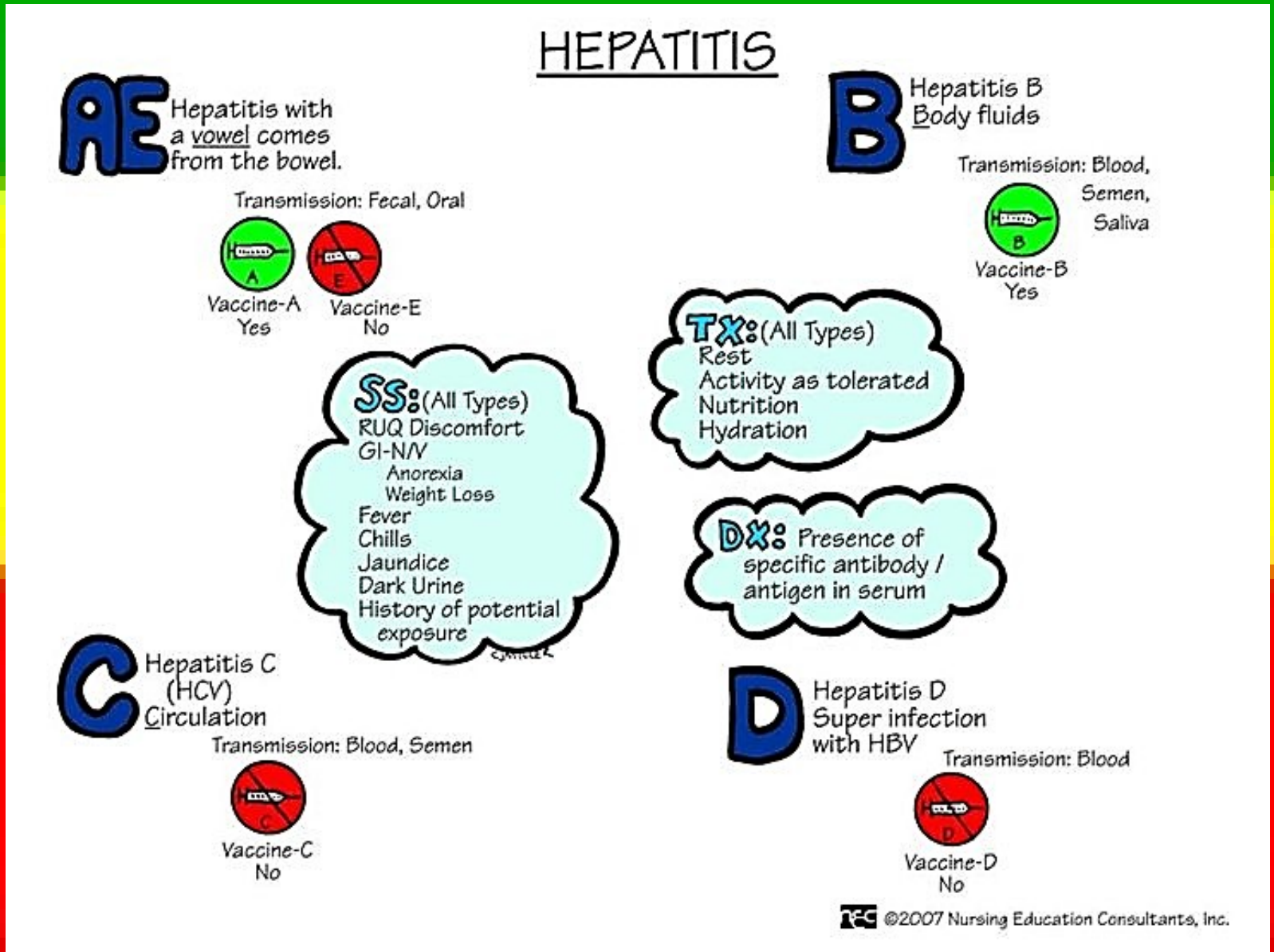
- The hepatitis D virus belongs to the genus Delta virus of the Deltaviridae family.
- The HDV virion is a **defective** single stranded circular RNA virus that requires the presence of HBV for HDV viral replication*.
- Replication of HDV cannot occur without HBV present causing coinfection (both hepatitis B and D infection occurring simultaneously)

PATHOPHYSIOLOGY

Hepatitis E

- Hepatitis E is a nonenveloped single stranded messenger RNA virus of the Hepevirus genus.
- The HEV is similar to HAV in that the virus is found in contaminated feces, thus infecting people via the fecal–oral route.
- High HEV levels in the bile often prompt viral shedding in the feces.
- Hepatitis E infections are usually self-limiting and rarely result in hepatic complications.
- Chronic hepatitis E occurs rarely and is more likely to occur in immunocompromised individuals such as patients with HIV or posttransplant recipients.

Tips for viral hepatitis



CLINICAL FEATURES

Incubation Period

Etiologies	Incubation (days)
HAV	15–45, mean 30
HBV	30–180, mean 60–90
HCV	15–160, mean 50
HDV	30–180, mean 60–90
HEV	14–60, mean 40

CLINICAL FEATURES, ACUTE

- **Prodromal symptoms (Preicteric phase):**
  - Systemic and variable
  - **Constitutional symptoms**: anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza
  - Precede the onset of jaundice by 1–2 weeks.
  - Low-grade fever (A and E > B or C)
  - Typically lasts 3 to 10 days
  - Viral titers are generally **highest** at this point, and serum **ALT** levels start to increase
  - Viral-specific antibody first appears during this phase

CLINICAL FEATURES, ACUTE

Icteric phase of illness

- Clinical jaundice
- Preceded by dark urine and clay-colored stools (1–5 days)
- Typically acute viral hepatitis is rarely diagnosed correctly before the onset of jaundice.
- With the onset of clinical jaundice, the constitutional prodromal symptoms usually diminish,
- If jaundice is severe, pruritus may appear.
- PE: jaundice and hepatic tenderness, hepatomegaly and splenomegaly
- Serum bilirubin levels (total and direct) rise, and ALT levels are greater than 10 times the upper limit of normal.
- Levels of hepatitis virus begin to decrease in serum and liver antibody titer increases
- The duration of clinical illness is variable it typically lasts 1 to 3 weeks.

CLINICAL FEATURES, ACUTE

3) Convalescence/Recovery phase/Posticteric

- Recovery is first manifested by return of appetite then disappearance of the constitutional symptoms.
- Generally resolution of the serum bilirubin and ALT elevations and clearance of virus is expected;
  - However some liver enlargement and abnormalities in liver biochemical tests may still be evident.
- The duration of the posticteric phase is variable, ranging 2–12 weeks, and is usually more prolonged in acute hepatitis B and C.

Outcome of Acute Viral Hepatitis

- Acute viral hepatitis is self limited
- Its outcome largely depend on the underlying **etiology**, **age**, **immune states**
- A substantial proportion of patients with viral hepatitis never become icteric so may not be diagnosed
- Hepatitis A and E: **complete** clinical and biochemical recovery is to be expected after 1–2 months
- Hepatitis B and C: 3–4 months after the onset of jaundice acute hepatitis B is self-limited in 95–99% while hepatitis C is self-limited in only 15%.
- Complications of acute viral hepatitis include fulminant hepatic failure, relapsing or cholestatic hepatitis, chronic infection and extrahepatic syndromes

Clinical Presentation of Chronic Hepatitis B

Signs and symptoms

- Easy fatigability, anxiety, anorexia, and malaise
- Ascites, jaundice, variceal bleeding, and hepatic encephalopathy can manifest with liver decompensation
- Hepatic encephalopathy: hyperexcitability, impaired mentation, confusion, obtundation, and eventually coma
- Vomiting and seizures

Physical examination

- Icteric sclera, skin, and secretions
- Decreased bowel sounds, and
- Detectable fluid wave

Diagnosis of Viral Hepatitis

- Diagnosing viral hepatitis may be difficult because most infected individuals are asymptomatic.
- Because symptoms cannot identify the specific type of hepatitis, laboratory serologies must be obtained
- In addition, liver function tests may aid in assessing the extent of cholestasis and hepatocellular injury.
- However, the definitive test to determine the amount of damage and inflammation of hepatic cells is a liver **biopsy**.

Diagnosis of Viral Hepatitis

A) Laboratory Features

1) The serum AST and ALT show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level .
   - ✡ The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage.
   - ✡ Peak levels are usually reached at the time the patient is clinically icteric.
2) Serum *alkaline phosphatase* may be normal or only mildly elevated
3) Serum bilirubin level may range from (5–20 mg/dL)
4) Prothrombin time (PT): reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis
5) Blood glucose level, serum albumin
6) CBC, RFT, B/F, ...

Diagnosis of Viral Hepatitis

B) Viral markers for etiologic diagnosis

Hepatitis A

- IgM anti-HAV in the serum indicates an acute infection.
  - IgM appears 3 weeks after exposure and becomes undetectable within 6 months.
- IgG anti-HAV indicates protection and lifelong immunity against hepatitis A
  - Appears in the serum at approximately the same time IgM antiHAV develops

Diagnosis of Viral Hepatitis

B) Viral markers for etiologic diagnosis

Hepatitis B

- Diagnosed when **HBsAg** is detectable in the serum
- Anti-HBc to IgM: indicates active infection.
- Anti-HBc to IgG: either chronic infection or possible immunity against HBV
- HBeAg is detected in the blood indicating active viral replication
- Measurement of HBV DNA is used to determine viral infectivity and quantify viral replication.

Diagnosis of Viral Hepatitis

B) Viral markers for etiologic diagnosis

Hepatitis C

- Diagnosed by testing for **anti-HCV** in the serum
- Confirmed by the presence of HCV RNA.
- HCV RNA levels quantify viral replication and are used to determine if antiviral treatment for HCV is effective.
- Once an infection has been confirmed, an **HCV genotype** should be obtained to determine the likelihood of response to antiviral therapy and the duration of treatment required

Diagnosis of Viral Hepatitis

B) Viral markers for etiologic diagnosis

Hepatitis D

- Hepatitis D infection requires the presence of HBV for HDV viral replication.
- Measuring HDV RNA levels in the serum PCR confirms the presence of the HDV
- The presence of **IgM anti-HD** indicates active disease, and **IgG anti-HD** also becomes detectable if the infection does not resolve spontaneously.

Diagnosis of Viral Hepatitis

B) Viral markers for etiologic diagnosis

Hepatitis E

- The diagnosis of hepatitis E is based on the presence of anti HEV antibodies (IgM anti-HEV).
- IgG anti-HEV emerges when the acute phase of the HEV infection resolves

PREVENTION AND TREATMENT

Desired Outcomes

(a)Prevent the spread of the disease,

(b)Prevent and treat symptoms,

(c)Suppress viral replication,

(d)Normalize hepatic aminotransferases,

(e)Improve histology on liver biopsy, and

(f) Decrease morbidity and mortality by preventing cirrhosis, HCC, and ESLD

General Approach

- **Prevention** of hepatitis A and B (and indirectly for hepatitis D) can be achieved with immune globulin or vaccines.
- **Acute viral hepatitis** is primarily managed with supportive care.
- **Liver transplantation** may be required in rare instances if **fulminant hepatitis** develops.
- Treatment is available for chronic liver disease (HBV, HCV, and HDV) to prevent ESLD and ultimately HCC.

Hepatitis A Prevention

- Good personal hygiene and proper disposal of sanitary waste
  - Frequent **hand washing** with soap and water after using the bathroom and prior to eating meals.
- Drinking bottled water
- Avoiding fruits, vegetables, and raw shellfish
- Individuals at high risk of acquiring hepatitis A should receive either serum **immune globulin** or the **hepatitis A vaccine**,

Hepatitis A Prevention

Immune Globulin

- Passive immunization against hepatitis A
- IG is available for either IV (IGIV) or intramuscular (IGIM) administration

Hepatitis A Prevention

Preexposure prophylaxis:

- Prophylaxis with IGIM is indicated for individuals at high risk, who

(a) Are younger than 12 months,

- Elect not to receive the hepatitis A vaccine,
- Cannot receive the hepatitis A vaccine (because of allergy to the components alum or 2phenoxyethanol).

(b) Travelers to endemic areas within 2 weeks:

1) Are older than 40 years,
2) Are immunocompromised, or
3) Have chronic liver disease or other chronic medical conditions

– Dose:

- Travel for < 3months, IGIM 0.02 mL/kg
- Travel for 5 months, IGIM 0.06 mL/kg
- Travel for longer than 5 months, repeat IGIM

Hepatitis A Prevention

- **Postexposure Prophylaxis**
  - Individuals in contact with people infected with acute HAV
    - Including household and sexual partners,
    - Staff and children from daycare facilities, and
    - Food handlers of restaurant establishments
  - IGIM 0.02 mL/kg is given **within 2 weeks** of being exposed to the HAV
  - The risk of infection may be decreased by 90%

Hepatitis A Prevention

Hepatitis A Vaccine

- To provide pre and postexposure prophylaxis against clinical hepatitis A infections
  - Given in two injections 6 months apart (referred to as months 0 and 6)
- **Preexposure prophylaxis**: for travelers to endemic hepatitis A countries.
- **Postexposure prophylaxis**: administered within 14 days after exposure.

Product	Age (years)	Dose (Units)	Volume (mL)	No. of doses	Schedule (months)
VAQTA	1 – 18	25	0.5	2	0, 6-18
	≥ 19	50	1	2	0, 6
HAVRIX	1 – 18	720	0.5	2	0, 6-12
	≥ 19	1440	1	2	0, 6-12

Hepatitis B Prevention

- Avoiding contaminated blood products or participating in high-risk behavior such as IV drug use.
- Those at high risk of acquiring the HBV should be vaccinated with the hepatitis B vaccine
- Universal hepatitis B vaccinations to all newborns
- Postexposure prophylaxis with hepatitis B immune globulin (HBIG)

Hepatitis B Prevention

Hepatitis B Immune Globulin (HBIG)

- Containing antibodies prepared from pooled human plasma that has a high concentration of anti-HBs
- Provides passive immunization for postexposure prophylaxis against HBV.
- A single dose of HBIG 0.06 mL/kg IM is effective in preventing chronic hepatitis B infections in adults
- Within 24 hours of exposure

Hepatitis B Prevention

Hepatitis B Vaccine

- The two vaccines available are: **Recombivax HB** and **EngerixB**
- Persons at high risk of acquiring the hepatitis B virus should be vaccinated with the hepatitis B vaccine
- The vaccine is indicated after exposure to prevent CHB
  - Accidental needle-stick, sexual contacts, or IV drug use
  - Within 24 hours of exposure
- Postexposure prophylaxis for perinatal exposure
  - For mothers who are HBsAg positive, newborns should be immunized within 12 to 24 hours after birth with the hepatitis B vaccine and HBIG 0.5 mL.
  - If the mother is HBsAg negative, the newborn should receive only the hepatitis B vaccine

Hepatitis B Prevention

Hepatitis B Vaccine

- Dosing Regimens for Hepatitis B

Product	Patient category	Dose (mcg)	Volume (mL)	No. of Doses	Schedule (months)
Recombivax HB	0 – 19	5	0.5	3	0, 1, 6
	≥20	10	1	3	0, 1, 6
Engerix-B	0 -19	10	0.5	3	0, 1, 6
	≥20	20	1	3	0, 1, 6

Hepatitis B Prevention

- Post Exposure Prophylaxis to the

Vaccination Status	Treatment to Administer
Unvaccinated	HBIG × 1 and initiate HB vaccine series
Previously vaccinated	Administer HB vaccine booster dose

Hepatitis B Prevention

Hepatitis B Prophylaxis to Prevent Perinatal Transmission

Treatment	Mother's HBsAg Status	
	Positive	Negative
HBIG (0.5 mL IM)	within 12 hours of birth	None
	P L U S	
Hepatitis B vaccine		
Dose 1	Within 12 hours of birth	Within 12 hours of birth
Dose 2	At month 1–2	At month 1–2
Dose 3	At month 6	At month 6

Chronic Hepatitis B Treatment

- Patients with HBeAg-positive CHB with persistently elevated ALT (>2X ULN) and elevated HBV DNA levels greater than 20,000 IU/mL.
- The drug of choice for CHB depends on
  - The patient's past medical history,
  - ALT, HBV DNA level,
  - HBeAg status,
  - Severity of liver disease, and
  - History of previous HBV therapy.
- Approved agents for the treatment of HBV: two interferons and five nucleoside/nucleotide

Chronic Hepatitis B Treatment

- **Entecavir**, **tenofovir** and **Pegylated interferon α_{2a}** are recommended as first line due to profound HBV DNA suppression and minimal resistance.
- **Adefovir** is second line to tenofovir because the drug is **less potent** in suppressing hepatitis B viral replication in treatment naive patients.
- **Lamivudine** is no longer recommended as first-line therapy due to a high rate of resistance

Chronic Hepatitis B Treatment

Interferon and Pegylated Interferon

- Pegylated interferon is interferon attached to a **polyethylene glycol** molecule that increases the half-life of the drug,
  - Allowing once weekly dosing versus thrice weekly administration of unmodified interferon
- Pegylated interferon is well tolerated with similar or better efficacy than unmodified interferon
- Dose: 180 mcg subcutaneously once weekly for 48 weeks.
- Advantages:
  - Finite duration of treatment
  - Lack of resistance, and
  - Possible HBsAg loss or seroconversion (development of anti-HBs),

Chronic Hepatitis B Treatment

- Disadvantages
  - Need for subcutaneous injections and
  - A pronounced adverse effect profile
    - May require dosage reductions or treatment discontinuation
    - Flulike symptoms (fevers, chills, rigors, and myalgias)
    - Irritability, depression, and, rarely, suicidal ideation.
  - 35% of patients develop an ALT flare when treated with interferon

Chronic Hepatitis B Treatment

Entecavir

- Entecavir is a guanosine nucleoside analog that is highly effective in suppressing HBV DNA polymerase.
- Dose: **0.5mg** once daily for patients with ***compensated*** liver disease and ***naive to lamivudine*** therapy.
  - ➲Higher dose of entecavir at **1mg** once daily is recommended for **lamivudine** or **telbivudine** resistance or **decompensated** liver disease.
- Entecavir should be given on an empty stomach.
- Monotherapy should not be recommended for patients coinfected with HIV and HBV

Chronic Hepatitis B Treatment

Tenofovir Disoproxil Fumarate

- Reverse transcriptase inhibitor
- Inhibits HIV and hepatitis B viral replication
- Indicated for HBeAg positive and HBeAg negative CHB and HIV when prescribed with other HAART therapies.
- Dose: of **tenofovir is 300 mg** orally once daily taken on an empty stomach.

Chronic Hepatitis B Treatment

Adefovir

- Inhibits DNA polymerase
- Developing cross resistance when switching from adefovir to tenofovir
- Dose: 10 mg once daily
- Side effects: asthenia, abdominal pain, diarrhea, dyspepsia, headaches, nausea, and flatulence.
  - Nephrotoxicity: Monitor SCr at baseline and Q 3 months

Chronic Hepatitis B Treatment

Lamivudine

- Antiviral effects against HIV and hepatitis B virus.
- Prolonged therapy (up to 5 years) may be needed to sustain seroconversion, but this leads to 3TC resistance as high as 60% to 70% at 5 years
- Dose: **100 mg orally once daily** for treatment of CHB without HIV coinfections.

Hepatitis C Prevention

- Risk of acquiring HCV is minimized by avoiding
  - Contaminated blood products and
  - High risk behaviors such as sharing needles among IV drug users.
- No vaccines are available for preventing hepatitis C

Chronic Hepatitis C Treatment

- Treatment for chronic hepatitis C depends on the patient's past medical history, previous HCV treatment history, severity of liver disease, and HCV genotype.
- Individuals with genotype 2 or 3 achieve a higher SVR than patients with genotype 1.
- **Pegylated interferon** plus **ribavirin** is the regimen of choice for chronic hepatitis C
- Treatment duration is 24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1.
- Dose: SC
  - ➲Pegylated interferon-α_{2a} is 180 mcg once weekly,
  - ➲Pegylated interferon-α_{2b} is 1.5 mcg/kg/week,
  - ➲Ribavirin: 15 mg/kg (in 2 divided daily doses)

Outcome Evaluation

Hepatitis B

- ALT: at baseline and Q 3 months
- HBV DNA: Q 3 to 6 months
- HBeAg, anti-HBe, HBsAg, ant-HBs: Q 3 to 6 months
- Once anti-HBe appears, **complete an additional 6 months of hepatitis B therapy**.
- Continue treatment in patients with HBeAg negative CHB until HBsAg is lost.
- Pegylated interferon therapy: CBC, TSH, lipid panel Q 4wks
- TDF and Adefovir: SCr Q 12wks

Outcome Evaluation

Hepatitis C

- SVR, undetectable HCV RNA level at 6 months posttreatment; ultimate goal
- HCV RNA level at week 12 of therapy
- Pegylated interferon and ribavirin: CBC

CIRRHOSIS

Objectives

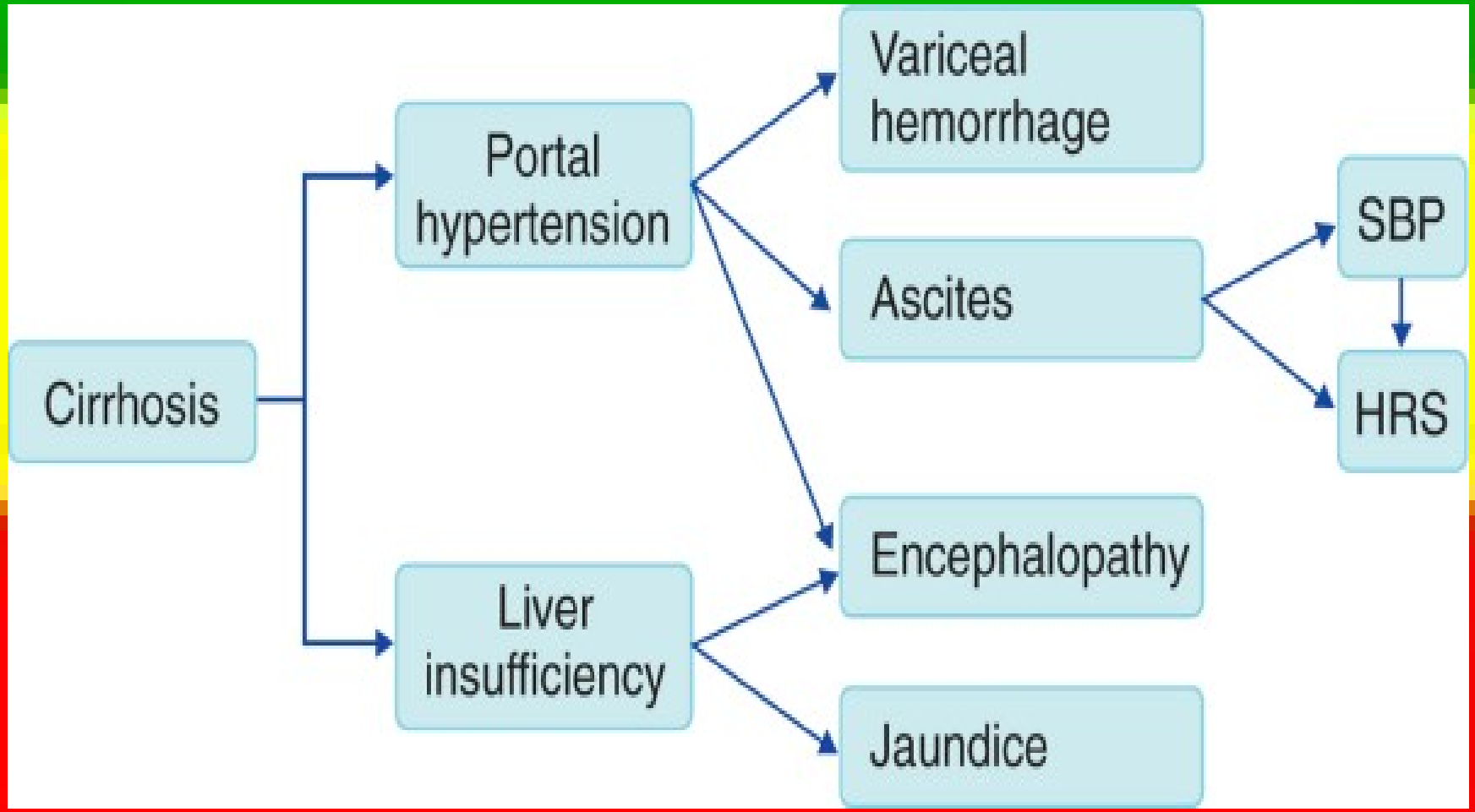
Upon completion of this session, you will be able to

1. Explain the pathophysiology of cirrhosis and portal hypertension.
2. Identify signs and symptoms of cirrhosis & com. in a given patient.
3. Identify laboratory abnormalities that result from cirrhosis & com and describe the pathophysiology of each abnormality.
4. Describe the consequences associated with decreased hepatic function.
5. Create treatment goals for a patient with portal hypertension and its complications.
6. Recommend a specific treatment regimen for a patient with cirrhosis

Introduction

- Cirrhosis is the progressive replacement of normal hepatic cells with **fibrous scar tissue**.
  - This scarring is accompanied by the loss of viable hepatocytes, which are the functional cells of the liver
- Cirrhosis is **irreversible** and leads to portal hypertension, which is in turn responsible for many of the complications of advanced liver disease.
- Cirrhotic complications include
  - Ascites,
  - Spontaneous bacterial peritonitis (SBP),
  - Hepatic encephalopathy (HE),
  - Hepatorenal syndrome(HRS), and
  - Variceal bleeding

Introduction



EPIDEMIOLOGY AND ETIOLOGY

- In patients between the ages of 25 and 64 years, damage from **excessive alcohol** use accounted for over one-half of the deaths.
- **Hepatitis B** accounts for the majority of cases worldwide.
- **Alcoholic cirrhosis** can develop with as little as 2 to 3 drinks per day in women and 3 to 4 drinks per day in men
- A **standard drink** (14 g of ethanol) is equivalent to 45 mL of hard liquor, 150 mL of wine, or a 360-mL beer.

EPIDEMIOLOGY AND ETIOLOGY

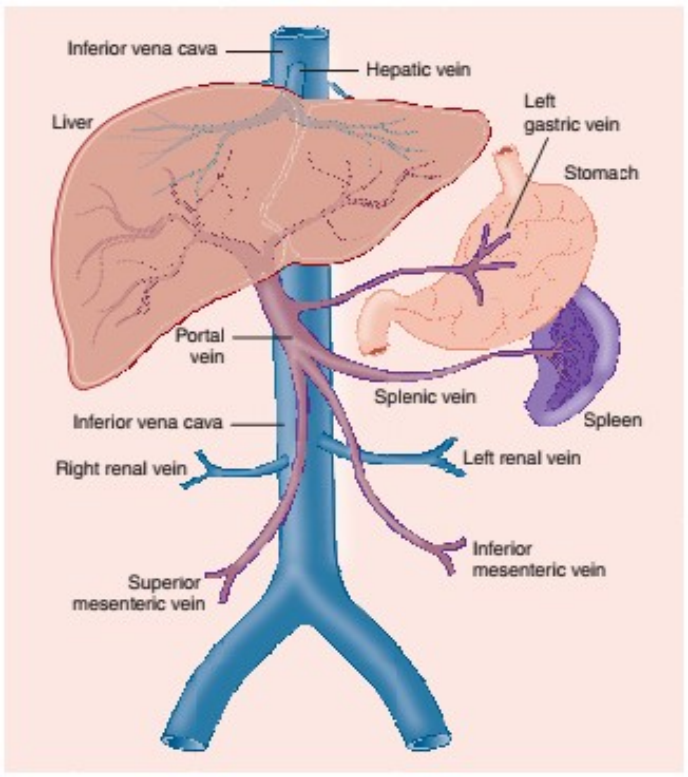
- With equivalent alcohol intake; **women usually develop cirrhosis more quickly than men.**
- Differences in alcohol metabolism may account for this gender disparity;
  - Women metabolize less alcohol in the GI tract;
    - This allows delivery of more ethanol (which is directly hepatotoxic) to the liver.
- Chronic infection with hepatitis B or C can lead to cirrhosis.

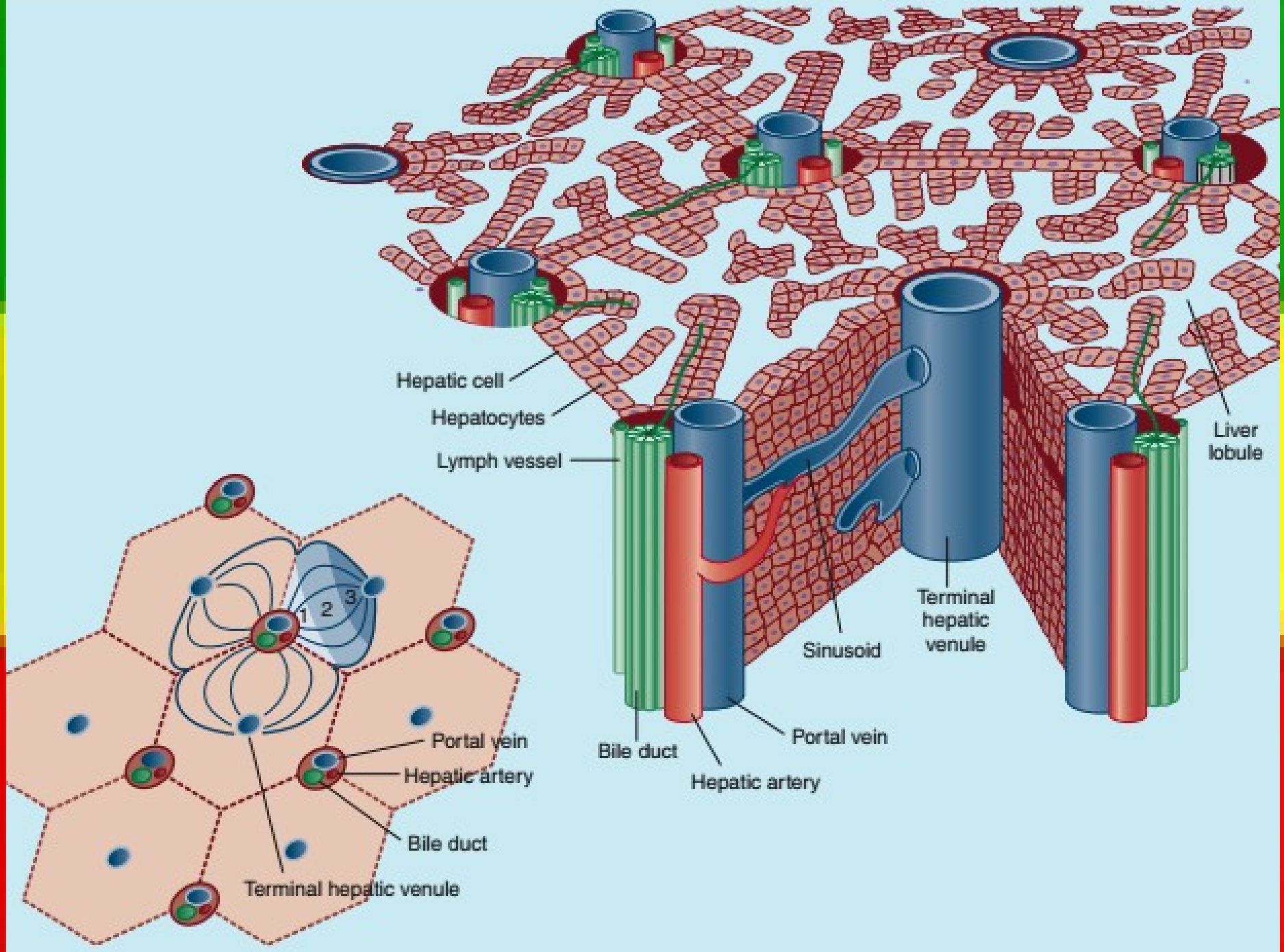
Portal Hypertension

- The **portal vein** is the primary vessel leading into the liver;
  - It receives deoxygenated venous blood from the splanchnic bed (intestines, stomach, pancreas, and spleen).
- Portal flow accounts for approximately 75% of blood delivered to the liver (approximately 1 to 1.5 L/min in noncirrhotics).
- The hepatic artery provides the remaining 25% in the form of oxygenated blood from the abdominal aorta.
- Normal portal vein pressure is **5 to 10 mm Hg**;
- Portal hypertension occurs when portal pressure exceeds 10 to 12 mm Hg.

Portal Hypertension

- Portal hypertension is a consequence of increased resistance to blood flow through the portal vein
- Intrahepatic (sinusoidal damage) cirrhosis
- Prehepatic **(**presinusoidal**):** porta vein occlusion from trauma, malignancy, or thrombosis.
- Posthepatic: outflow obstruction of the hepatic vein.




Hepatic cell
Hepatocytes
Lymph vessel
Liver lobule
Terminal hepatic venule
Sinusoid
Portal vein
Bile duct
Hepatic artery
1
2
3
Portal vein
Hepatic artery
Bile duct
Terminal hepatic venule

Portal Hypertension

Increased intrahepatic resistance to portal flow increases pressure on the entire splanchnic bed.

Portal hypertension mediates systemic and splanchnic **arterial vasodilation** through production of **nitric oxide** and other vasodilators in an attempt to counteract the increased pressure gradient.

NO causes a fall in systemic arterial pressure; this drop in pressure activates the **RAAS** and the **sympathetic nervous system**, and increases **antidiuretic hormone** (vasopressin) production.

Maintain arterial blood pressure and renal blood flow by increasing sodium and water retention.

Excess sodium and water retention put increased pressure on the vascular system.

Ascites

Ascites is the accumulation of fluid in the peritoneal space.

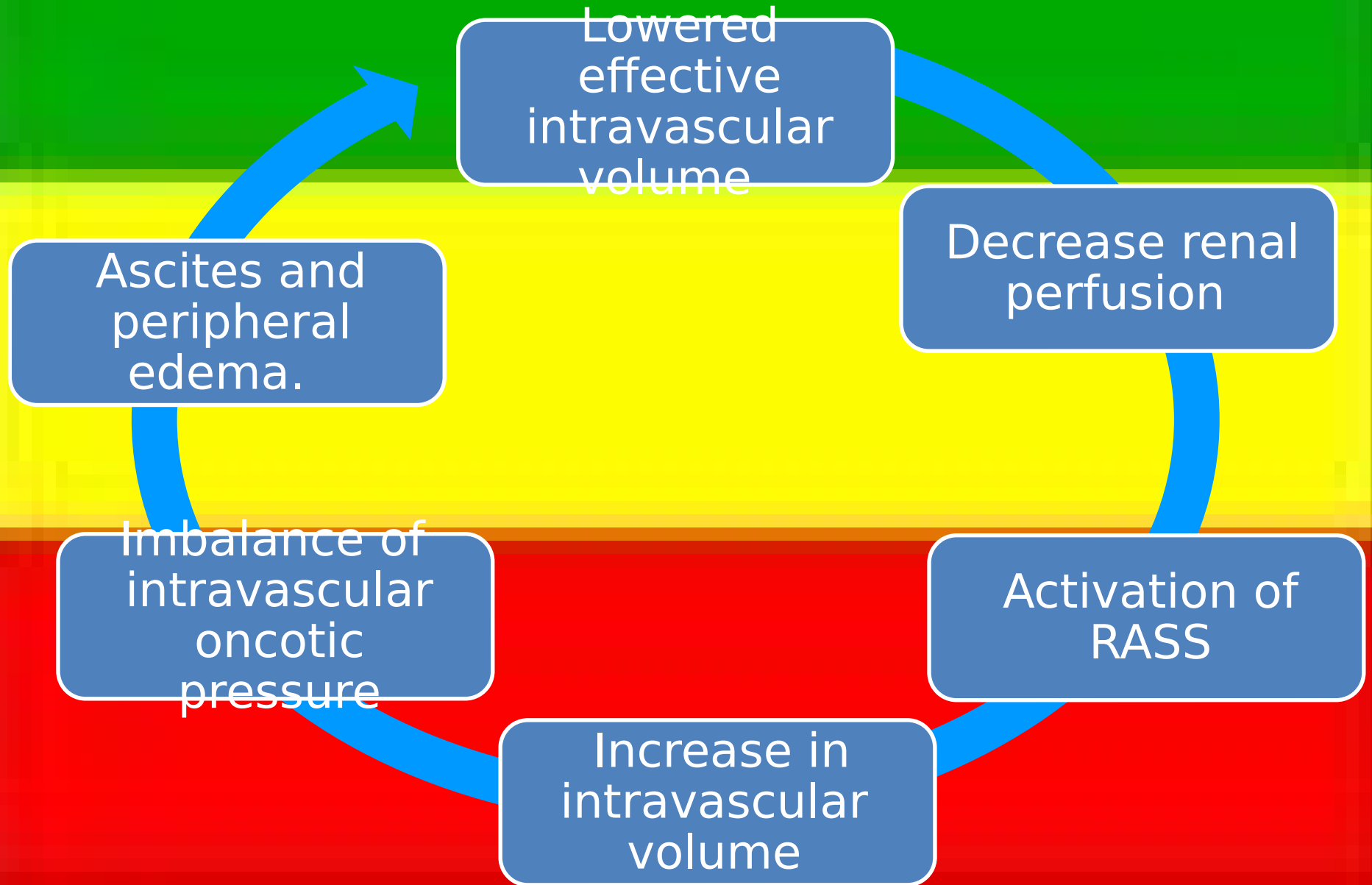
Cirrhotic changes and subsequent decreases in synthetic function lead to decreased albumin production (**hypoalbuminemia**).

↓Oncotic pressure (Albumin is the primary intravascular protein responsible for maintaining oncotic pressure within the vascular system)

↓Serum albumin, ↑hydrostatic pressure, ↑capillary permeability, obstruction of hepatic sinusoids and hepatic lymph nodes allow fluid to leak from the vascular space into body tissues.

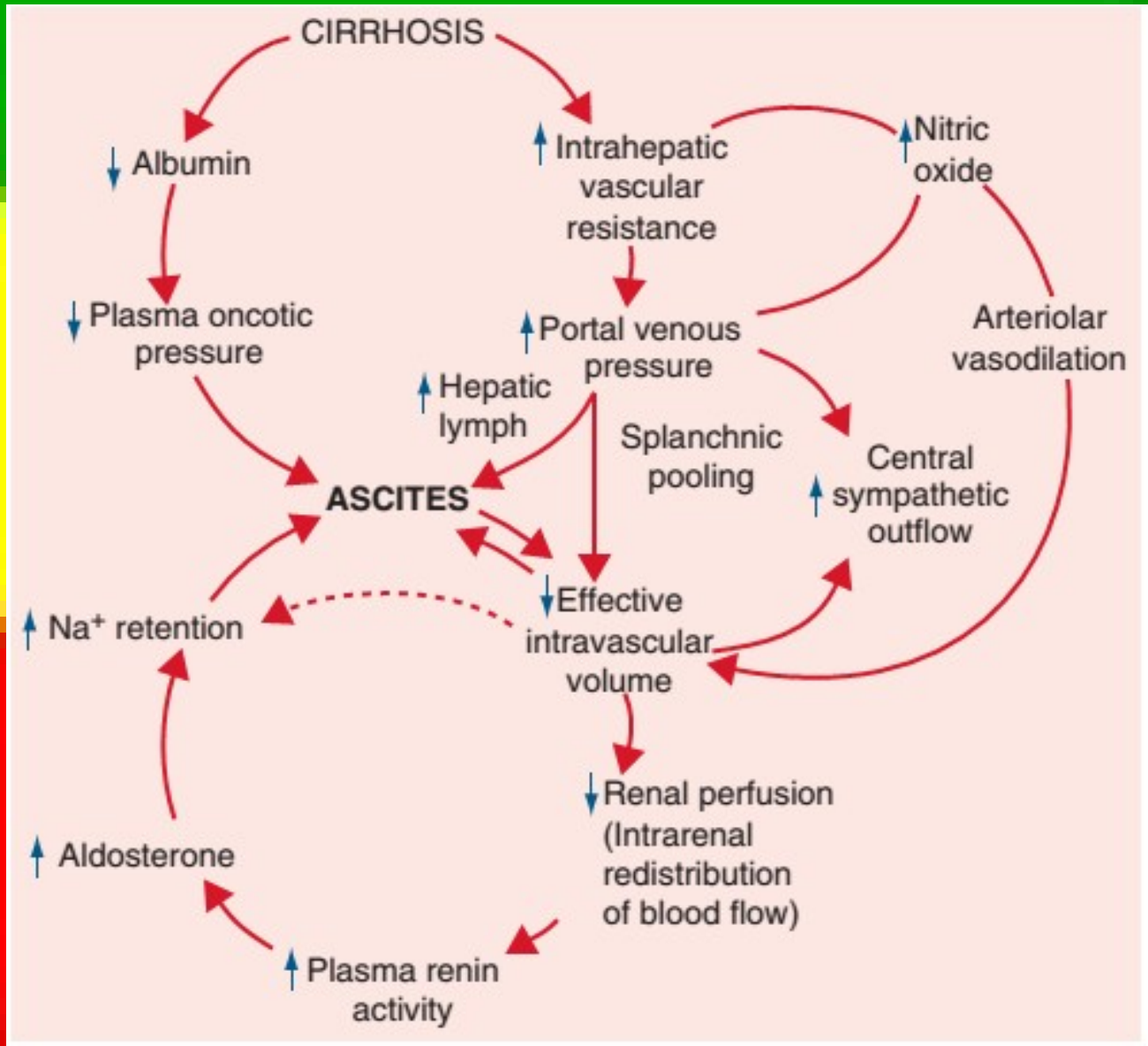
Ascites, peripheral edema, and fluid in the pulmonary system.

Loop of Ascites



Cirrhosis, Portal Hypertension and Ascites

The pathophysiology of ascites, portal hypertension, and cirrhosis are interrelated



Hepatorenal Syndrome

- Hepatorenal syndrome is a decline renal function in the setting of cirrhosis that is not caused by intrinsic renal disease
- Due to:
  - Renal artery vasoconstriction (by the sympathetic nervous system) and
  - Decreased mean arterial pressure (by nitric oxide)
- The kidneys attempt to counteract this drop in renal perfusion through RAAS
  - Renin stimulates fluid retention and peripheral vasoconstriction => increase renal blood flow
- Prostaglandin E and prostacyclin production are increased to stimulate **renal vasodilation**.

Hepatorenal Syndrome

- SCr and blood urea nitrogen (BUN) tend to be low in cirrhotic patients secondary to
  - Reduced muscle mass and
  - Decreased hepatic urea production.
  - Small changes may represent large changes in renal function.

Varices

- The splanchnic system drains venous blood from the GI tract to the liver.
- In portal hypertension, there is increased resistance to drainage from the originating organ,
  - So collateral vessels (varices) develop in the esophagus, stomach, and rectum to compensate for the increased blood volume.
- Varices are weak superficial vessels; any additional increase in pressure can cause them to rupture and bleed

Spontaneous Bacterial Peritonitis

- SBP is an acute bacterial infection of peritoneal (ascitic) fluid in the absence of intra-abdominal infection or intestinal perforation
  - From 10% to 30% of ascites patients
- Translocation of intestinal bacteria to mesenteric lymph nodes, which then seed the ascitic fluid
  - **Delay in intestinal transit time** and increased intestinal wall **permeability**
- Hematogenous spread of bacteria into the peritoneal space
- Low protein is correlated to low antibacterial activity

Spontaneous Bacterial Peritonitis

- Enteric gram-negative aerobes are the most common bacteria isolated from ascitic fluid, usually
  - Escherichia coli or
  - Klebsiella pneumoniae.
- Streptococcus pneumonia is the most common gram-positive pathogen
- SBP is rarely polymicrobial

Hepatic Encephalopathy

- In severe hepatic disease, systemic circulation bypasses the liver;
- So many substances normally metabolized by the liver remain in the systemic circulation and accumulate.
- In excess, these metabolic byproducts, especially nitrogenous waste, cause alterations in CNS functioning
- Ammonia (NH_3):
  - Metabolic by-product of protein catabolism;
  - It is also generated by bacteria in the GI tract
- Normal liver: hepatocytes degrade ammonia to form urea,
- In cirrhosis, the conversion to urea is retarded and NH_3 accumulates => HE
- Patients with HE commonly have elevated serum [NH_3]

Hepatic Encephalopathy

- High levels of false neurotransmitters
  - Aromatic amino acids,
  - γ-aminobutyric acid, and
  - Endogenous benzodiazepines
- Decreased cognition, confusion, and changes in behavior

Bleeding and Synthetic Failure

- The liver produces procoagulation and anticoagulant factors essential for blood clotting and maintenance of blood homeostasis.
  - In advanced disease: extended clotting times (e.g., prothrombin time) and bleeding irregularities
- **Thrombocytopenia**: decreased platelet production in the bone marrow (triggered by a lack of **thrombopoietin** stimulation by the liver)
- **Macrocytic anemia** occurs because of decreased intake, metabolism, and storage of **folate** and **vitamin B_{12}**

CLINICAL PRESENTATION

Symptoms

- Patients with cirrhosis may be asymptomatic until acute complications develop
- **Nonspecific symptoms**: anorexia, fatigue, weakness, and changes in libido and sleep patterns
- **Easy bruising** and may **bleed** from minor injuries
- **Pruritus**, particularly with biliary involvement.
- **Ascites**: abdominal pain, nausea, increasing tightness and fullness in the abdomen, shortness of breath, and early satiety.

CLINICAL PRESENTATION

Symptoms

- **Esophageal or gastric varices:**
  - Melena, pallor, fatigue, and weakness from blood loss
  - Nausea, vomiting, and hematemesis
  - **Digestion of swallowed blood represents a high protein load precipitate symptoms of HE**
- **HE**: disruption of sleep patterns and day-to-night inversion; patients have delayed bedtime and wake times
- **SBP**: fever, chills, abdominal pain, and mental status changes

CLINICAL PRESENTATION

Signs

- **Nonspecific signs on PE:**
  - Jaundice, scleral icterus, tea-colored urine, bruising, hepatomegaly, splenomegaly, palmar erythema, gynecomastia, and testicular atrophy
- **Ascites**: shifting dullness and a fluid wave
- **Variceal bleeding**: pallor, hypotension, tachycardia, mental status changes, and hematemesis
- **HE**: decreased cognition, confusion, changes in behavior, and asterixis
- **SBP**: fever, painful tympanic abdomen, and changes in mental status.

Diagnosis

Cihrrosis

- Liver biopsy
- Ultrasound and computed tomography

Ascites & SBP

- Ultrasound for obese patients or small fluid
- Analysis of ascitic fluid (paracentesis)
  - CBC with differential
  - Albumin, total protein,
  - Gram stain, and bacterial cultures
  - Serum ascites-albumin gradient (SAAG)
    - $Alb_{serum} - Alb_{ascites} = SAAG$
    - ≥1.1 g/dL, portal hypertension as the cause of the ascites

Diagnosis

HE

- Increased blood ammonia concentration

Hepatorenal syndrome

- Increased serum creatinine

TREATMENT

- Cirrhosis is irreversible; treatments are directed at limiting disease progression and minimizing complications.

Desired Outcomes

- Immediate treatment goals:
  - To stabilize acute complications such as variceal bleeding and prevent SBP
- Preventing complications and further liver damage

Nonpharmacologic Therapy

- Lifestyle modifications can limit disease complications and slow further liver damage
  - Cessation of **alcohol** use
  - Patients with ascites require **dietary sodium restriction**
  - **Medication** use must be monitored carefully for potential **hepatotoxicity**.
  - During episodes of acute HE, temporary **protein restriction** to decrease ammonia production
- For variceal bleeding, ***nasogastric*** (***NG***) ***suction*** reduces the risk of aspirating stomach contents
- Endoscopic ***band ligation*** (application of a stricture around the varix) is used to stop bleeding varices

Nonpharmacologic Therapy

- **Hepatitis A and B vaccination** is recommended in patients with cirrhosis to prevent additional liver damage from an acute viral infection.
- **Pneumococcal** and **influenza vaccination** may also be appropriate and can reduce hospitalizations.

Pharmacologic Therapy

Portal Hypertension

- Nonselective β-blockers such as **propranolol** and **nadolol** are first-line treatments to reduce portal hypertension

Pharmacologic Therapy

Ascites

- Therapeutic paracentesis: 1to 2 L of ascitic fluid
- Diuretics: spironolactone is an aldosterone antagonist and counteracts the effects of activation of the RAAS
  - In hepatic disease, not only is aldosterone production increased, but its half-life is prolonged because of decreased hepatic metabolism
- **Spironolactone** is typically used with a loop diuretic (**furosemide**) for more potent diuresis
- A ratio of 40 mg furosemide to each 100 mg spironolactone
- Doses should be titrated at intervals no more frequent than every 2 to 3 days.

Pharmacologic Therapy

Varices

- Octreotide
  - Is a synthetic somatostatin analog;
  - It causes selective vasoconstriction of the splanchnic bed
  - Decrease splanchnic arterial blood flow
  - Decreasing portal venous pressure
  - Dose: 50- to 100-mcg IV loading dose followed by a 25 to 50 mcg/h continuous IV infusion
  - Continue for at least 24 to 72 hours after bleeding has stopped

Pharmacologic Therapy

SBP

- **Prophylactic antibiotic therapy** is recommended during acute variceal bleeding to prevent SBP
  - A third-generation cephalosporin (1g IV ceftriaxone daily) or
  - A fluoroquinolone (norfloxacin 400 mg orally twice daily, ciprofloxacin 500 mg orally twice daily, or ciprofloxacin 400 mg IV twice daily) for 7 days.
- **Empiric antibiotic therapy**
  - IV third-generation cephalosporin (cefotaxime 2 g every 8hours, ceftriaxone 1 g every 24 hours),
  - An IV extended-spectrum penicillin (piperacillin-tazobactam 3.375 g every 6 hours or 4.5 g every 8 hours), or
  - An IV fluoroquinolone (ciprofloxacin 400 mg IV every 12 hours;

Pharmacologic Therapy

SBP

- **Long-term antibiotic prophylaxis** for SBP
- Indications:
  - A history of SBP and low-protein ascites (ascitic fluid albumin <1.5 g/dL) plus one of the following:
    - SCr 1.5 mg/dL or greater, BUN 25 mg/dL or greater,
    - Serum sodium 130 mEq/L or less, or
    - Child–Pugh score of at least 9, with bilirubin of at least 3 mg/dL.
- Recommended oral regimens
  - Trimethoprim-sulfamethoxazole double-strength tablet daily, or
  - Norfloxacin 400 mg daily, or
  - Ciprofloxacin 750 mg daily.

Child-Pugh Classification of the Severity of Cirrhosis

Variable	Score		
	1 Point	2 Points	3 Points
Encephalopathy	Absent	Mild-moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/L)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds above normal)	1–4	4–6	> 6

Class A = total score of 5 or 6;
Class B = total score of 7–9;
Class C = total score of 10 or more

Pharmacologic Therapy

Encephalopathy

- **Lactulose**

- It is a nondigestible synthetic disaccharide **laxative** that is hydrolyzed in the gut to an osmotically active compound that draws water into the colon and stimulates defecation.
- Lactulose **lowers colonic pH**, which favors the conversion of ammonia (NH_3) to ammonium (NH_4^+).
- Ammonium is ionic and cannot cross back from the gut into systemic circulation; it is eliminated in the feces.
- Lactulose is usually initiated at 15 to 30 mL two to three times per day

Pancreatitis

Pancreatitis

- The pancreas is a gland in the abdomen lying in the curvature of the stomach as it empties into the duodenum
- It functions:
  - Exocrine gland: Amylase, lipase, proteolytic enzymes
  - Endocrine

Acute pancreatitis

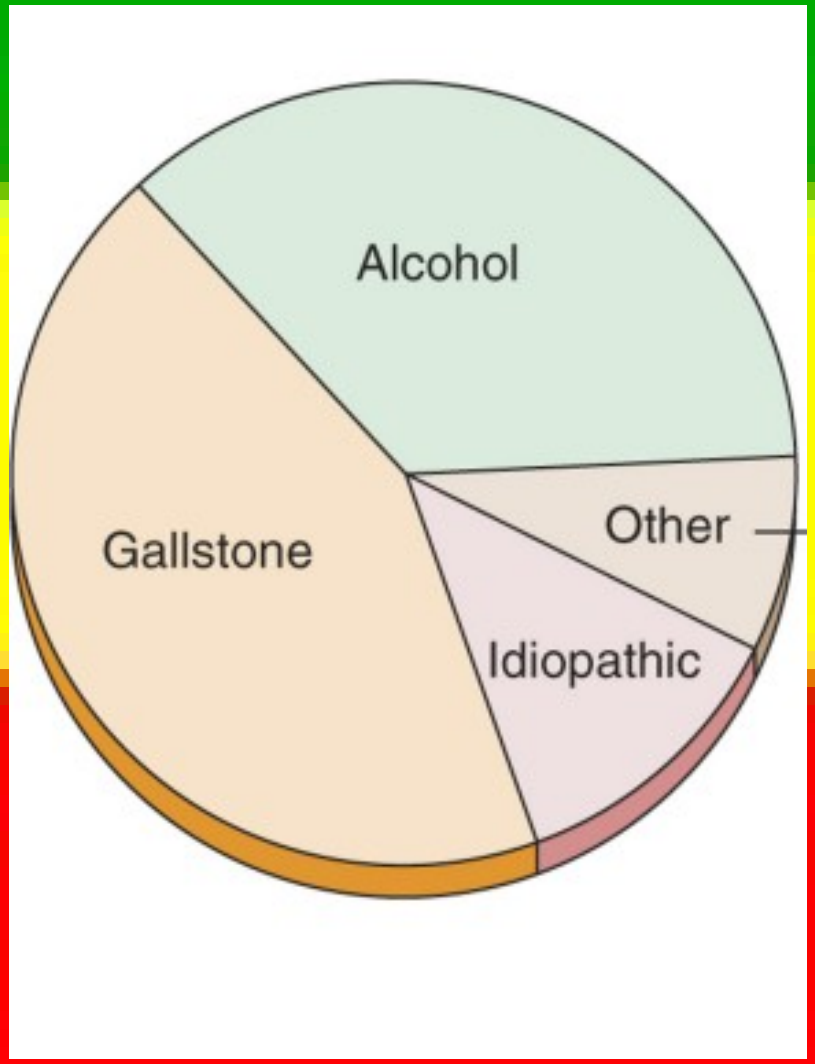
- Acute pancreatitis is characterized by a discrete episode of abdominal pain and elevated serum amylase and lipase levels.
- In contrast to chronic pancreatitis, which is characterized by **changes in pancreatic structure and by persistence of dysfunction even after the precipitating cause has been corrected**, acute pancreatitis is distinguished by complete restitution of the pancreas both morphologically and functionally after the derangements that precipitated the attack have been corrected

Acute Pancreatitis

Causes:

- Gallstones the leading cause (30% to 40%)
- Ethanol use is the second most important cause: 30%
- Other common causes
  - Hypertriglyceridemia,
  - Endoscopic retrograde cholangiopancreatography (ERCP),
  - Pregnancy, and
  - Autodigestion due to early activation of pancreatic enzymes

Acute Pancreatitis



Pathophysiology

- **Alcohol**: chronic inflammation and fibrosis loss of exocrine function
- **Gallstones**: obstruct the ampulla of Vater pancreatic enzymes or bile to move in a retrograde fashion into the pancreas
- Autolysis of the pancreas can occur when zymogens are activated in the pancreas before being released into the duodenum.

Clinical Presentation

- **Signs and Symptoms**
  - Sudden upper abdominal pain
  - Pain may radiate to the back, and ecchymosis may be present in the flank and periumbilical areas.
  - Nausea and vomiting are other common symptoms.
  - Tachycardia, hypotension, fever, and abdominal distention may be present

Labs

- The serum amylase may be elevated to >3x ULN (with in 12 hrs onset).
- Serum lipase rises within 4 to 8 hours of onset
- Other: WBC, hyperglycemia, hypocalcemia, hyperbilirubinemia, elevated LDH, and hypertriglyceridemia.

TREATMENT

- Goals of Therapy

(a)Resolution of nausea, vomiting, abdominal pain, and fever;

(b)Ability to tolerate oral intake;

(c)Normalization of serum amylase, lipase, and WBC

(d)Resolution of abscess, pseudocyst, or fluid collection as measured by CT scan.

Non pharmacologic

- Therapy of acute pancreatitis is primarily supportive unless a specific etiology is identified.
- Supportive therapy involves
  - Fluid repletion,
  - Nutrition support, and
  - Analgesia
- Electrolytes such as potassium and magnesium may be added to the infusions if necessary.
- **Hyperglycemia** can be managed with insulin-containing IV infusions.
- In severe pancreatitis, **enteral nutrition**: nasogastric or nasojejunal feedings

Pharmacologic Therapy

- **Analgesics**
  - Meperidine: first line
  - Alternatives: hydromorphone, morphine, and fentany
- **Antibiotics**
  - For **necrotizing pancreatitis**
  - Not indicated if mild disease or a known noninfectious cause.

Antimicrobial regimen for Pancreatic necrosis

Drug	Usual dose	Notes
Meropenem	1gm Q8hrs	
Piperacillin/ tazobactam	3.375 – 4.5gm Q6-8hrs	
Cefepime + metronidazole	2gm Q12hr + 500mg Q8 -12hrs	
Aztreonam + vancomycin +metronidazole	1 g every 8 hours + 15 mg/kg every 8–12 hours + 500 mg every 6 hours	For penicillin allergy

CHRONIC PANCREATITIS

- Chronic pancreatitis is an inflammatory disease of the pancreas characterized by the presence of permanent and progressive morphologic or functional damage to the pancreas.
- The most common cause of CP in adults in Western countries is ethanol abuse.
- Cigarette smoking is an independent risk factor for CP

Clinical Presentation

- Patients with chronic pancreatitis seek medical attention predominantly because of two symptoms:
  - Abdominal pain or mal-digestion.
- Weight lose
- **Diarrhea** and **steatorrhea** secondary to inadequate digestion of fats (lipase deficiency)
- **Osmotic diarrhea** secondary to diminished carbohydrate digestion (amylase deficiency)
- Maldigestion of proteins (protease deficiency)
- Even though maldigestion affects all nutrients the most clinically significant problem concerns maldigestion of fat and fat-soluble vitamins (A, D, E, and K).
- **Clinical diabetes** occurs relatively late in the disease

Treatment of Chronic Pancreatitis

Desired Outcomes

- The goals of pharmacotherapy for CP are:
  - Prevention and resolution of chronic abdominal pain and other sign and symptoms; and
  - Correction of dietary malabsorption with exogenous pancreatic enzymes.

Nonpharmacologic Therapy

- Lifestyle modifications are an important part of the therapy for chronic pancreatitis.
- Avoidance of ethanol and fatty meals can decrease the pain of chronic pancreatitis.

Pharmacotherapy of Chronic Pancreatitis

Analgesics

- Pain management is important component of therapy.
- Non-opioid analgesics are preferred, but the severe and persistent nature of the pain often requires opioid therapy.
- Patients can require chronic doses of opioid analgesics, with a resulting risk of addiction.

Pharmacotherapy of Chronic Pancreatitis

Pancreatic Enzymes

- Goal of pancreatic enzyme supplementation is to deliver exogenous enzyme to duodenum without causing further GI side effects from the medication.

- Supplementation with pancreatic enzymes may reduce the pain and fatty diarrhea.

Pharmacotherapy of Chronic Pancreatitis

- Common pancreatic enzyme supplements contain **lipase**, **amylase**, and **protease** in varying proportions.
- Dose can be tailored to patient's requirement for exogenous enzyme supplementation and response to therapy.
- At least 25,000 to 30,000 units of lipase per meal is necessary to provide adequate lipolysis
- Enzyme supplements should be taken immediately **prior** to meals to aid in the digestion and absorption of food.

Outcome Evaluation

- Monitor for adequate pain control and the need for escalation or de-escalation of analgesia.
- If pain relief is achieved by avoiding ethanol or fatty meals, encourage continuation of these practices.
- When dietary malabsorption exists, monitor patients for weight gain or loss, activity level, and ability to perform activities of daily living.
- Educate patients that compliance with and proper use of dietary pancreatic enzyme supplementation is key to improved outcomes.

Inflammatory Bowel Disease

Definition

- IBD encompasses ulcerative colitis (UC) and Crohn disease (CD).
- Both disorders are associated with acute and chronic inflammation of the GI tract.
- Differences exist between UC and CD with regard to
  - Regions of the GI tract that affected
  - Distribution and depth of intestinal inflammation.
- Patients with IBD may also develop inflammation

Epidemiology

- Inflammatory bowel disease is most prevalent in Western countries and in areas of northern latitude
- A higher incidence of IBD occurs in the Jewish population,
  - Black and Asian populations have a relatively lower incidence of IBD
- Both sexes are affected somewhat equally with IBD

Etiology

- The exact etiology of UC and CD is unknown;
  - Factors believed responsible for both conditions:
    - Infectious
    - Genetic
    - Environmental
    - Immunologic factors.

Infectious Factors

- Microorganisms are proposed to be a major factor in the initiation of inflammation in IBD.
- The presence of more **proinflammatory** bacteria in the GI tract, often referred to as dysbiosis.
- Patients with IBD have an **increased density** of intestinal microbiotica compared with those without IBD
- The development and composition of the intestinal microbiotica may be influenced by **dietary factors**.
- The pathogenesis of IBD may involve a **loss of tolerance** toward normal GI bacterial flora.

Genetic Factors

- Studies of monozygotic twins demonstrate a high concordance rate of IBD in both individuals (particularly CD).
- First-degree relatives of patients with IBD may have up to a 20-fold increase in the risk of disease

Immunologic Mechanisms

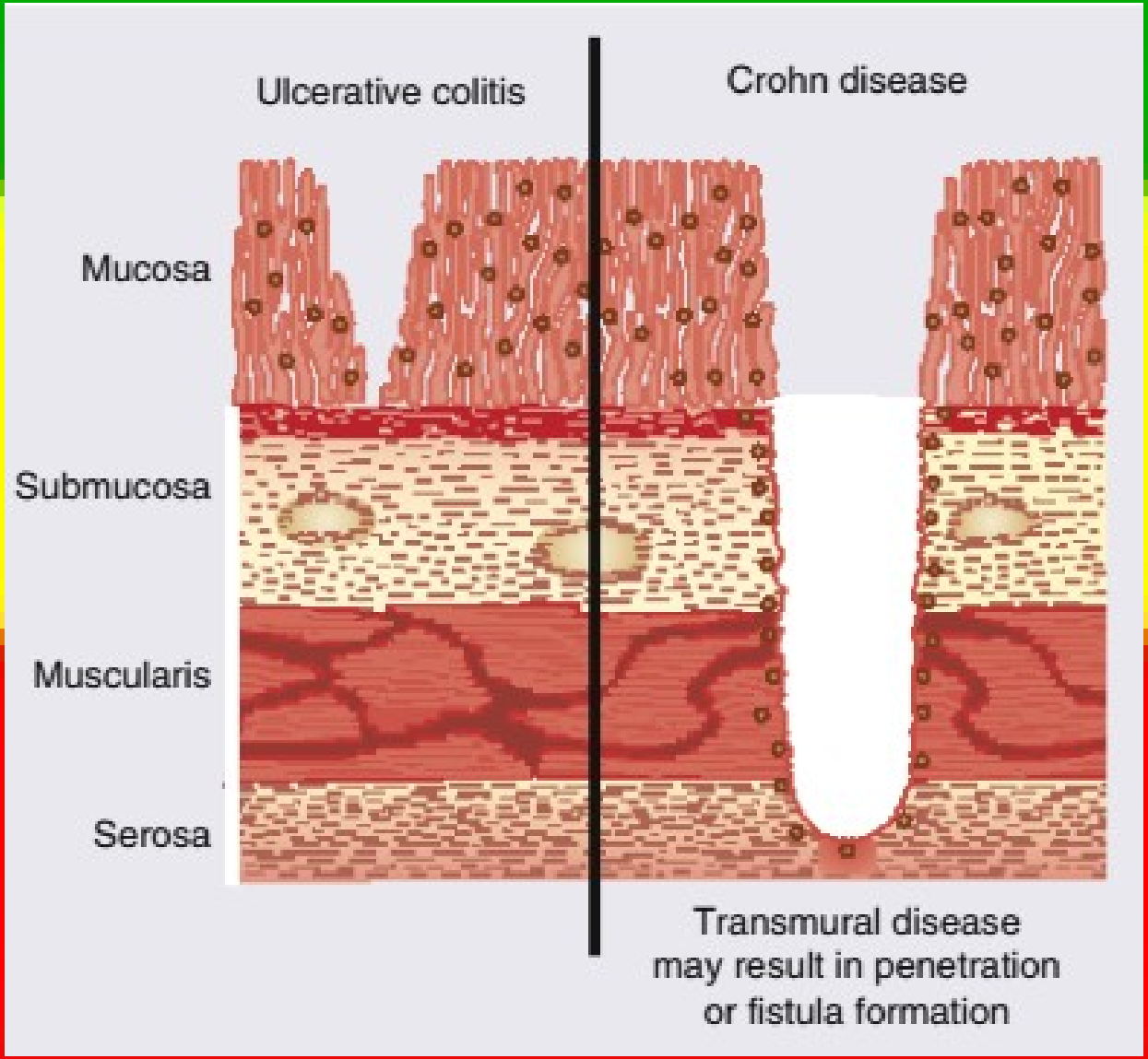
- The innate immune system largely involves the intestinal wall epithelial barrier and its associated secretions in response to contact with organisms.
- NOD proteins (for recognition of organisms) and toll-like membrane receptors (TLRs) are involved in
  - Intestinal **surveillance** and
  - Release of antibacterial peptides such as defensins
- Reduction in defensin secretion is thought to be one contributing factor in the loss of effective barrier function.
- Consequently, the bowel wall in CD is infiltrated with lymphocytes, plasma cells, mast cells, macrophages, and neutrophils, often leading to formation of granulomas

Lifestyle, Dietary, and Drug-Related Causes

- Intake of refined sugars has been associated with development of CD, while increased protein intake has been associated with a higher risk of developing IBD.
- Diet composition may directly influence the makeup of the gut microbiotica, possibly triggering IBD.
- The “hygiene hypothesis” proposes that cleaner conditions in more industrialized countries expose patients to fewer microorganisms at an early age.
- The immune response to these organisms is altered when encountered later in life.
- Diets low in fruits & vegetables and high in ω-6 polyunsaturated fats have been suggested to increase the risk of CD
- Smoking, NSAIDs, antibiotics

Pathophysiology

- UC and CD differ in two general respects:
  - Extent and distribution of inflammation within the GI tract
  - Depth of involvement within the bowel wall


Ulcerative colitis
Crohn disease
Mucosa
Submucosa
Muscularis
Serosa
Transmural disease
may result in penetration
or fistula formation

Ulcerative Colitis

- UC is confined to the **rectum** and **colon**
- Affects the mucosal and the submucosal layers.
- The deeper longitudinal muscular layers, serosa, and regional lymph nodes are not usually involved.
- Fistula, perforation, or obstruction is uncommon because this is a superficial inflammation.
- Complications of UC may be local, including hemorrhoids, anal fissures, or perirectal abscesses
- Toxic megacolon: colonic distension of >6 cm, 7.9% of UC patients, death rates of up to 50%

Crohn's Disease

- CD is characterized as a transmural inflammatory process.
- The **terminal ileum** is most common site of the disorder,
  - but it may occur in any part of the GI tract from mouth to anus.
- Ulcers are typically deep and elongated
- "Cobblestone" appearance of the bowel wall
- Complications: bowel stricture and obstruction, fistula formation, nutritional deficiencies



Clinical Presentation

- Presenting symptoms common to both diseases include
  - Fever,
  - Abdominal pain,
  - Diarrhea (may be bloody, watery, or mucopurulent),
  - Rectal bleeding, and
  - Weight loss.

Clinical Features of IBD

Clinical Findings	Ulcerative Colitis	Crohn Disease
Bowel involvement	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) occurs in a minority of patients	May be anywhere from mouth to anus (66% of cases located in ileum)
Perianal involvement	Unlikely	Yes
Depth of ulceration	Superfcial	May extend to submucosa or deeper

Clinical Features of IBD

Clinical Findings	Ulcerative Colitis	Crohn Disease
Histology	Nontransmural, crypt abscesses	Transmural lesions Granulomas
Fistula, perforation, or strictures	No	Yes
Development of toxic megacolon	Yes	No
Malabsorption or malnutrition	Rare	Yes, vitamin deficiencies; possible growth retardation in children

Clinical Features of IBD

- Systemic (Extra-intestinal) manifestations
  - a) **Hepatobiliary**: Primary sclerosing cholangitis, cholangiocarcinoma, hepatitis, cirrhosis, cholelithiasis, steatosis
  - b) **Rheumatologic:** arthritis, sacroiliitis, ankylosing spondylitis
  - c) **Dermatologic**: Erythema nodosum, aphthous ulcers, pyoderma gangrenosum
  - d) **Ocular**: Iritis or uveitis, episcleritis

Clinical Severity

Clinical Severity of Ulcerative Colitis

Mild	Moderate	Severe	Fulminant
≤ 4 stools/day (±blood)	> 4 stools/day (±blood)	> 6 stools/day with blood	> 10 stools/day with continuous blood
No fever, anemia, or tachycardia	Minimal signs of systemic toxicity	Temp > 99.5°F HR > 90 beats/min	Temp > 99.5°F HR > 90 beats/min
Normal ESR		ESR > 30 mm/hr	ESR > 30 mm/hr
		Hb < 75% of normal	Transfusions required
		Abdominal tenderness Bowel wall edema	Abdominal pain Dilated colon

Clinical Severity

Crohn disease

I. **Mild-moderate**: Tolerates oral administration; absence of fever, dehydration, and abdominal tenderness; less than 10% weight loss

II. **Moderate-severe**: Failed treatment of mild-moderate; these symptoms usually present; possibly anemia, nausea and vomiting, considerable weight loss

III. **Severe-fulminant**: No response to outpatient steroids; high temperature, abdominal pain, persistent vomiting; possible obstruction, abscess, cachexia, rebound tenderness

Treatment

- Goals of therapy
  - Resolution of acute inflammatory processes,
  - Resolution of complications (e.g., fistulae and abscesses),
  - Alleviation of extraintestinal manifestations,
  - Maintenance of remission, or
  - Surgical palliation or cure.

Treatment

General management considerations

- Rule out possible infectious causes of bloody diarrhea in patients with acute symptoms.
- Most patients will receive a colonoscopy to confirm the diagnosis and extent of disease.
- *Surgery*: complications (abscess, fistula, perforation) occur or when fulminant disease is unresponsive to medical treatment
- Most patients will require maintenance therapy because of the high incidence of relapse after induction therapy;
  - The relapse rate is 35 – 80% at 2 years for CD and 50 – 70% at 1 year for UC

Treatment

Adjunctive therapies:

- Loperamide: May be useful for proctitis or diarrhea; 2 mg after each loose stool (16 mg/day maximum)
- Antispasmodics
  a. Dicyclomine, 10–40 mg orally four times daily
  b. Propantheline, 7.5–15 mg orally three times daily
  c. Hyoscyamine, 0.125–0.25 mg orally/slow release every 4 hours as needed
- Cholestyramine: Possibly for bile salt–induced diarrhea after ileal resection

Treatment

Aminosalicylates

- Used for both induction and maintenance of remission

- **Sulfasalazine**: Prototype agent
  - Cleaved by colonic bacteria to the active (5-aminosalicylate) and the inactive carrier molecule sulfapyridine.
  - Efficacy is best in colonic disease (colonic activation of the drug)
  - Adverse effects: GI disturbance, headache, arthralgia, folate malabsorption, rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis, decreased sperm production
  - Avoid in patients with a sulfa allergy
  - Doses are 4–6 g/day for induction and 2–4 g/day for maintenance;

Treatment

- 5-Aminosalicylates (non – sulfa containing)
  - Better tolerated than sulfasalazine; considered first line in mild-moderate UC and CD
  - Rare instances of nephrotoxicity
  - Product selection depends on location of disease.
  - Olsalazine is associated with secretory diarrhea in up to 25% of patients.

5-Aminosalicylates

Drug	Formulation	Daily Dosage Range (g)	Site of action
Mesalamine	Enema	4	Rectum, terminal colon
	Delayed release capsule	1.6 – 4.8	Distal ileum Colon
	Suppository	1	Rectum
	Delayed-release tablet	2.4 – 4.8	Colon
Olsalazine	Capsule	1 – 3	

Treatment

Corticosteroids

- Work quickly to suppress inflammation during acute flares
- No role in maintenance therapy; however, more than 50% of patients with severe disease may become steroid-dependent
- Budesonide is about 15 times more potent than prednisone;
  - Because of its high first-pass metabolism and limited systemic exposure, allow a 2-week overlap when changing from prednisone to budesonide to prevent adrenal insufficiency.

Treatment

Route	Agents	Dose	Comments
Oral	Prednisone Prednisolone	20–60 mg/day	Taper ASAP
	Budesonide capsule	9 mg/day PO; then 6 mg/day for up to 3 mo	Minimal absorption, minimal systemic adverse effects; indicated for treatment and maintenance of mild-moderate active CD involving terminal ileum or ascending colon
	Budesonide tablet	9 mg/day in the a.m. for 8 wk	
	Hydrocortisone	100 mg every 8 hr	7- to 10-day course;

Treatment

- **Immunosuppressive**
  - Indicated only for maintenance because of long onset of action (3–15 months)

Drug	Initial Dose
Mercaptopurine	1-2.5mg/kg/day
Methotrexate	15-25mg/wk
Azathioprine	1-2.5mg/kg/day
Cyclosporine	2-4mg/kg/day

Treatment

- **Biologic Agents**
  - TNF-α inhibitors
    - Reduction in TNF-α activity is associated with improvement in the underlying inflammatory process
  - Infliximab
  - Adalimumab,
  - Golimumab,
  - Certolizumab



- GERD
- PUD
- VIRAL HEPATITIS
- CIHRROSIS
- PORTAL HYPERTENSION
- ACITES
- ESOPHAGEAL VARICES
- HE, SBP, HRS
- Pancreatitis
- IBD

Reading Assignments

1. Diarrhea
2. Constipation
3. Nausea and vomiting
4. Alcoholic liver disease
5. Drug induced hepatotoxicity

THANK YOU!