Integrated Therapeutics II

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Contents

1. **Renal Disorders (14 hrs)**
2. **Cardiovascular Disorders (30 hrs)**
3. **Respiratory Disorders (8 hrs)**
4. **Musculoskeletal Disorders (8 hrs)**
5. **Eye & ENT Disorders (4 hrs)**

Assessment mechanisms

- Mid exam, tests and quiz ➲ 40%
- Final exam ➲ 40%
- Bedside portfolio➲ 20%

Delivery Methods

- Illustrated lectures
- Group discussions
- Case studies
- Audiovisuals
- Ward attachment

References

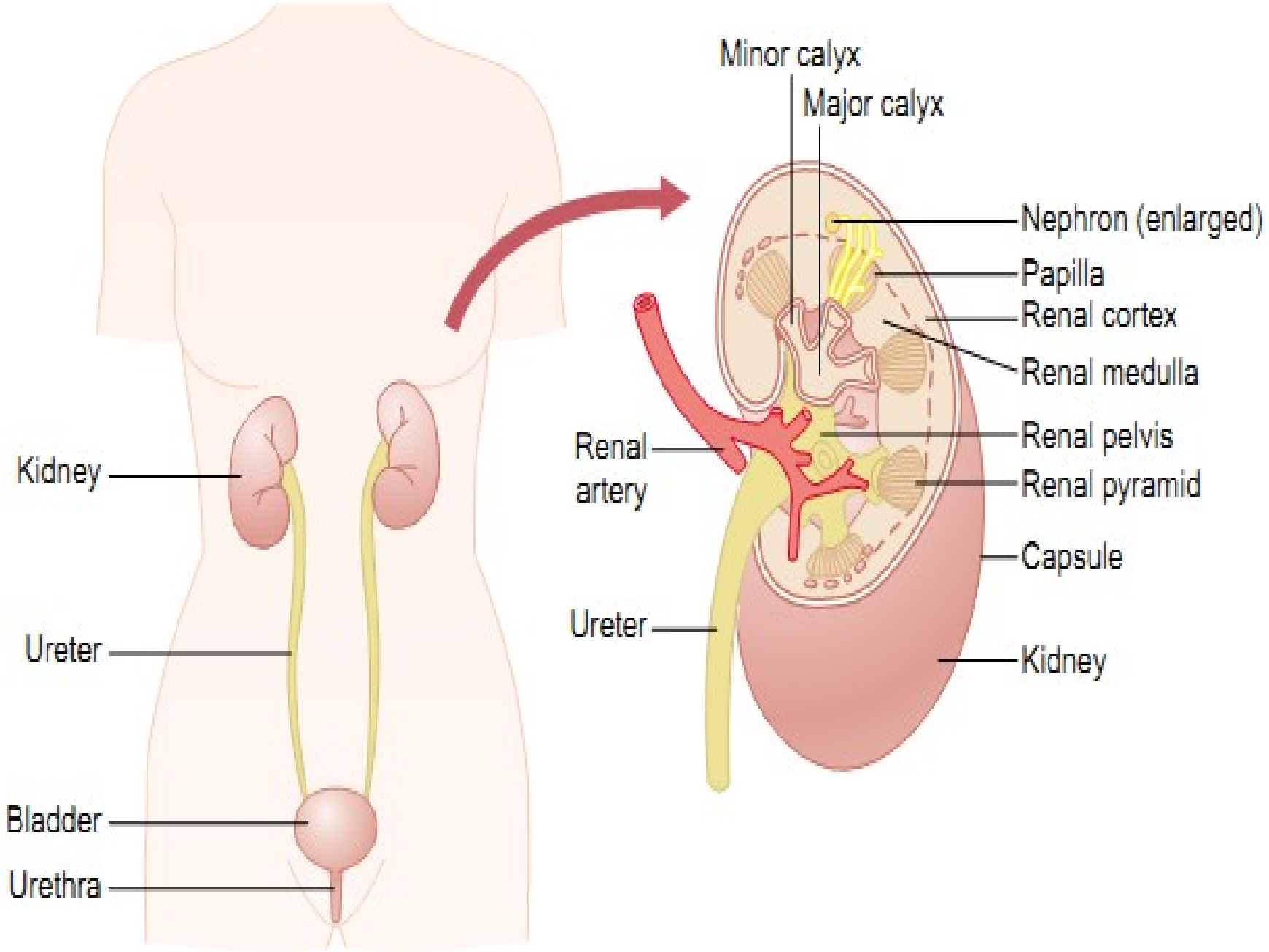
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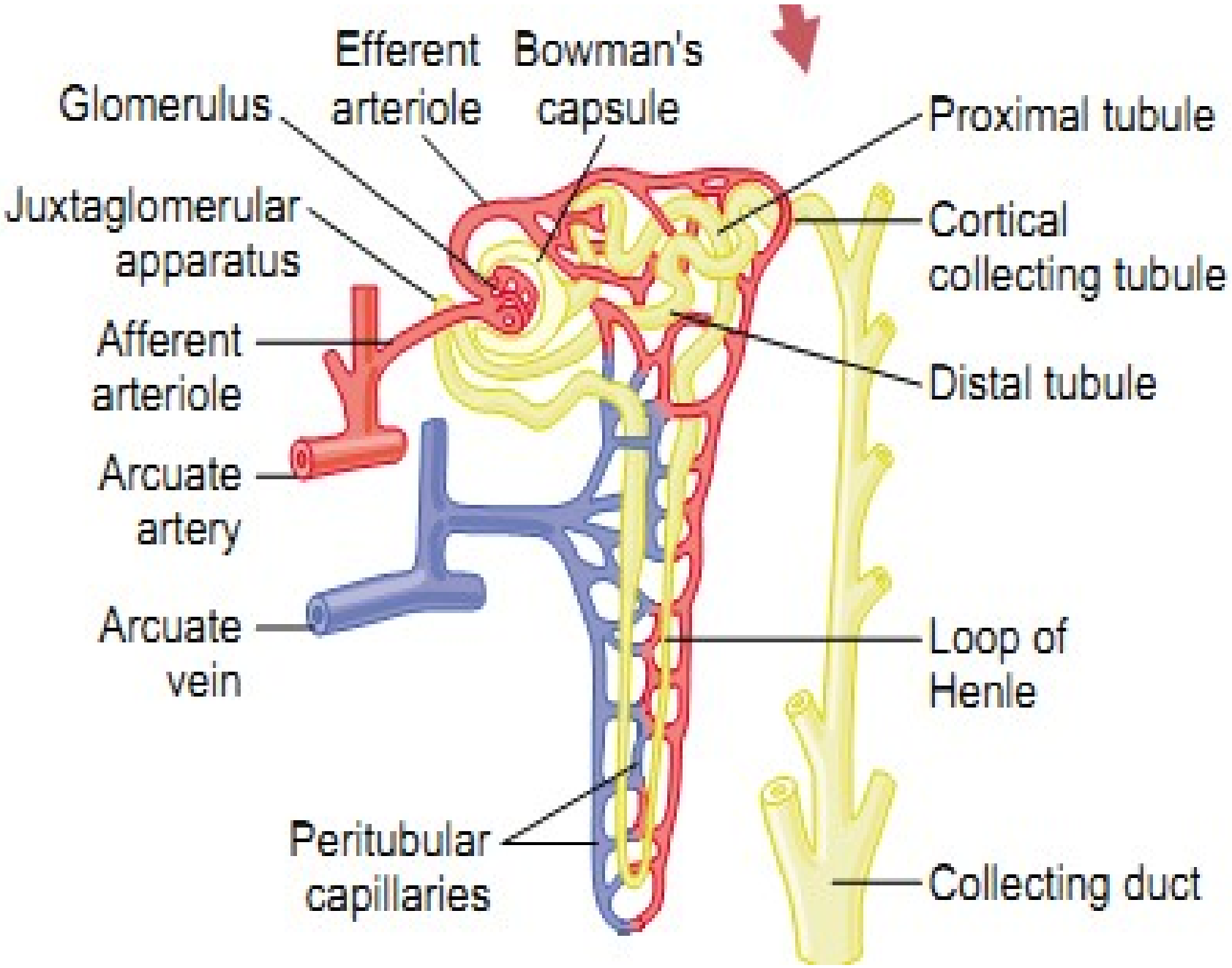
RENAL DISORDERS

Chapter One

Introduction

- Functions of the Kidneys in Homeostasis
  1. Excretion of metabolic waste products, foreign chemicals, drugs, and hormone metabolites
  2. Regulation of water and electrolyte balances
  3. Regulation of erythrocyte production
  4. Regulation of arterial pressure
  5. Regulation of acid-base balance
  6. Regulation of 1,25–Dihydroxyvitamin D_3 (calcitriol) production
  7. Gluconeogenesis


Minor calyx
Major calyx
Nephron (enlarged)
Papilla
Renal cortex
Renal medulla
Renal pelvis
Renal pyramid
Capsule
Kidney
Renal artery
Ureter
Kidney
Ureter
Bladder
Urethra


Efferent arteriole
Bowman's capsule
Glomerulus
Proximal tubule
Juxtaglomerular apparatus
Cortical collecting tubule
Afferent arteriole
Distal tubule
Arcuate artery
Arcuate vein
Loop of Henle
Peritubular capillaries
Collecting duct

ACUTE KIDNEY INJURY

Acute Kidney Injury

- **Definition**: AKI is a decrease in glomerular filtration rate (GFR),
  - Generally occurring over hours to days, sometimes over weeks,
  - Associated with an accumulation of waste products (urea and creatinine), disturbance in extracellular fluid volume and electrolyte and acid base homeostasis.
- Diagnostic criteria
  - Increase in Scr by at least 0.3 mg/dL within 48 hours or
  - Increase in Scr by at least 1.5 times baseline within the prior 7 days or
  - Decrease in urine volume to < 0.5 mL/kg/h for 6 hours

Acute Kidney Injury

- Based on the ***amount of urine output*** acute renal failure may be classified as:
  - ✓ **Anuric**: if urine volume is <100 ml/day
  - ✓ **Oliguric**: if urine volume is <400 ml/day
  - ✓ **Non-oliguric**: if urine volume is ≥400 ml/day

Risk Factors

- Older age
- Higher baseline serum creatinine (SCr)
- Chronic kidney disease (CKD)
- Diabetes
- Chronic respiratory illness
- Underlying cardiovascular disease
- Prior heart surgery
- Dehydration resulting in oliguria
- Acute infection
- Renal outflow obstruction, and
- Exposure to nephrotoxins.

PATHOPHYSIOLOGY

- Prerenal AKI
- Intrinsic AKI
- Post renal AKI

Prerenal AKI

- Prerenal AKI is the most common (**55%)** form of AKI
  - Represents a physiologic response to mild to moderate renal **hypoperfusion.**
- Prerenal AKI is rapidly **reversible** upon restoration of renal blood flow and glomerular ultrafiltration pressure.
- More severe hypoperfusion may lead to ischemic injury of renal parenchyma and intrinsic renal AKI

Prerenal AKI

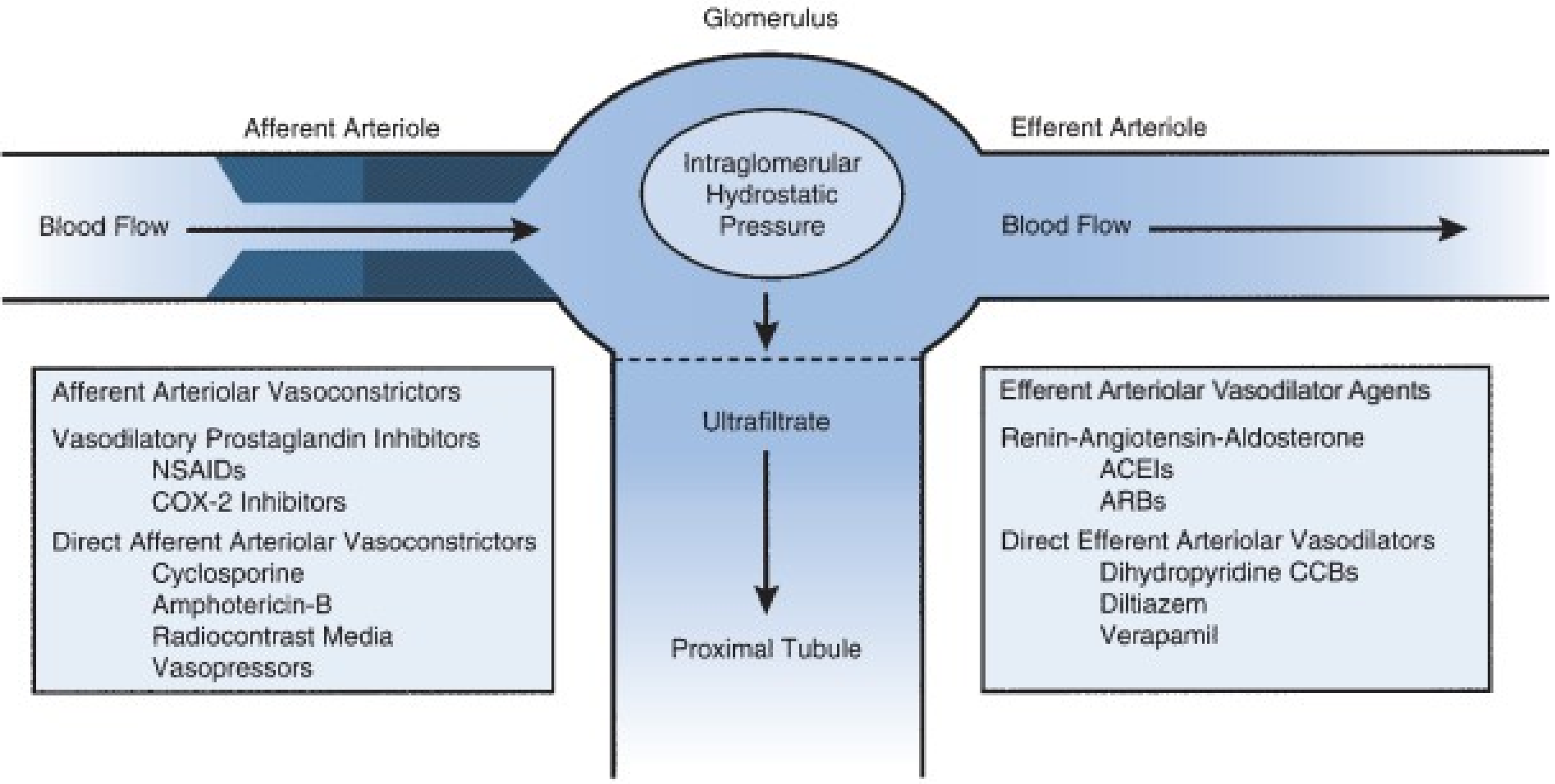
Major causes of prerenal AKI

1. Hypovolemia

- ✓ Hemorrhage, burns, dehydration
- ✓ GI fluid loss: vomiting, surgical drainage, diarrhea
- ✓ Renal fluid loss: diuretics, osmotic diuresis (e.g., diabetes mellitus), hypoaldestronism
- ✓ Sequestration in extravascular space: pancreatitis, peritonitis, trauma, burns, severe hypoalbuminemia

Prerenal AKI

2. **Low cardiac output**
   - ✓ Diseases of myocardium, valves, and pericardium; arrhythmias; tamponade
   - ✓ Other: pulmonary hypertension, massive pulmonary embolus
3. **Systemic vasodilatation**: sepsis, anaphylaxis
4. **Impairment of renal autoregulatory responses**
   - ✓ NSAIDS, ACE inhibition


Glomerulus
Afferent Arteriole
Efferent Arteriole
Intraglomerular Hydrostatic Pressure
Blood Flow
Blood Flow
Afferent Arteriolar Vasoconstrictors
Vasodilatory Prostaglandin Inhibitors
NSAIDs
COX-2 Inhibitors
Direct Afferent Arteriolar Vasoconstrictors
Cyclosporine
Amphotericin-B
Radiocontrast Media
Vasopressors
Ultrafiltrate
Proximal Tubule
Efferent Arteriolar Vasodilator Agents
Renin-Angiotensin-Aldosterone
ACEIs
ARBs
Direct Efferent Arteriolar Vasodilators
Dihydropyridine CCBs
Diltiazem
Verapamil

Intrinsic AKI

- Acute intrinsic AKI results from **damage to the kidney** itself
- Account for nearly **40%** of all ARF

1. Renovascular obstruction (bilateral or unilateral)
2. Disease of glomeruli or renal microvasculature
3. Acute tubular necrosis (ATN): Ischemia, toxins
4. Interstitial nephritis (inflammation within the renal parenchyma)

Post Renal AKI (Obstruction)

- Account for ~**5%** of AKI.
  - ***Ureteric***: Calculi, blood clot, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
  - ***Bladder neck***: Neurogenic bladder, prostatic hypertrophy, calculi, cancer, blood clot
  - ***Urethra***: Stricture, congenital valve, phimosis

Signs and Symptoms of ARF

- Peripheral edema
- Weight gain
- Nausea/vomiting/ diarrhea/anorexia
- Mental status changes
- Fatigue
- Shortness of breath
- Pruritus
- Volume depletion (prerenal)
- Colored/foaming urine
- Anuria alternating with polyuria (postrenal)
- Colicky abdominal pain radiating from flank to groin (postrenal)

Diagnosis

Laboratory Evaluation

1. **Glomerular filtration rate(GFR):** measures of overall kidney function.
   - ✓ GFR ranges from approximately **90** to **120 mL/minute** with normal kidney function.
   - ✓ Decreased creatinine clearance in ARF
   - ✓ Direct measurement of CrCl requires collection of urine over an extended time interval (24 hrs) with measurement of urine volume, urine creatinine and serum creatinine levels.

Diagnosis

Urine Collection Method

$$CrCl(ml/min) = \frac{UcrV}{ScrT}$$

- Ucr = urine creatinine concentration, mg/dL
- V = volume of urine, mL
- Scr = serum creatinine concentration, mg/dL
- T = time of urine collection, minute
- (Note: time equals 1440 minutes for a 24-hour collection)

Cockcroft-Gault Equation for Adults

$$CrCl\left(\frac{ml}{min}\right) = (140 - age)\frac{BW}{Scr * 72} \times (0.85\ if\ women)$$

Age, in years

BW = ideal body weight

- ⇒ Male IBW = 50 + (2.3×height >60 inches);
- ⇒ Female IBW = 45 + (2.3 × height >60 inches)

- Scr = serum creatinine concentration, mg/dL

Diagnosis

2. **Elevated serum creatinine concentration** (normal 0.6 to 1.2 mg/dL)

3. **Elevated BUN concentration** (normal 8 to 25 mg/dL)

4. **BUN: creatinine ratio** (elevated in prerenal AKI): >20:1 but <20:1 (intrinsic or postrenal AKI)

Diagnosis

5. **Urinalysis**

- ✓ Red cell casts - vasculitis or glomerulonephritis
- ✓ Muddy brown granular casts and epithelial cell casts in a patient - acute tubular necrosis

6. **Radiologic/imaging studies**

- ✓ To assess urinary tract obstruction, kidney stones, renal cyst or mass
- ✓ Renal ultrasonography, plain film of the abdomen (KUB)

PREVENTION AND TREATMENT

Desired Outcome

a. To prevent AKI

b. Avoid or minimize further renal insults that would worsen the existing injury or delay recovery, and

c. Provide supportive measures until kidney function returns

GENERAL APPROACH TO TREATMENT

- **Prerenal** and **postrenal** AKI can be reversed if the underlying problem is promptly identified and corrected, while treatment of **intrinsic renal** failure is more supportive in nature
- Supportive therapy such as fluid, electrolyte, and nutritional support, renal replacement therapy (RRT), and treatment of non-renal complications such as sepsis and gastrointestinal bleeding while regeneration of the renal epithelium occurs.
- In addition, prevention of adverse drug reactions by **discontinuing nephrotoxic drugs *or* adjustment of drug dosages** based on the patient's renal function is desired.

Pharmacologic Therapy

1. **Loop Diuretics** (furosemide, bumetanide, torsemide, and ethacrynic acid)

- ✓ Diuretics currently have no role in preventing AKI progression or reducing mortality,
  - ➢ But they can prevent complications, such as pulmonary edema.
- ✓ Loop diuretics are limited to instances of volume overload and edema
- ✓ A usual starting dose of IV furosemide for the treatment of AKI is **40** mg.

Pharmacologic Therapy

- For edema, IV furosemide (**80** to **120** mg) is preferred because of its potency
- Oral furosemide therapy should be avoided
- If urine output does not increase to about **1**mL/kg/hr, the dosage can be increased to a maximum of **160** to **200** mg of furosemide or its equivalent
- Torsemide has excellent oral BA and is unaffected by gut edema

Pharmacologic Therapy

- Closely monitor patient vital signs (weight, temperature, BP, pulse, and respirations) several times per day.
- Diuresis should aim for a weight loss of 0.5 to **1.0** kg per day.
- The patient's volume status should be assessed daily

Pharmacologic Therapy

- Other methods to improve diuresis can be initiated sequentially, such as:
  - Shortening the dosage interval;
  - Adding HCT and
  - Switching to a continuous infusion loop diuretic.
- **Thiazide diuretics**, when used as single agents, are generally not effective for fluid removal when creatinine clearance is less than **30** mL/minute.

Pharmacologic Therapy

- **Potassium – sparing diuretics**, which inhibit sodium reabsorption in the distal nephron and collecting duct, are not sufficiently effective in removing fluid.
  - ✓ In addition, they increase the risk of hyperkalemia in patients already at risk.

☞ Thus, loop diuretics are the diuretics of choice for the management of volume overload in ARF.

Pharmacologic Therapy

2. Dopamine:

- ✓ Low-dose dopamine, in doses ranging from 0.5 to 3 mcg/kg per minute
- ✓ Predominantly stimulates D_1 receptors, leading to renal vascular vasodilation and increased renal blood flow

Nonpharmacologic Therapies

Renal Replacement Therapy

- RRT may be necessary in patients with ARF
  - To treat volume overload that is unresponsive to diuretics,
  - To minimize the accumulation of nitrogenous waste products, and
  - To correct electrolyte and acid-base abnormalities

RRT

Indications for RRT – AEIOU

A – Acid–base abnormalities	Metabolic acidosis resulting from the accumulation of organic and inorganic acids
E – Electrolyte imbalance	Hyperkalemia, hypermagnesemia
I – Intoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O – fluid Overload	Postoperative fluid gain/overload
U – Uremia	High catabolism of uremic toxins

Nonpharmacologic Therapies

Supportive Therapy

- Supportive therapy in ARF includes
  - Adequate nutrition,
  - Correction of electrolyte and acid-base abnormalities (particularly hyperkalemia and metabolic acidosis)
  - Fluid management, and
  - Correction of any hematologic abnormalities.
- Finally, all drugs should be reviewed, and dosage adjustments made based on an estimate of the patient's glomerular filtration rate

Prevention of Acute Kidney Injury

- Avoidance: The best preventive measure for AKI, especially in individuals at high risk, is to avoid medications that are known to precipitate AKI.
- Nephrotoxicity is a significant side effect of
  - Aminoglycosides,
  - Angiotensin-converting enzyme inhibitors,
  - Angiotensin receptor antagonists,
  - Amphotericin B,
  - Nonsteroidal anti-inflammatory drugs,
  - Cyclosporine, tacrolimus, and
  - Radiographic contrast agents

Drug-Induced AKI: Aminoglycosides

- Treatment with aminoglycosides (gentamicin, tobramycin, and amikacin) can cause non-oliguric **intrinsic** AKI.
- Injury is due to the binding of aminoglycosides to proximal tubular cells, and subsequent cellular uptake and cell death
- A **prolonged course** of aminoglycoside therapy (typically longer than 7 to 10 days) is a risk factor for the development of AKI, especially in those with **preexisting CKD** and in the **elderly**
- Methods to minimize drug exposure include
  1) Maintaining trough concentrations less
  2) Short length of therapy
  3) Avoiding repeated courses of aminoglycosides
  4) Utilizing extended-interval dosing methods

Drug-Induced AKI: Amphotericin B

- Amphotericin B–induced AKI occurs in as many as 40% to 65% of patients treated with the conventional **desoxycholate formulation.**
- Nephrotoxicity is due to renal arterial vasoconstriction and distal renal tubule cell damage.
- Risk factors include high doses, treatment for at least 7 days, preexisting kidney dysfunction, and concomitant use of other nephrotoxic drugs
- Three lipid-based formulations of amphotericin B have been developed in an attempt to decrease the incidence of AKI:
  a) Amphotericin B lipid complex,
  b) Amphotericin colloidal dispersion, and
  c) Liposomal amphotericin B.

Drug-Induced AKI: Amphotericin B

- ✓ The range of nephrotoxicity reported is 15% to 25% for these formulations.
- ☞ The mechanism for decreased nephrotoxicity is thought to be due to preferential release of amphotericin B from macrophages at the site of infection, with less of an affinity for the kidney
- ☐ The liposomal preparation does not contain deoxycholate, which has direct tubular toxicity.

Drug-Induced AKI: Radiocontrast Agents

- Patients at risk for developing ARF include patients with chronic kidney disease, diabetic nephropathy, dehydration, and higher dose of contrast dye

- The mechanism of nephrotoxicity is not fully understood; however, direct tubular toxicity, renal ischemia, and tubular obstruction have been implicated

Drug-Induced AKI: Radiocontrast Agents

- The incidence of nephrotoxicity with ionic and non-ionic agents is similar in patients at low risk for developing AKI; however, in high-risk patients, nephrotoxicity is significantly greater when **ionic contrast agents** are used
- Therapeutic measures to decrease the incidence of contrast-induced nephropathy include:
  1) Extracellular volume expansion,
  2) Minimization of the amount of contrast administered
  3) Treatment with oral acetylcysteine.

Drug-Induced AKI: ACEIs and ARBs

- In instances of decreased renal blood flow, production of angiotensin II increases, resulting in **efferent arteriole vasoconstriction** and maintenance of glomerular capillary pressure and GFR
- In patients initiated on ACE inhibitors or ARBs, angiotensin II synthesis decreases thereby **dilating efferent arterioles** and decreasing glomerular capillary pressure and GFR.
- Risk factors for developing AKI are preexisting renal dysfunction, severe atherosclerotic renal artery stenosis, volume depletion, and severe CHF
- Discontinuation of the drug usually results in return of renal function to baseline

Drug-Induced AKI: NSAIDs

- Cause prerenal AKI through inhibition of prostaglandin-mediated renal vasodilation.
- Risk factors: preexisting renal dysfunction, severe atherosclerotic renal artery stenosis, volume depletion, severe CHF, hepatic disease with ascites, and advanced age
- It is usually reversible with drug discontinuation.

OUTCOME EVALUATION

- Maintain a state of euvolemia with good urine output (at least 1 ml/kg per hour), to return serum creatinine and BUN to baseline, and to correct electrolyte and acid-base abnormalities
- Vital signs, weight, fluid intake, urine output, BUN, creatinine, and electrolytes should be assessed daily in the unstable patient

Case study, AKI

- A.W. is a 71-year-old (70 KG) man who had a ST-segment elevation myocardial infarction (STEMI) 2 months ago. His ejection fraction is currently 15% (normal, 50%–60%).
- He presents today complaining of shortness of breath, dyspnea on exertion, and inability to produce much urine.
- His medical history is significant for longstanding hypertension, coronary artery disease, osteoarthritis, and recent-onset heart failure (HF) after his MI.

Case study, AKI

- His home medications include (all are taken orally)
  - **Furosemide** 40 mg every day,
  - **Enalapril** 5 mg daily, metoprolol XL 100 mg daily,
  - **Digoxin** 0.125 mg daily,
  - **Atorvastatin** 40 mg QD, and
  - **Naproxen sodium** 550 mg twice daily (BID),
- With the exception of naproxen, A.W. often forgets to take his medications.

Case study, AKI

- Physical examination reveals lower leg 3+ pitting edema, pulmonary crackles and wheezes, positive jugular venous distention, and an S_3 heart sound. His vital signs are significant for a blood pressure (BP) of 198/97 mm Hg and a weight gain of 4 kg since his last visit 2 months ago.
- Three days back, his BUN and SrCr were 23 (normal, 5–20) and 1.1 mg/dL (normal, 0.5–1.2), respectively. Current BUN and creatinine are 56 mg/dL and of 1.5 mg/dL.

Case study, AKI

1. What are A.W.'s risk factors for AKI?
2. What laboratory findings suggest pre-renal AKI?
3. Estimate A.W.’s GFR based CG equation
4. How should A.W.'s AKI be treated?

CHRONIC KIDNEY DISEASE

Chronic Kidney Disease

Definition

a. Kidney damage for **more than 3 months**, as defined by structural or functional abnormality of the kidney, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests

b. GFR <90 mL/minute/1.73m^2 for more than 3 months, with or without kidney damage

- CKD is categorized by the level of kidney function (as defined by GFR) into stages 0 through 5, with each increasing number indicating a more advanced stage of the disease

Chronic Kidney Disease

Classification of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
0	With risk factors for CKD	>90
1	Kidney damage with normal or ↑ GFR	≧90*
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure (ESRD)	<15

Chronic Kidney Disease

- Normal kidney function in adults is about **120 mL/min/1.73 m²** of GFR.
- Even though a GFR of >90 mL/min/1.73 m^2 is considered normal kidney function, a patient can be diagnosed with CKD if the patient has proteinuria, hematuria, or evidence of structural damage from a kidney biopsy.
- Stage 5 CKD is referred to as **end-stage renal disease (ESRD)** or end-stage kidney disease.

ETIOLOGY

1. Susceptibility Factors

- Associated with an **increased risk**, but not proven to directly cause CKD
  - Advanced age,
  - Low income or education,
  - Racial/ethnic minority status,
  - Reduced kidney mass,
  - Low birth weight,
  - Family history of CKD,
  - Systemic inflammation,
  - Dyslipidemia
- Mostly **not modifiable**

ETIOLOGY

2. Initiation Factors

- Initiation factors are conditions that directly **result in kidney damage**
- **Modifiable** by pharmacologic therapy.
  - Diabetes mellitus,
  - Hypertension,
  - Autoimmune diseases,
  - Polycystic kidney disease,
  - Systemic infections,
  - Urinary tract infections,
  - Urinary stones,
  - Lower urinary tract obstructions, and
  - Drug toxicity

ETIOLOGY

3. Progression Factors

- Progression risk factors are those associated with **further kidney damage**.
- The most important predictors of progressive CKD
  - Proteinuria,
  - Elevated blood pressure,
  - Hyperglycemia,
  - Hyperlipidemia, and
  - Smoking.

PATHOPHYSIOLOGY

- Damage to the kidney results from any of the **initiation factors** which resulting in **loss of nephron mass**.
- The resultant effect is **hypertrophy of the remaining nephrons** to compensate for the loss of renal function and nephron mass.
- These adaptive changes result in an **increase in glomerular filtration and tubular function**, both reabsorption and secretion, in the remaining nephrons
- As time progresses, **glomerular capillary pressure is increased,** mediated by **angiotensin II**, to maintain the hyper filtration state of the functioning nephrons.

PATHOPHYSIOLOGY

- Increased glomerular capillary pressure **expands the pores** in the glomerular basement membrane, altering the size-selective barrier and allowing **proteins** to be filtered through the glomerulus.
- Filtered proteins are **reabsorbed** in the renal tubules, which activates the tubular cells to produce **inflammatory and vasoactive cytokines and triggers complement activation.**
- These in turn cause interstitial damage and scarring within the renal tubules, leading to damage and **loss of more nephrons.**

CLINICAL PRESENTATION OF CKD

Symptoms

- Stages **1** and **2** CKD are generally asymptomatic.
- Stages **3** and **4** CKD may be associated with minimal symptoms.
- Typical symptoms associated with stage **5** CKD include pruritus, dysgeusia, nausea, vomiting, constipation, muscle pain, fatigue, and bleeding abnormalities.

CLINICAL PRESENTATION OF CKD

- **Signs**

- Cardiovascular: worsening hypertension, edema, dyslipidemia, left ventricular hypertrophy, electrocardiographic changes and chronic heart failure.

- Genitourinary: changes in urine volume and consistency, “foaming” of urine (indicative of proteinuria), and sexual dysfunction.

Laboratory Tests for CKD

1. Increased BUN and SCr and decreased GFR
2. Increased K, P, and Mg; decreased bicarbonate (metabolic acidosis); calcium levels are generally low in earlier stages of CKD and may be elevated in stage **5** CKD, secondary to the use of calcium-containing phosphate binders.
3. Decreased albumin, if inadequate nutrition intake in advanced stages.
4. Decreased RBC count, Hgb and Hct

Laboratory Tests for CKD

5. Proteinurea/albuminurea: urine positive for albumin or protein
   - ✓ Normal: **<30mg/24hrs**
   - ✓ Microalbuminurea: **30-300mg/24hrs**
   - ✓ Macroalbuminurea (overt protienurea): **>300mg/24hrs**
   - ✓ Nephrotic range proteinurea: **>3g/24hrs**.
6. Increased parathyroid hormone (PTH) level
7. Decreased vitamin D levels (stages **4** or **5** CKD).

TREATMENT OF CKD

- Desired Outcomes

✓ The primary goal is to slow and prevent the progression of CKD

TREATMENT OF CKD

Nonpharmacologic Therapy

- **Dietary Protein Restriction**:

- ✓ Shown to slow the progression of kidney disease.
- ✓ However, protein restriction must be balanced with the risk of malnutrition in patients with CKD.
- ✓ Patients with a GFR less than 25mL/minute/1.73m^2 received the most benefit from protein restriction; therefore, patients with a GFR above this level should not restrict protein intake

TREATMENT OF CKD

- Patients who have a GFR <25 mL/min /1.73 m^2 who are not receiving dialysis should restrict protein intake to **0.6** g/kg per day.
- Malnutrition is common in patients with ESRD due to:
  - ✓ Decreased appetite
  - ✓ Hypercatabolism
  - ✓ Nutrient losses through dialysis.
- For this reason, patients receiving dialysis should maintain protein intake of 1.2 – 1.3 g/kg per day

TREATMENT OF CKD

Pharmacologic Therapy

1. Intensive Blood Glucose Control:

- ✓ Intensive insulin therapy to maintain preprandial blood glucose levels between **70** and **125** g/dL and postprandial blood glucose levels less than **180** g/dL

2. Optimal Blood Pressure Control:

- ✓ Stages **1-4**: goal BP of less than **130/80** mm Hg
- ✓ Stage **5**: receiving hemodialysis, goal BP of **<140/90** mm Hg before hemodialysis and **<130/80** after hemodialysis.

TREATMENT OF CKD

3. Reduction in Proteinuria

- **ACE inhibitors and ARBs:**

- ✓ Decrease glomerular capillary pressure and volume because of their effects on angiotensin II.
- ✓ This, in turn, reduces the amount of protein filtered through the glomerulus, independent of the reduction in blood pressure
- ✓ Antihypertensive agents of choice for all patients with CKD.

TREATMENT OF CKD

4. Hyperlipidemia Treatment

- ✓ CKD patients are among the highest-risk group for cardiovascular conditions (i.e., equivalent to that of patients with known coronary heart disease)
- ✓ Should be treated aggressively for dyslipidemia to an LDL cholesterol goal below 100 mg/dL

COMPLICATIONS OF CKD

1. Fluid and Electrolyte Abnormalities

a) Impaired Sodium and Water Homeostasis

- Sodium and water balance are primarily regulated by the kidney.
- Reductions in nephron mass GF reabsorption of sodium and water edema.
- Treatment
  - ✓ **Nonpharmacologic:** Sodium and fluid restrictions
  - ✓ **Pharmacologic:** Loop diuretics therapy

COMPLICATIONS OF CKD

b) Impaired Potassium Homeostasis

- ✓ Potassium balance is primarily regulated by the kidney via the distal tubular cells.
- ✓ Reduction in nephron mass decreases tubular secretion of potassium, leading to **hyperkalemia**.
- ✓ Nonpharmacologic: avoid abrupt increases in dietary intake of potassium, dialysis

COMPLICATIONS OF CKD

b) Impaired Potassium Homeostasis

- **Pharmacologic**

✓ Patients who present with **cardiac abnormalities** caused by hyperkalemia should receive **calcium gluconate or chloride** (1 g IV) to reverse the cardiac effects

✓ Temporary measures can be employed to shift extracellular potassium into the intracellular compartment to stabilize cellular membrane effects of excessive serum potassium levels.

✓ The use of **regular insulin** (5 to 10 units IV) and **dextrose** (5% to 50% IV), or nebulized **albuterol** (10 to 20 mg).

COMPLICATIONS OF CKD

b) Impaired Potassium Homeostasis

- These measures will decrease serum potassium levels within 30 to 60 minutes after treatment, but potassium must still be removed from the body.
- Shifting potassium to the intracellular compartment, however, decreases potassium removal by dialysis.
- Often, **multiple dialysis sessions** are required to remove potassium that is redistributed from the intracellular space back into the serum.
- **Sodium polystyrene sulfonate** (SPS, 15 to 30 g orally), a sodium-potassium exchange resin, promotes potassium excretion from the GI tract

COMPLICATIONS OF CKD

2. Metabolic Acidosis

- Normal metabolism of ingested food produces approximately 1 mEq/kg of metabolic acid daily, which must be excreted by the kidneys (primarily as ammonium ion) to maintain acid-base balance
- Reduced bicarbonate reabsorption and impaired production of ammonia by the kidneys are the major factors responsible for development of metabolic acidosis in advanced kidney disease.
- Treatment: Na bicarbonate, Dialysis

COMPLICATIONS OF CKD

c) Anemia of CKD

- The progenitor cells of the kidney produce 90% of the hormone **erythropoietin (EPO),** which stimulates red blood cell (RBC) production.
- Reduction in nephron mass decreases renal production of EPO anemia in patients with CKD.
- Anemia of CKD decreased oxygen delivery and utilization, increased cardiac output and left ventricular hypertrophy (LVH) the cardiovascular risk and mortality in patients with CKD.
- The result is a **normochromic, normocytic anemia**.

COMPLICATIONS OF CKD

- Uremia decreases the lifespan of RBCs from a normal of **120** days to as low as **60** days in patients with stage 5 CKD.

- Iron deficiency and **blood loss from regular laboratory testing and hemodialysis** also contribute to the development of anemia in patients with CKD

COMPLICATIONS OF CKD

Treatment

- The goal of treatment for anemia of CKD is to increase Hgb levels greater than **11** g/dL

Nonpharmacologic Therapy

1. Sufficient dietary iron intake must be maintained in patients with anemia of CKD.
   - ✓ Approximately **1** to **2** mg of iron is absorbed daily from the diet.
   - ✓ This small amount is generally not adequate to preserve adequate iron stores to promote RBC production.
2. RBC transfusions

COMPLICATIONS OF CKD

Pharmacologic Therapy

- **Iron supplementation** to correct and prevent iron deficiency caused by ongoing blood loss and increased iron demands associated with the initiation of erythropoietic therapy
- **ESA** to correct erythropoietin deficiency: epoetin alfa, epoetin beta and darbepoetin alfa
  - The first-line treatment for anemia of CKD involves replacement of erythropoietin with ESAs

COMPLICATIONS OF CKD

- Darbepoetin alfa differs from epoetin alfa by the addition of carbohydrate side chains that increase the half-life of darbepoetin alfa compared to epoetin alfa and endogenous EPO, allowing for less frequent dosing than that of epoetin alfa.
- The most common adverse effect seen with ESA is increased blood pressure
- The starting doses of epoetin alfa are **80** to **120** units/kg per week for SC administration and **120** to **180** units/kg per week for IV administration, divided two to three times per week.
- The starting dose of darbepoetin alfa is **0.45** mcg/kg administered SC or IV once weekly

COMPLICATIONS OF CKD

4. Secondary Hyperparathyroidism and Renal Osteodystrophy

- As renal function declines in patients with CKD, **decreased phosphorus excretion** disrupts the balance of calcium and phosphorus homeostasis.
- The rise in serum phosphate causes **increased binding of phosphate with calcium** in the plasma, thus **decreasing the plasma serum ionized calcium concentration**
- The parathyroid glands release PTH in response to decreased serum **ionized** calcium and increased serum phosphorus levels.

COMPLICATIONS OF CKD

- The actions of PTH include:

- ✓ **Increasing calcium resorption** from bone
- ✓ **Increasing calcium reabsorption** from the proximal tubules in the kidney
- ✓ **Decreasing phosphorus reabsorption** in the proximal tubules in the kidney
- ✓ **Stimulating activation of vitamin D** by 1-a-hydroxylase to calcitriol (1,25-dihydroxyvitmin D_3) to promote calcium absorption in the GI tract and increased calcium mobilization from bone

COMPLICATIONS OF CKD

- Calcitriol : the active form of vitamin D
  - ✓ Increases gut absorption of calcium
  - ✓ Suppress PTH release (negative feedback)
- As kidney function continues to decline and the GFR falls less than **60**,
  - ✓ Phosphorus excretion continues to decrease (hyperphosphatemia)
  - ✓ Calcitriol production decreases

⇒ **Secondary hyperparathyroidism (sHPT).**

COMPLICATIONS OF CKD

Treatment

- **Nonpharmacologic Therapy**
  - ✓ Dietary phosphorus restriction
  - ✓ Restriction of aluminum exposure and
  - ✓ Parathyroidectomy.

COMPLICATIONS OF CKD

Pharmacologic Therapy

1. Phosphate-Binding Agents

- ✓ Used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces

i. Calcium-based phosphate binders:

- ✓ **Calcium carbonate** (**40%** elemental Ca) and **calcium acetate** (**25%** elemental Ca)
- ✓ Starting Dose **0.5–1** g elemental Ca 3xday
- ✓ Adverse effects: constipation and hypercalcemia

COMPLICATIONS OF CKD

ii. **Aluminum/magnesium**-based phosphate binders:

- ✓ **Aluminum hydroxide, aluminum carbonate, Magnesium hydroxide, magnesium carbonate**
- ✓ Not recommended for chronic use

iii. **Lanthanum carbonate**:

- ✓ Quickly dissociates in the acidic environment of the stomach, where the lanthanum ion binds to dietary phosphorus, forming an insoluble compound that is excreted in the feces

COMPLICATIONS OF CKD

2. Vitamin D (calcitriol)

- Vitamin D occurs naturally as **ergocalciferol** (vitamin D_2) and **cholecalciferol** (vitamin D_3), both of which are inactive precursors of active forms of vitamin D.
- An intermediate activation step (25-hydroxylation) occurs in the liver to produce 25-hydroxy vitamin D (25-hydroxycalciferol), which is also relatively inactive.
- Final activation (1-hydroxylation) occurs in the kidney, yielding calcitriol (1,25-dihydroxycholecalciferol), the active form of vitamin D
- Exogenous vitamin D compounds that mimic the activity of calcitriol decrease PTH secretion. ***(calcitriol, paricalcitol, doxercalciferol, alfacalcidiol)***
- Dosing: usually **0.25–0.5** mcg/day

Renal Replacement Therapy

- Patients who progress to ESRD require renal replacement therapy (RRT).
- The modalities that are used for RRT are
  1. Dialysis
  2. Kidney transplantation.

GLOMERULONEPHRITIS

Objectives

- At the end of this session, students will be able to:
  - To identify various causes of glomerulonephritis
  - Differentiate between nephrotic and nephritic syndrome
  - Recommend appropriate treatment for glomerulonephritis
  - Identify monitoring parameters for nephrotic and nephritic syndromes

Introduction

- The glomerulus consists of two important components:

1. The filtration barrier (capillary wall)
   - Consists of three well-defined layers:
     - Fenestrated endothelium,
     - Glomerular basement membrane (GBM),
     - Epithelial cell layer (podocytes)
2. The mesangium
   - Provides support for the glomerular capillaries

Introduction

- The passage of solutes through the glomerular membrane is impacted by both the **size** and **charge** of the solute.
- The unique capillary bed of the glomerulus;
  - Allows free passage of **small** nonprotein plasma constituents up to the size of inulin (MW of 5.2 kDa)
  - Excludes macromolecules equal to or larger than albumin (MW of 69 kDa)

Introduction

- Fixed, negatively charged sites are found within the glomeruli in all three layers of the capillary wall.
- The movement of negatively charged molecules is thus restricted more than that of neutral or positively charged molecules.
- Different glomerular diseases affect this size - and charge-selective barrier to different extents

Pathogenesis

- **Genetic mutations** producing familial disease
- **Systemic hypertension and atherosclerosis** can produce pressure stress, ischemia, or lipid oxidants that lead to chronic glomerulosclerosis
- **Diabetic nephropathy**: thickening of the GBM secondary to the long-standing effects of **hyperglycemia**, advanced **glycosylation** end products, and reactive oxygen species.
- **Infections**: Bacteria, fungi, and viruses can directly infect the kidney producing their own antigens.
- **Poststreptococcal glomerulonephritis (PSGN)**
- **Autoimmune diseases**

Clinical Presentation

- Patients with glomerular disease are often categorized into one of two broad classifications:
  - **Nephritic syndrome**
    - Reflects glomerular *inflammation* and frequently results in **hematuria**
  - **Nephrotic syndrome**
    - *Noninflammatory injury* to the glomerular structures and results in few cells or cellular casts in the urine

Nephritic Syndrome

- Acute nephritic syndromes classically present with
  - Hypertension,
  - Hematuria,
  - Red blood cell casts,
  - Pyuria, and
  - Mild to moderate proteinuria.
- Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension

Nephritic Syndrome

Poststreptococcal Glomerulonephritis

- Affects children between the ages of 2 and 14 years
- Skin (impetigo) and throat infections (pharyngitis) with particular M types of streptococci (nephritogenic strains) antedate glomerular disease
- PSGN due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.
- Treatment is supportive, with control of hypertension, edema, and dialysis as needed.
- Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants

Nephritic Syndrome

- Other causes
  - Subacute Bacterial Endocarditis
  - Lupus Nephritis
  - Antiglomerular Basement Membrane Disease
  - IgA Nephropathy

Nephrotic Syndrome

- Nephrotic syndrome classically presents with
  - Heavy proteinuria (>3.5 g/day per 1.73 m^2),
    - Urine dipstick 3+/4+
  - Hypoalbuminemia, <2.5g/dL
  - Hypercholesterolemia, >200mg/dL
  - Edema, and
  - Hypertension
  - Hypercoagulable state

Nephrotic Syndrome

- **Causes**
  - **Minimal Change Disease:** alters capillary charge and podocyte integrity
  - **Focal Segmental Glomerulosclerosis**
  - **Membranous Glomerulonephritis:** malignancy (solid tumors of the breast, lung, colon), infection (hepatitis B, malaria, schistosomiasis), or rheumatologic disorders like lupus or rarely rheumatoid arthritis
  - **Diabetic Nephropathy**

Diagnosis

- **Laboratory evaluation**
  - Urinalysis
    - To determine nephrotic nature of glomerular disease
      - ✓Proteinuria, >3.5 g/day/1.73 m^2
      - ✓Lipiduria
    - To determine nephritic nature of glomerular disease
      - ✓Hematuria
      - ✓Pyuria
      - ✓Cellular, granular casts
  - Glomerular filtration rate
    - To determine extent of glomerular damage

Diagnosis

- **Other tests**
  - To identify type and etiology of glomerular disease
    - Serum complement concentration
    - Antinuclear and anti-DNA antibodies
    - Antistreptolysin antibodies: PSGN
    - Circulating antiglomerular basement membrane antibodies
    - Cryoglobulins
- Percutaneous renal biopsy
  - To provide definitive diagnosis of glomerular disease

Treatment

Supportive Therapy

- **Edema:**
  - Salt restriction, bedrest, and use of support stockings
  - Diuretics:
    - Furosemide: 160 to 480 mg
- **Hypertension**
  - Goal: < 130/80 mm Hg
  - ACEI/ARBs
  - CCB (nondihydropyridines)
- **Proteinuria**
  - Dietary protein restriction
  - ACEI/ARB

Treatment

Supportive, continued

- **Hyperlipidemia**
  - A low-fat diet
  - Statins: lovastatin, pravastatin, simvastatin, and fluvastatin
- **Anticoagulation**
  - Warfarin
    - Patients who have documented thromboembolic episodes
    - Albumin < 2.0 to 2.5 g/dL

Treatment

- **Prednisolone**
  - ✓ **Initial**: 2 mg/kg/day or 60 mg/m² /day (maximum: 80 mg/day) in divided doses until urine is protein free for 3 consecutive days (maximum: 28 days); followed by 1-1.5 mg/kg/dose or 40 mg/m²/dose given every other day for 4 weeks
  - ✓ **Maintenance** (for frequent relapses): 0.5-1 mg/kg/dose given every other day for 3-6 months with tapering
- **Nonsteroidal therapy**
  - Cyclophosphamide at a dose of 2 mg/kg per day

Evaluation of Therapeutic Outcomes

- For therapeutic response and treatment-related toxicities
  - Serum creatinine concentration and creatinine clearance
  - Blood pressure should be monitored periodically
  - Serum lipid concentrations
  - Urinalysis and a complete blood count
  - Patient's appetite and energy level

CARDIOVASCULAR DISORDERS

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Chapter Two

HYPERTENSION

Objectives

- Classify BP levels and treatment goals.
- Recognize underlying causes and contributing factors in the development of hypertension.
- Describe the appropriate measurement of BP.
- Recommend appropriate lifestyle modifications and pharmacotherapy for patients with hypertension.
- Identify populations requiring special consideration when designing a treatment plan.
- Construct an appropriate monitoring plan to assess hypertension treatment.

Definition

Classification	SBP (mm Hg)	Vs	DBP(mm Hg)
Normal	<120	and	<80
Elevated BP	120-129	or	<80
Stage 1 Hypertension	130-139	or	80-89
Stage 2 Hypertension	≥140	or	≥90

- Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
- Starting at a blood pressure of 115/75 mm Hg, every increase of 20 mm Hg in SBP and/or increase of 10 mm Hg in DBP is associated with a doubling of the risk of death from stroke, heart disease, or other vascular disease

ACC/AHA, 2017

Introduction

- BP Measurement
  - Periodic screening for all people older than 21 years
  - Patient should be seated quietly in chair for at least 5 minutes.
  - Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
  - Take BP at least twice, separated by at least 2 minutes.
  - The average BP on two separate visits is required to diagnose HTN accurately.

Instructions for Home BP Measurement

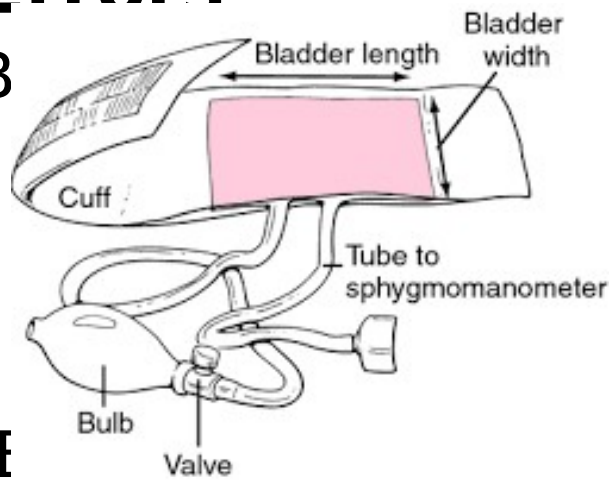
- **Step 1**: Obtain an appropriate home BP measurement device.
  - Choose a fully automated device (avoid auscultatory home devices).
  - Choose an arm device (brachial BP). Use wrist monitors only for patients whose arm circumference prevents proper fitting
  - Choose validated devices, if possible.
  - Ensure correct cuff size.
- **Step 2**: Prepare for BP measurement.
  - Empty bladder; refrain from drinking caffeine or smoking 30 min before measurement.
  - Rest at least 5 min before BP measurement.
  - Sit with back supported and feet flat on the floor (legs uncrossed).
  - Place cuff directly above the antecubital fossa.

Instructions for Home BP Measurement

- **Step 3:** Measure BP.
  - Take two readings 2 min apart.
  - Avoid unnecessary movement or talking during measurement.
  - Minimize excessive measurements.
- **Step 4:** Record BP values with date and time, noting anything unusual (e.g., pain, stress, illness, missed medication).

BP Measurement

- **Causes of BP Measurement Errors**
  - Factors that can falsely increase B
    - Bladder distension
    - Cuff too small
    - Insufficient rest period
    - Talking during measurement
  - Factors that can falsely decrease B
    - Cuff too large
  - Factors that have mixed errors on BP measurements:
    - Deflating the cuff too quickly
    - Standing or supine position rather than sitting position
    - White-coat effect



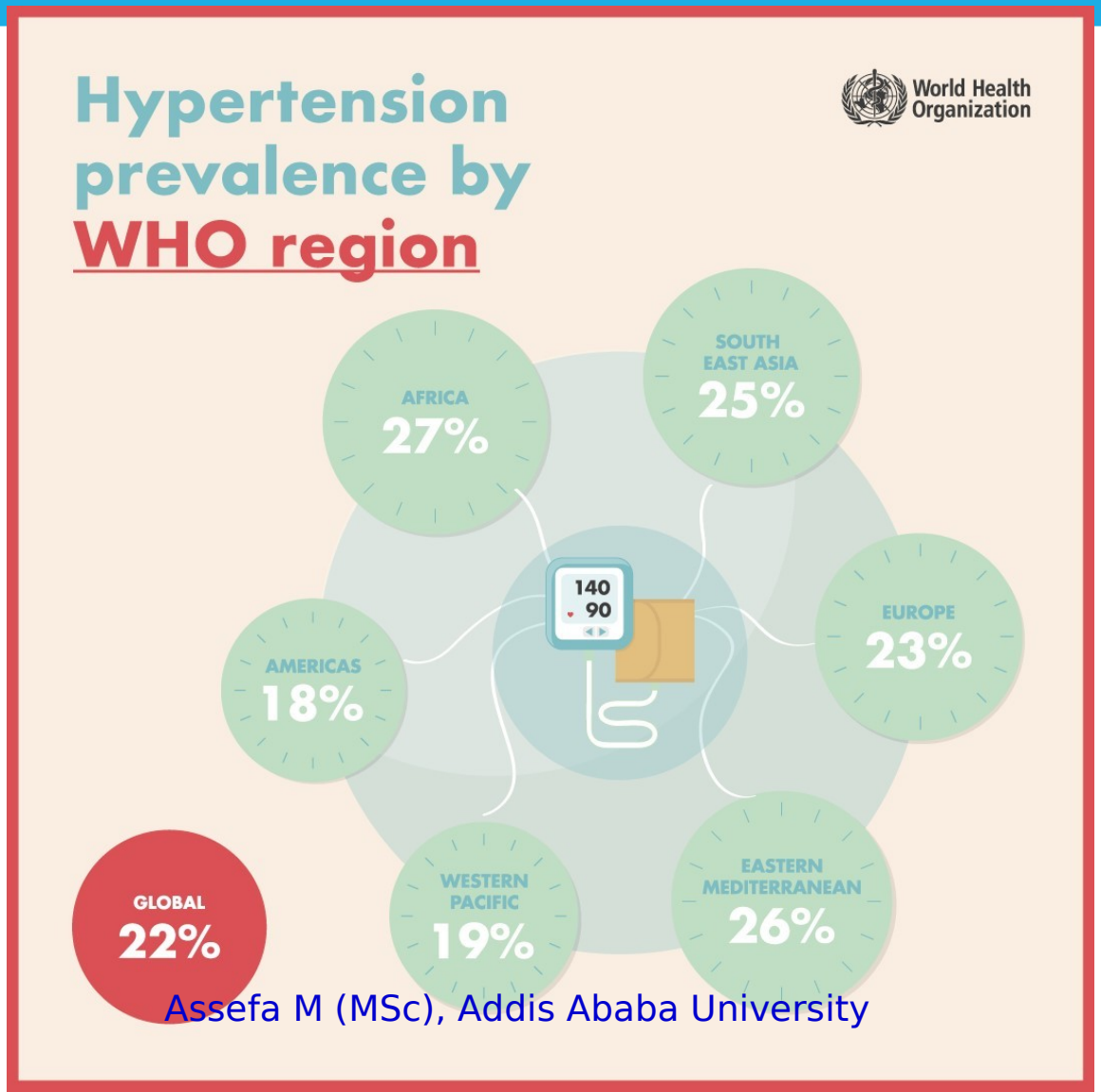
Epidemiology

- Prevalence
  - Major modifiable risk factor for CV disease and stroke
  - 1.13 billion of the global population.
  - Prevalence depends on:
    - ✓ **Race**: blacks > whites
    - ✓ **Age**: 50% among those 60-69 year, 75% in >70 year.
    - ✓ **Gender**: less in younger women. F:M= 0.6 at 30 yr but 1.1-1.2 at 65 year
  - HTN is adequately controlled in only 52.5% of patients with HTN.

Epidemiology



Epidemiology



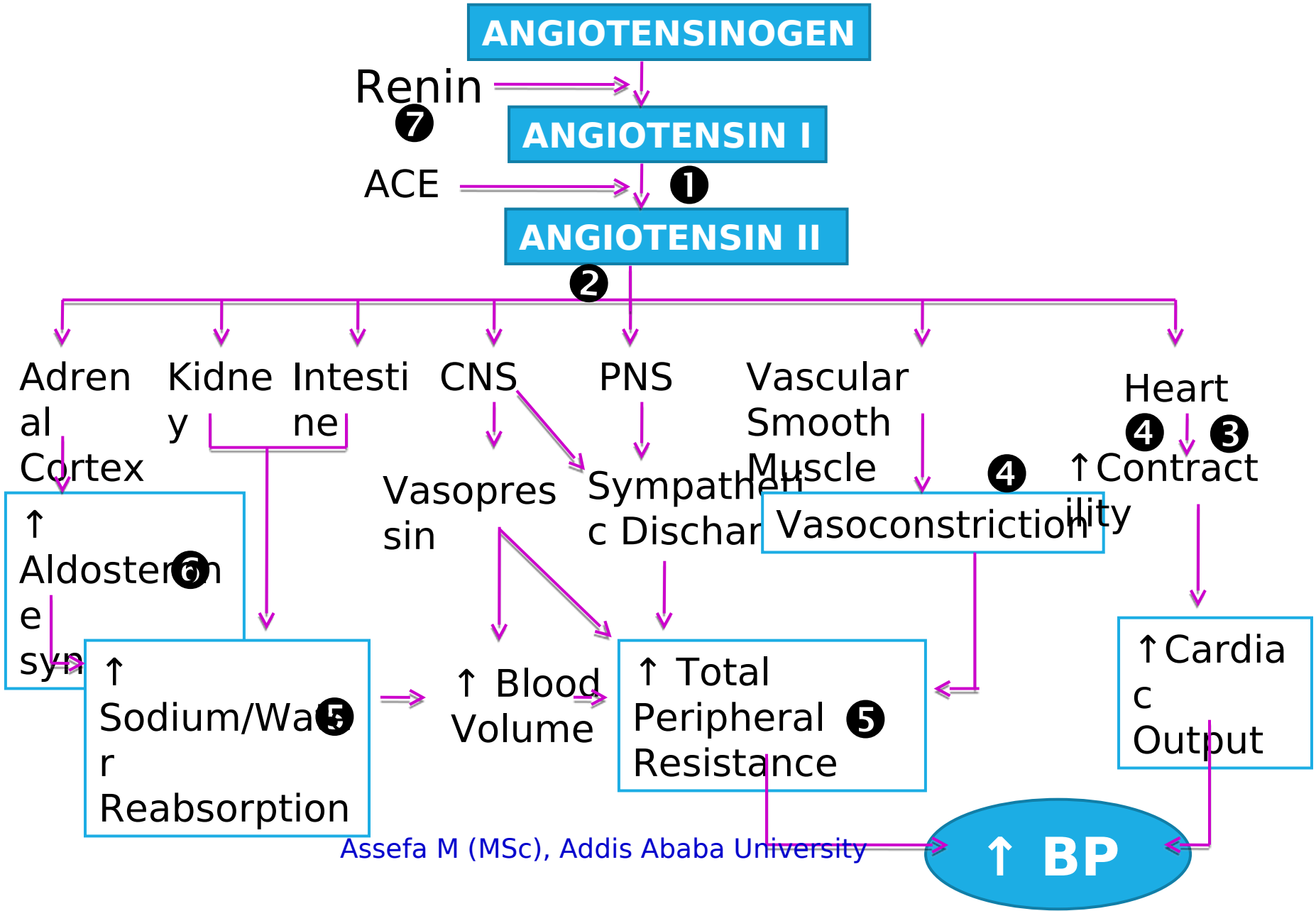
Pathophysiology

- Multiple factors that control BP are potential contributing components in the development of hypertension.
- These include malfunctions in either humoral (i.e., the renin–angiotensin–aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormone.

The RAAS

- Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney.
- The release of renin is modulated by several factors:
  - Intrarenal factors
    - ↓renal perfusion pressure
    - Catecholamines → stimulate sympathetic nerves on the afferent arterioles
    - ↓angiotensin II
  - Extrarenal factors (↓sodium, chloride, and potassium).

The RAAS


ANGIOTENSINOGEN
Renin
7
ANGIOTENSIN I
ACE
1
ANGIOTENSIN II
2
Adrenal Cortex
Kidney
Intestine
CNS
PNS
Vascular Smooth Muscle
Heart
4
3
↑ Aldosterone synthesis
6
Vasopressin
Sympathetic Discharge
4
Vasoconstriction
↑ Contractility
↑ Sodium/Water Reabsorption
5
↑ Blood Volume
↑ Total Peripheral Resistance
5
↑ Cardiac Output
↑ BP

Etiology

- HTN broadly classified into two:

1. Essential
2. Secondary

Essential HTN

- HTN with no definable etiology.
- 80-95% of hypertensive patients.
- A common phenotype of separate disease entities involving systems that regulate ABP.

Essential HTN

- Cannot be cured, but it can be controlled
- Multifactorial
  - **Genetic**: Family history
    - 15 – 35% of heritability
    - Among identical twins concordances are ~60% for males and 30–40% for females
  - **Environmental:**
    - Urbanization
    - Obesity: 60% of hypertensives are overweight by > 20%
    - Increased salt intake
    - Low dietary intakes of calcium and potassium
    - Alcohol, physical inactivity

Secondary HTN

- Results from a specific cause.
- Accounts for only **5-20%** of cases.
- Identifying pts is important b/c
  - Correction of the cause may be curative

Secondary HTN

1. **Renal HTN**
   a) Reno-vascular HTN
   b) Renal parenchymal HTN
   c) Renin secreting tumors
2. **Endocrine HTN**
   a) Conn’s syndrome (primary aldosteronism)
   b) Cushing’s syndrome.
   c) Pheochromocytoma

Secondary HTN

D. Use of combined OCP

- Most common cause of endocrine HTN.
- The RAAS may be involved, since estrogen stimulates the hepatic production of renin substrate (**angiotensinogen**).
- 5% of OCP users develop HTN within 5yr
- Age > 35yr, Hx of PIH, smoking are risk factors.
- BP falls to normal in 50% of cases 3-6 mo after withdrawal.

E. **Others**: Acromegally, hyperparathyroidism, thyrotoxicosis

Assefa M (MSc), Addis Ababa University

Secondary HTN

3. Vascular

A. Coarctation of the aorta

- Leads to renal hypoperfusion→ activation of RAAS and SNS→ HTN.

Factors Affecting the Course of HPN

- **Race**: blacks have 4x risk of HTN related mortality compared to whites.
- **Age**: the younger onset, the greater the reduction of life expectancy
- **Gender**: females fare better up to 65 yr
- **DBP**: Persistently > 115 mmHg → poor prognosis
- Smoking
- Diabetes mellitus
- Obesity
- Dyslipidemia
- Excess alcohol intake
- Evidence of end organ damage.

Effects of HTN

- HTN is a risk factor for atherosclerosis
- It results in injury to major organs – **target organ damage.**
- The heart, the CNS, and the kidneys are major target organs.
- Target organ damage can be acute or chronic.

Effects of HTN

1. Effects on the Heart

- HTN → hypertensive heart diseases a result of:
  - Increased afterload
  - Coronary atherosclerosis
- Most deaths in HTN are cardiac (from CHF or AMI).

Effects of HTN

2. Effects on CNS

i) **Retinopathy**

ii) **Cerebral infraction/ischemia**: due to atherosclerosis of cerebral arteries

- TIA
- Ischemic stroke

iii) **Cerebral Hemorrhages**: due to elevation of ABP and development of **microaneurysms**.

iv) **Hypertensive encephalopathy**

Effects of HTN

3. Effects on Kidneys

- Glomerular atherosclerosis of the afferent and efferent arterioles and the glomerular capillary tufts → CKD.
- Pathology: hypertensive nephrosclerosis
- Manifest as proteinuria + microscopic hematuria.

Clinical Presentation

General

- The patient may appear very healthy, or may have the presence of additional CV risk factors:
  - ✓ Age (≥55 years for men and 65 years for women)
  - ✓ Diabetes mellitus
  - ✓ Dyslipidemia
  - ✓ Microalbuminuria
  - ✓ Family history of premature CV disease
  - ✓ Obesity (body mass index ≥30 kg/m^2)
  - ✓ Physical inactivity
  - ✓ Tobacco use

Clinical Presentation

Symptoms

- Most patients are asymptomatic and are identified only in the course of a physical examination.

Signs

- Previous BP values in the prehypertension or hypertension category.

Investigations

- **Basic tests** (always included)
  - ✓ U/A
  - ✓ CBC
  - ✓ Serum Na, Ca, K
  - ✓ Scr with eGFR
  - ✓ FBG
  - ✓ Lipid profile
  - ✓ ECG
  - ✓ TSH
- **Optional tests** (usually included)
  - ➢ Uric acid
  - ➢ CXR
  - ➢ Echocardiography
  - ➢ Urine albumin

Management

- Benefits of treating elevated BP
  a) Decreased risk of stroke (by 35-40%)
  b) Decreased risk of MI (by 20-25%)
  c) Decreased risk of HF (by 50%)

Recommended Lifestyle Modifications

Modifcation	Recommendation	Approximate SBP Reduction
Weight reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m^2)	5–20 mm Hg per 10-kg weight loss
Adopt DASH eating plan (includes substantial K intake)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Reduce Na intake	Reduce Na intake to ≤ 2400 mg/day Reducing Na intake further to ≤ 1500 mg/day is associated with greater BP reduction	2–8 mm Hg

Recommended Lifestyle Modifications

Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to: Men: 2 drinks/day (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey) Women and those of lower body weight: 1 drink/day	2–4 mm Hg

Goal BP Values Recommended by Various Organizations

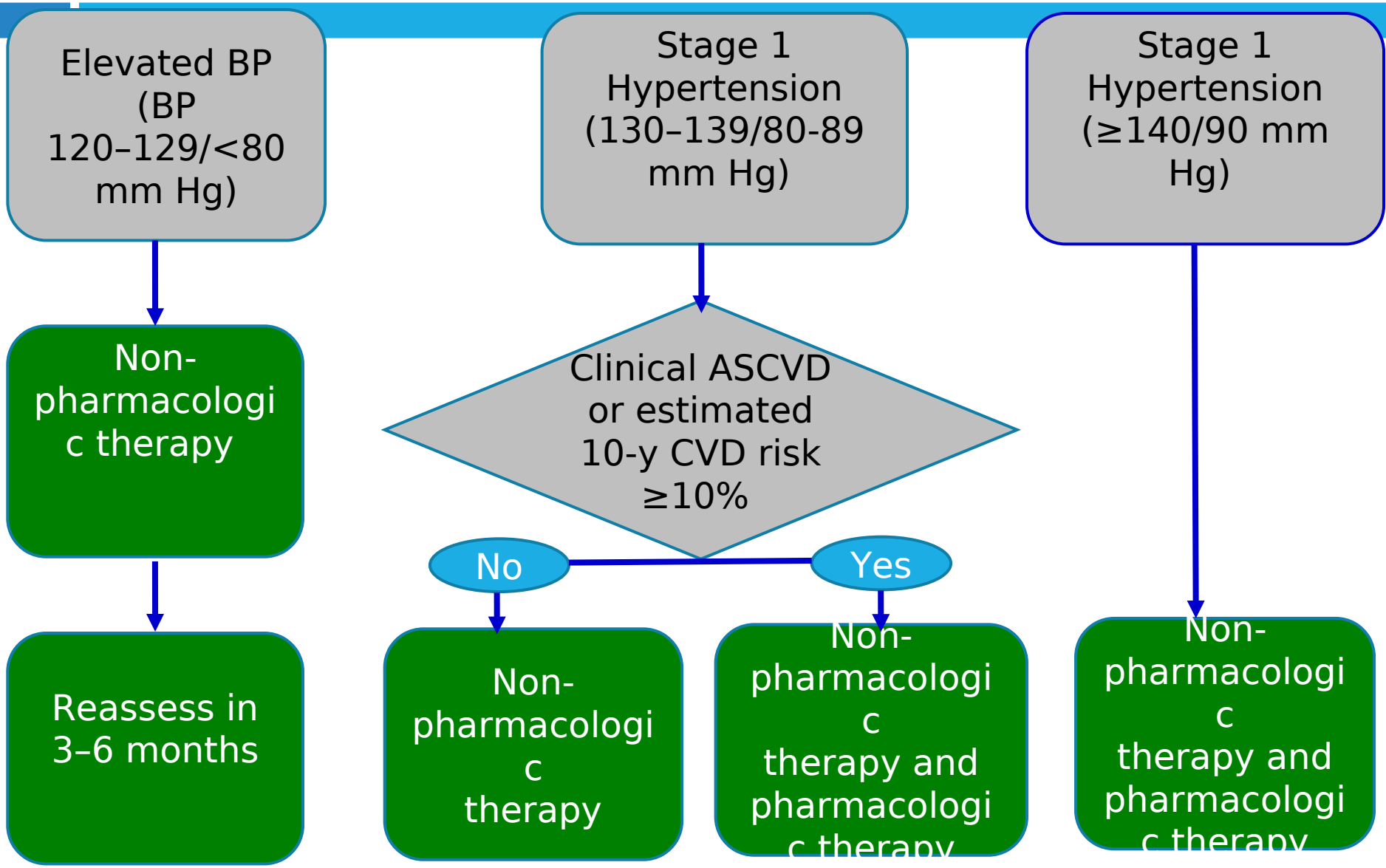
Patient Population	Goal BP (mm Hg)	Guideline
✓ General population ≥ 60 yr	< 150/90	JNC8, ACP/AAFP
✓ General population < 60 yr	< 140/90	JNC8
✓ Adults 18–80 yr	< 140/90	ASH/ISH
✓ Patients with DM ≥ 18 yr (a lower SBP target of < 130 mm Hg may be appropriate in patients at high risk of cardiovascular disease)	< 140/90	ADA
✓ Pregnancy with DM	120-160/ 80-105	ADA
✓ Patients with CKD	≤ 140/90	JNC8, KDIGO
✓ In adults both with and without DM having a urine albumin excretion <30 mg/24 hr (or equivalent) whose BP is consistently > 140/90 mm Hg	≤ 140/90	KDIGO
✓ In adults both with and without DM	< 130/80	

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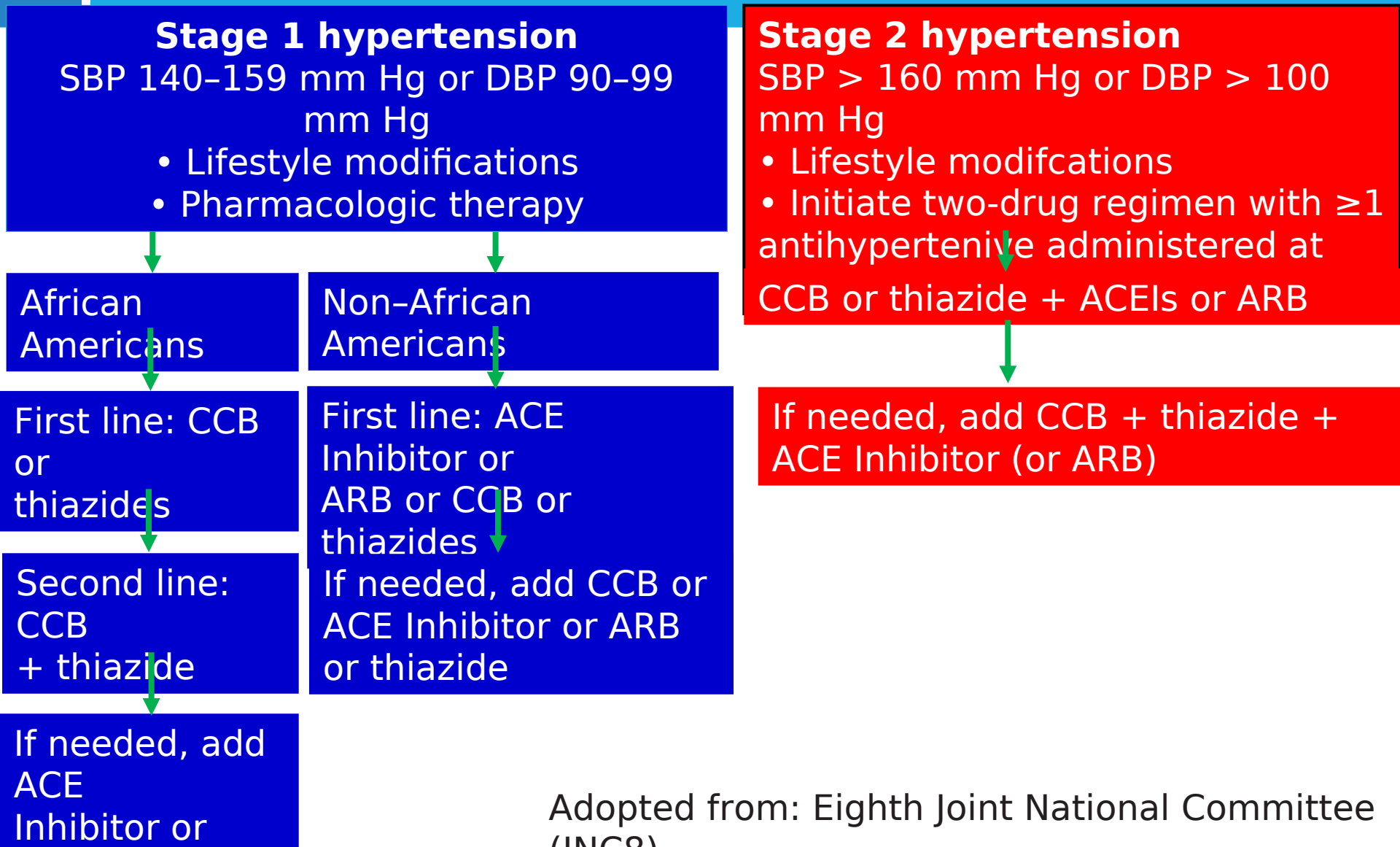
Therapeutic Management

- **First-line treatment**
  - For patients with stage 1 hypertension whose 10-year
    ASCVD risk score is less than 10%, lifestyle modification alone is reasonable.
  - A combination of lifestyle modification and antihypertensives should be used in patients with
    - Stage 1 hypertension with established CV disease or a 10-year ASCVD risk score >10%, and
    - Stage 2 hypertension

Therapeutic Management (ACC/AHA, 2019)



HTN Management Algorithm



Adopted from: Eighth Joint National Committee (JNC8)

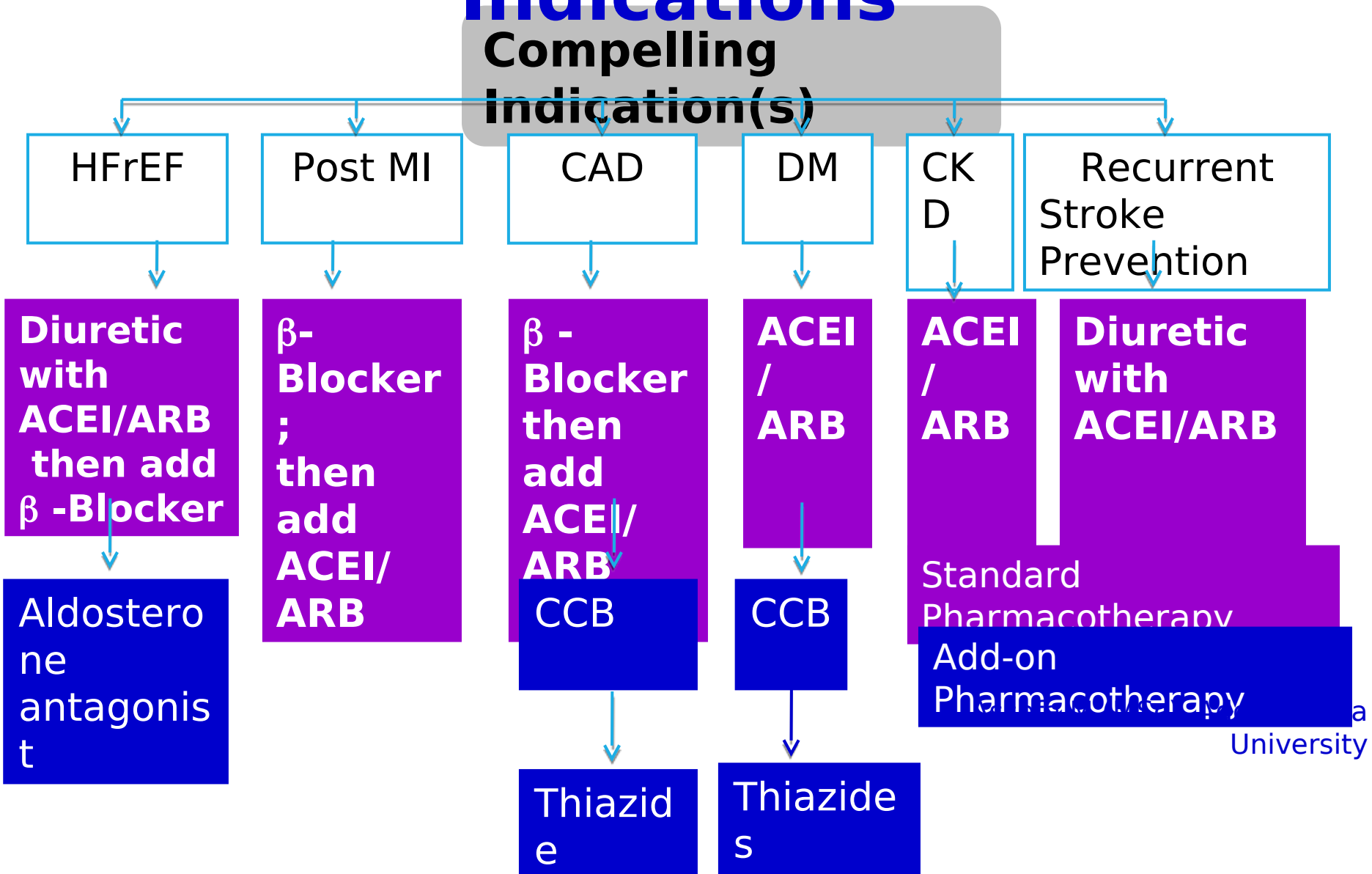
Therapeutic Management

- If BP is still not controlled after an adequate trial of optimally dosed ACE Inhibitor (or ARB), thiazide diuretic, and CCB, consider adding other agents:
  - Spironolactone,
  - Central-acting agents,
  - β-blockers,
  - Vasodilators,
  - α-blockers.
- Avoid combination use of ACE inhibitor and ARB

Patients with Compelling Indications

- **Compelling indications** represent specific comorbid conditions where evidence from clinical trials supports using specific antihypertensive classes to treat both the compelling indication and hypertension
- Six compelling indications

Patients with Compelling Indications



Thiazides

- Hydrochlorothiazide, chlorthalidone, indapamide
- Hydrochlorothiazide is consistently inferior to other antihypertensive drugs at lowering ambulatory blood pressure
- Can worsen gout by increasing serum uric acid
- Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy
- Greater risk of developing DM than with ACEI, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
- Can assist in the management of osteoporosis by preventing urine calcium loss

Aldosterone Antagonist

- Spironolactone is an effective and well-tolerated **add-on** therapy for appropriately selected patients.
- Because of its structural similarity to progesterone, dose-dependent antiandrogenic effects can occur
  - Responsible for gynecomastia and erectile dysfunction in men,
  - Can cause breast pain or tenderness in both sexes, and
  - Can lead to menstrual irregularities in premenopausal women.
- Spironolactone is contraindicated in pregnancy because of the risk of feminizing male fetuses.
- For patients with resistant hypertension who do not tolerate spironolactone, **eplerenone** is a good alternative.

Diuretics

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
Diuretics	Thiazides	HCT	12.5 – 25	1
		Chlorthalidone	12.5 – 100	1
		Indapamide	1.25 –5	1
	Aldosterone Antagonists	Spironolactone	25 – 50	1 or 2
		Epilerone	50 – 100	2

ACE and ARBs

- In patients with greater RAS activation, initial therapy with an ACEI or ARB is logical
  - In patients restricting salt intake,
  - Younger, white patients, and/or
  - Those with higher measured renin concentrations
- ACE inhibitors and ARBs are contraindicated in
  - Pregnancy
  - Bilateral renal artery stenosis
  - Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.

ACE and ARBs

- Dry cough may occur in up to 20% of patients treated with ACEIs; **cough** is more common among Asian Americans.
- Angioedema is an infrequent but more serious risk that is 2–4 times more common in **African American patients** than in whites
- Historically, ACEIs offered a significant cost advantage over ARBs
- Patients who experience cough with ACEIs may safely be changed to ARBs.
- Those who experience ACEI-induced angioedema should discontinue the ACEI for at least 6 weeks.

ACEIs

Class	Drug	Usual Dose Range, mg/day	Daily Frequency
ACEIs	Captopril	12.5–50	2 to 3
	Enalapril	5 – 40	1 or 2
	Lisinopril	10 - 40	1
	Perindopil	4 – 16	1

ARBs

Class	Drug	Usual Dose Range, mg/day	Daily Frequency
ARBs	Candesartan	8 – 32	1 or 2
	Irbesartan	150 – 300	1
	Losartan	50 –100	1
	Valsartan	80 – 320	1

Calcium Channel Blockers

i. Dihydropyridine CCBs: Amlodipine, felodipine, nifedipine
   - Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension
   - Useful for isolated systolic hypertension or use in African American patients

ii. Non-dihydropyridine CCBs: Diltiazem, verapamil
   - Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g. atrial fibrillation, stable angina)
   - Contraindicated in heart block and sick sinus syndrome

CCBs

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
CCB	Dihydropyridines	Amlodipine	2.5 - 10	1 or 2
		Felodipine	5 – 10	1
		Nifedipine XL	30 – 90	1
	Non-dihydropyridines	Diltiazem LA	120 – 540	1
		Verapamil	100 – 400	1

β-Blockers

- β-Blockers have been shown to be inferior to other first-line agents in patients with uncomplicated hypertension
- Caution with asthma or severe COPD (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.
- Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
- Can mask some signs of hypoglycemia in patients with DM
- Can cause depression

β-Blockers

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
BBs	Cardioselective	Atenolol	25 - 100	1
		Metoprolol	50 – 100	1
	Non-selective	Propranolol	160 – 480	2
		Timolol	10 – 40	1
	Mixed α - and β - blockers	Carvedilol	12.5 – 50	1
		Labetalol	200 – 800	2

Special Populations

1) **Patients with CHD:**
   - Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)
2) **Older adult patients:**
   - Caution with antihypertensive agents & orthostatic hypotension
   - Initiate with low dose and titrate slowly.

- **African American patients:**
   - β-Blockers and ACE inhibitors are generally less effective as monotherapy than in non–African American patients; however, combination therapy with thiazides improves effectiveness;
   - β-blockers and ACE inhibitors should still be used if comorbid conditions dictate

Special Populations

4) Women

- Oral estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.
- HTN increases the risk to mother and fetus in women who are pregnant.
- Preferred medications include methyldopa and labetalol. ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects
- Hypertension during pregnancy is categorized as preeclampsia, eclampsia, gestational, chronic, and superimposition of preeclampsia on chronic hypertension
- Preeclampsia: defined as a elevated BP greater than or equal to130/80 mm Hg that appears after 20 weeks gestation accompanied by new-onset proteinuria (≥300 mg/24 hours)
- Eclampsia: the onset of convulsions in preeclampsia, is a medical emergency

Special Populations

- **Gestational hypertension** is new-onset hypertension arising after midpregnancy in the absence of proteinuria
- **Chronic hypertension** is elevated BP that is noted before pregnancy
- Hypertensive disease of pregnancy is associated with a number of complications, including
  - Superimposed preeclampsia,
  - Preterm delivery,
  - Fetal growth restriction or demise,
  - Placental abruption,
  - Heart failure, and
  - Acute kidney failure

Special Populations

- Definitive treatment of preeclampsia is delivery
- Antihypertensive agents are used prior to induction of labor if DBP is greater than 105 to 110 mm Hg with a target DBP of 95 to 105 mm Hg.
  - Hydralazine beginning with 5 mg IV, followed by 5 to 10 mg boluses as necessary every 20 minutes
  - Labetalol beginning with 10 or 20 mg intravenously followed by doubling the dose at 10-minute intervals up to 80 mg
- Treatment of convulsions:
  - $MgSO_4$
    - Loading dose: 5gm IV over 20 min
    - Maintenance dose: 1 to 3 g/hour IV
- For chronic hypertension in pregnancy, **methyldopa** is considered the drug of choice

Resistant HTN

- Failure to reach goal BP in patients who are prescribed full doses of an appropriate three-drug regimen that includes a diuretic
  - **Pseudoresistance**: blood pressure is uncontrolled because of factors such as nonadherence, poor BP measurement technique, or a white-coat effect
  - Causes
    - Improper BP measurement
    - Volume overload
    - Excessive Na intake
    - Drug-induced causes
      i) Nonadherence
      ii) Inadequate doses of antihypertensive medications
      iii) Inappropriate drug combinations
      iv) Specific drugs

Resistant HTN

- Specific drugs
  1. NSAIDs
  2. Cocaine, amphetamines
  3. Sympathomimetics
  4. Oral contraceptives
  5. Adrenal steroids
  6. Cyclosporine or tacrolimus
  7. Erythropoietin
  8. Licorice
  9. Dietary supplements

Resistant HTN

- **Treatment**:
  - Rule out and/or treat, if possible, causes of resistant HTN.
  - Administer one or more antihypertensive drug at bedtime for increased efficacy
  - For patients with uncontrolled HTN on ACE inhibitor (or ARB) plus thiazide-like diuretic plus CCB, consider adding one (or more) of the following:
    - ARA (e.g., spironolactone)
    - β-Blocker
    - α1-Blocker
    - Vasodilator
    - Centrally acting agent

Hypertensive Crises

- **Hypertensive crises:** are clinical situations where BP values are very elevated, typically **greater than 180/120** mm Hg.
  - ✓ They are categorized as either a hypertensive emergency or hypertensive urgency.
  - ✓ **Hypertensive emergencies:** are extreme elevations in BP that are accompanied by acute or progressing target-organ damage.
  - ✓ **Hypertensive urgencies:** are high elevations in BP without acute or progressing target-organ injury.

Hypertensive Crises

- **Hypertensive Urgency**
  - There is no role for intravenous BP lowering drugs
  - Possible precipitating factors for hypertensive urgency include
    - Non-adherence to anti-hypertensive medications,
    - Less effective outpatient blood pressure control,
    - Acute pain,
    - Herbal supplement and
    - Emotional stress
  - Acute administration of a short-acting oral antihypertensive (e.g., captopril, clonidine, or labetalol)

Hypertensive Crises

- **Hypertensive Emergency**
  - Immediate BP reduction to limit new or progressing target-organ damage
  - The goal in hypertensive emergencies is not to lower BP to <140/90 mm Hg;
  - The initial target is a reduction in MAP of up to 25% within minutes to hours
  - Gradual reductions toward goal BP values can be attempted after 24 to 48 hours.

Hypertensive Crises

- **Hypertensive Emergency**
  - IV medication is used to treat hypertensive emergencies
    - Nitroprusside 0.5 – 10 mcg/kg/min IV infusion
    - IV nitroglycerin 5 – 100 mcg/min infusion
    - Fenoldopam,
    - Nicardipine, and clevidipine
    - Hydralazine 12 – 20 IV or 10 – 50 IM

Follow-up Evaluation

- At a minimum, assessment of response to medications should be done at 1-month intervals.
- In patients with stage 2 hypertension or those with comorbidities (eg, DM, vascular disease, HF, or CKD), shorter time frame of ≤2 weeks is more appropriate
- Once BP is controlled, annual or semiannual monitoring of serum biochemistries such as serum creatinine or potassium are recommended

Safety Monitoring Parameters

Class	Parameters
Diuretics	BP; BUN/Scr; serum electrolytes (K, Mg, Na); uric acid (for thiazides)
Aldosterone antagonists	BP; BUN/Scr; serum K
ACE inhibitors	BP; BUN/Scr; serum K
ARBs	BP; BUN/Scr; serum K
CCBs	BP; HR
BBs	BP; HR

HEART FAILURE

Objectives

- Describe the pathophysiology of HF
- Differentiate between the common underlying etiologies of heart failure
- Classify patients by NYHA Functional Classification and ACC/AHA Heart Failure Staging.
- Describe the goals of therapy for a patient with acute or chronic HF
- Develop a specific evidence-based treatment plan for a patient with acute or chronic HF

Background

- **Heart Failure:** is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
- **Heart failure** is clinical state in which an abnormality of the heart is responsible for its inability to **fill with** or **eject** blood at a rate proportional to the requirements of the metabolizing tissues.
- HF is frequently, caused by a defect in myocardial contraction, and then the term **myocardial failure** is appropriate.
- **Prevalence**:
  - Affects 5.1 million Americans
  - Prevalence in developed nations ~ 2%.
  - Increase with age: affects 6–10% of people over the age of 65

Forms of Heart Failure

Low-output Vs High-output Heart Failure

- **Low-output HF:** occurs secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease
- **High-output HF:** occurs in patients with reduced systemic vascular resistance, i.e., hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease

Forms of Heart Failure

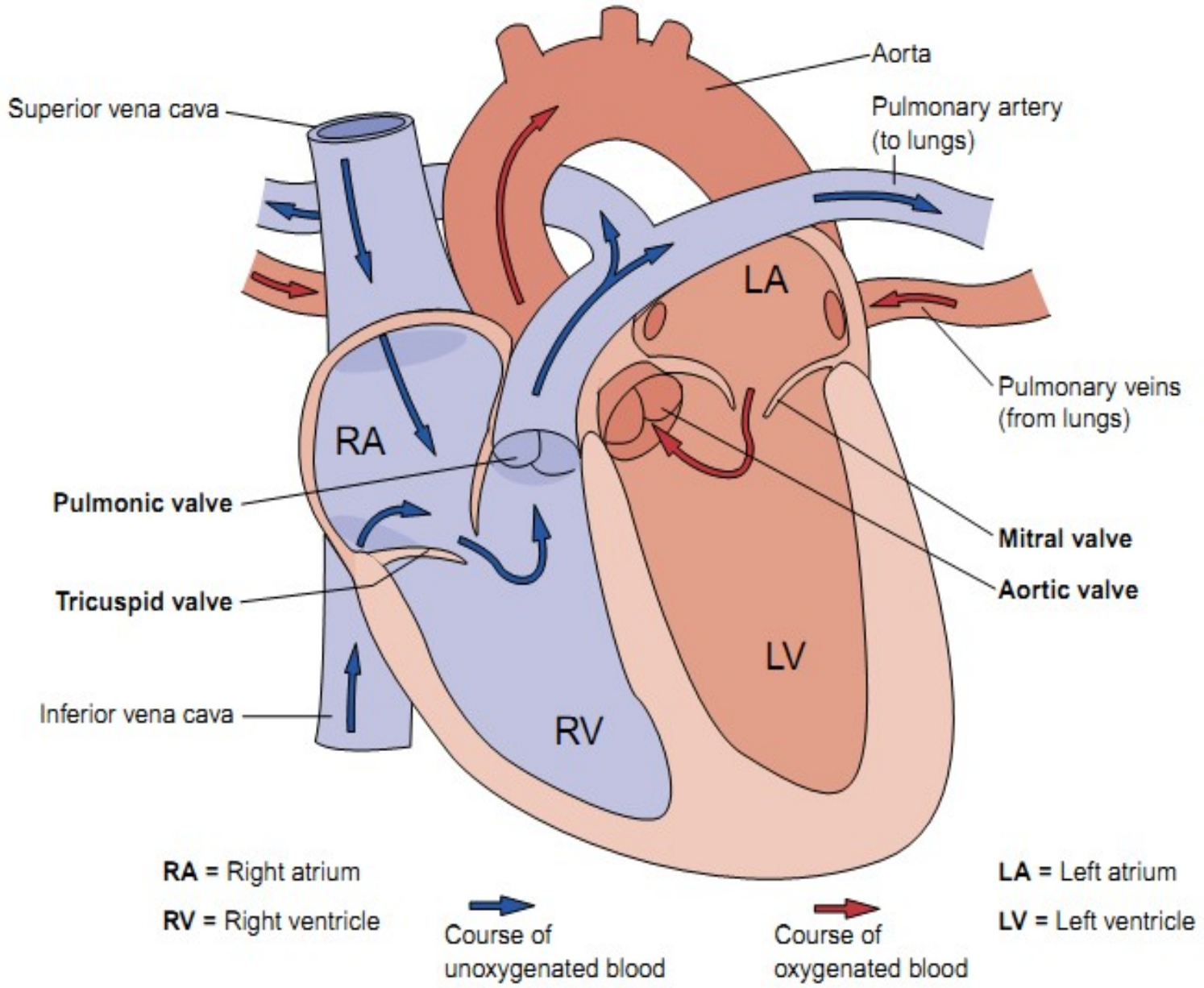
Acute Versus Chronic Heart Failure

- In **acute HF** the ***sudden*** reduction in cardiac output often results in systemic hypotension without peripheral edema.
- **Chronic HF** is typically observed in patients with dilated cardiomyopathy or multivalvular heart disease and ***develops*** or ***progresses slowly***.

Forms of Heart Failure

Right-sided Vs Left-sided Heart Failure

- **Left-sided HF:** in patients in whom the **left ventricle** is hemodynamically overloaded (e.g., aortic regurgitation) or weakened due to myocyte loss (e.g., post MI)
  - ✓ Develop **dyspnea** and **orthopnea** as a result of pulmonary congestion
- **Right-sided HF:** When the underlying abnormality affects the **right ventricle** primarily (e.g., primary pulmonary hypertension secondary to chronic pulmonary thromboembolism)
  - ✓ Develop edema, congestive hepatomegaly, and systemic venous distention


Aorta
Superior vena cava
Pulmonary artery
(to lungs)
LA
Pulmonary veins
(from lungs)
RA
Pulmonic valve
Mitral valve
Aortic valve
Tricuspid valve
LV
Inferior vena cava
RV
RA = Right atrium
RV = Right ventricle
Course of
unoxygenated blood
Course of
oxygenated blood
LA = Left atrium
LV = Left ventricle

Forms of Heart Failure

Heart failure with reduced EF (HF*r*EF)

- Defined as a clinical diagnosis of HF and an LVEF of 40% or less
- Systolic dysfunction
- Dilated ventricle
- Two thirds of cases are attributable to chronic heart disease (CHD).
- One third of cases are attributable to nonischemic cardiomyopathy.

Forms of Heart Failure

Heart Failure with Preserved EF (HF*p*EF)

- Diastolic dysfunction
- Defined as an LVEF of 50% or greater; borderline HF*p*EF is LVEF 41%–49%
- Impaired ventricular relaxation and filling
- Normal wall motion
- Most common cause is HTN (60%–89%)

Causes of Heart Failure

UNDERLYING CAUSES

- **Ischemic heart disease** is responsible for about three-quarters of all cases.
- Cardiomyopathies are second in frequency,
- HTN remains an important cause
- Congenital and valvular are less common causes.

Causes of Heart Failure

- Systolic Dysfunction (Decreased Contractility)
  - Reduction in muscle mass (e.g., myocardial infarction)
  - Dilated cardiomyopathies
  - Ventricular hypertrophy
  - Pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
  - Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Causes of Heart Failure

- Diastolic Dysfunction (Restriction in Ventricular Filling)
  - Increased ventricular stiffness
  - Ventricular hypertrophy (e.g., hypertrophic cardiomyopathy,
    pressure and/or volume overload)
  - Infiltrative myocardial diseases (eg, amyloidosis, sarcoidosis,
    endomyocardial fibrosis)
  - Myocardial ischemia and infarction
  - Mitral or tricuspid valve stenosis
  - Pericardial disease (eg, pericarditis, pericardial tamponade)

Causes of Heart Failure

- Non-Ischemic Etiologies
  - Hypertension
  - Viral illness
  - Thyroid disease
  - Excessive alcohol use
  - Illicit drug use
  - Pregnancy-related heart disease
  - Familial congenital disease
  - Valvular disorders such as mitral or tricuspid valve regurgitation or stenosis

CAUSES OF HEART FAILURE

Precipitating Causes

1. **Infection*:*** The resulting fever, tachycardia, hypoxemia, and the increased metabolic demands may place a further burden on an overloaded, but compensated, myocardium of a patient with chronic heart disease.

2. **Arrhythmias***:*

   a) **Tachy arrhythmias** reduce the time available for ventricular filling, contributing especially to diastolic HF; cause ischemic myocardial dysfunction in patients with IHD

   b) **Slowing of the heart rate** associated with complete AV block or other severe bradyarrhythmias reduces cardiac output

Causes of Heart Failure

Precipitating Causes…

3. **Physical, Dietary, Fluid, Environmental, and Emotional Excesses:** The sudden sodium intake as with a large holiday meal, the inappropriate d/c of drugs or other therapy for HF, blood transfusions, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate HF in patients who were previously compensated.

4. **Myocardial Infarction**: a new infarct may further impair ventricular function and precipitate HF

5. **Pulmonary Embolism:** Pulmonary emboli may result in further elevation of pulmonary arterial pressure, which in turn may produce or intensify ventricular failure

CAUSES OF HEART FAILURE

Precipitating Causes…

6. **Anemia**: In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output

- ✓ However, a diseased, overloaded, but otherwise compensated heart may be unable to augment sufficiently the volume of blood that it delivers to the periphery.

7. **Thyrotoxicosis and Pregnancy**: Similar to anemia and fever, thyrotoxicosis and pregnancy are also high cardiac output states.

- ✓ The development or intensification of HF in a patient with previously compensated heart disease may actually be one of the first clinical manifestations of hyperthyroidism

Causes of Heart Failure

Precipitating Causes …

8. Aggravation of Hypertension

9. Rheumatic, Viral, and Other Forms of Myocarditis:

✓Acute rheumatic fever and a variety of other inflammatory or infectious processes affecting the myocardium may precipitate HF in patients with or without preexisting heart disease

10. Infective Endocarditis*:* The additional valvular damage, anemia, fever, and myocarditis that often occur as a consequence of infective endocarditis may, singly or in combination, precipitate HF

Causes of Heart Failure

- **Drugs Precipitate or Exacerbate Heart Failure**

1) Agents Causing Negative Inotropic Effect
   - Antiarrhythmics (eg, disopyramide, flecainide, and others)
   - β-blockers (eg, propranolol, metoprolol, atenolol, and others)
   - Nondihydropyridine calcium channel blockers (eg, verapamil)
   - Itraconazole
   - Terbinafine

Causes of Heart Failure

2) Cardiotoxic Agents
   - Doxorubicin
   - Daunomycin
   - Cyclophosphamide
3) Agents Causing Sodium and Water Retention
   - Nonsteroidal anti-inflammatory drugs
   - COX-2 inhibitors
   - Glucocorticoids
   - Androgens
   - Estrogens
   - Salicylates (high dose)
   - Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)
   - Thiazolidinediones (eg, pioglitazone)

PATHOPHYSIOLOGY

- Heart failure is a progressive disorder initiated by an event that impairs the ability of the heart to **contract** and/or **relax**
- The **decrease in the heart's pumping capacity** results in the heart having to rely on **compensatory responses** to maintain an adequate cardiac output
- These **compensatory responses** include
  a) Tachycardia and increased contractility through sympathetic nervous system (SNS) activation
  b) An in preload results in an increase in stroke volume
  c) Vasoconstriction and
  d) Ventricular hypertrophy and remodeling.

PATHOPHYSIOLOGY

a) **Increased preload (through Na+ and water retention)**

- ✓ **Renal perfusion in heart failure is reduced** because of depressed cardiac output and redistribution of blood away from non vital organs.
- ✓ The kidney interprets the reduced perfusion as an ineffective blood volume, resulting in activation of the RAAS in an attempt to maintain blood pressure and increase renal sodium and water retention.
- *Optimize stroke volume*
- ☝ Pulmonary and systemic congestion and edema formation
- ☝ Increased myocardial oxygen demand

PATHOPHYSIOLOGY

b) Vasoconstriction and Increased Afterload

- To *redistribute blood flow away from nonessential organs to coronary and cerebral circulations* to support blood pressure, which may be reduced secondary to a decrease in cardiac output

  (mean arterial pressure = CO × SVR)

- A number of neurohormones contribute to the vasoconstriction including **NE**, **angiotensin II**, **endothelin-1**, *and* **arginine vasopressin** *(AVP)*
  - Maintain BP in face of reduced CO
  - Shunt blood from nonessential organs to brain and heart
  - Increased myocardial oxygen demand
  - Increased afterload decreases stroke volume and further activates the compensatory responses

PATHOPHYSIOLOGY

c) Tachycardia and increased contractility (because of SNS activation)

- The change in heart rate and contractility that rapidly occurs in response to a drop in cardiac output is primarily a result of release of norepinephrine (NE) from adrenergic nerve terminals,
  - Helps maintain CO
  - Increased myocardial oxygen demand
  - Shortened diastolic filling time
  - Precipitation of ventricular arrhythmias

PATHOPHYSIOLOGY

d) Ventricular hypertrophy and remodeling

- **Ventricular hypertrophy** is a term used to describe an *increase in ventricular muscle mass*.
- **Cardiac or ventricular remodeling** is a broader term describing changes in both *myocardial cells* and *extracellular matrix* that result in changes in the *size*, *shape*, *structure*, and *function* of the heart
- *Angiotensin II*, *NE*, *endothelin*, *aldosterone*, *vasopressin* and *cytokines*, that are activated both systemically and locally in the heart play an important role in initiating the signal–transduction cascade responsible for ventricular remodeling

Ventricular Hypertrophy and Remodeling

- Pressure overload (and probably hormonal activation) associated with **hypertension** produces a **concentric hypertrophy** (*increase in the ventricular wall thickness without chamber enlargement).*
- Conversely, **eccentric left ventricular hypertrophy** (myocyte lengthening with *increased chamber size* with minimal increase in wall thickness) characterizes the hypertrophy seen in patients with *systolic dysfunction* or *previous MI*

Ventricular Hypertrophy and Remodeling

- Helps maintain CO
- Reduces myocardial wall stress
- ☞ Increased risk of myocardial cell death
- ☞ Diastolic dysfunction
- ☞ Systolic dysfunction
- ☞ Increased risk of myocardial ischemia
- ☞ Increased arrhythmia risk
- ☞ Fibrosis

Clinical Features; Symptoms

- Respiratory:
  - Exertional dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Night cough
- Others:
  - Fatigue
  - Edema: from feet upwards
  - Anorexia and weight loss

Clinical Features; Signs

- Pulmonary rales, pleural effusion
- Neck vein distension and raised JVP
- Displaced apical impulse
- Gallop rhythm
- Tender hepatomegally
- Cachexia
- Extremity edema

INVESTIGATIONS

- **Diagnostic:**
  - CXR: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions.
  - ECG: To assess HR, rhythm, LVH, conduction, previous MI
  - Echocardiography: ventricular performance, cardiac structure.
  - Other tests:
  - Blood chemistry: Electrolytes, RFT, FPG, Lipid profile,
  - CBC: Hgb/HCT, WBC,
  - U/A

DX: Framingham Criteria

Major criteria

- PND
- Neck vein distension
- +ve HJR
- Bibasal rales
- Cardiomegaly
- S_3 gallop
- Raised JVP

Minor criteria

- Extremity edema
- Night cough
- Exertional dyspnea
- Hepatomegally
- Pleural effusion
- Tachycardia(≥120 bpm)

2 major or **1 major + 2 minor** criteria establish clinical DX of HF.

Stages and Functional Class of HF

Stage		NYHA Functional Class	
A	At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HF symptoms
		II	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
		IV	Symptoms of HF at rest or unable

Management

Goals of therapy

- Modify or control risk factors (HTN, obesity, DM)
- Manage structural heart disease
- Reduce morbidity and mortality
- Prevent or minimize Na and water retention
- Eliminate or minimize HF symptoms
- Slow progression of worsening cardiac function

HF*r*EF or Systolic HF

- Nonpharmacologic therapy

1) Prevent further cardiac injury.
   - Discontinue smoking.
   - Reduce weight if obese
   - Control HTN (goal BP < 130/80 mm Hg)
   - Control DM.
   - Decrease alcohol intake
   - Limit Na intake
   - Educate patient about appropriate self-care

- Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low
- Modest exercise

1) Monitor for thyroid disease

HF*r*EF or Systolic HF

- **Diuretics**
  - Place in therapy: Indicated in patients with evidence of fluid retention
  - Benefits
    (a) Short-term benefit (days)
      - Decreased jugular venous distension
      - Decreased pulmonary congestion
      - Decreased peripheral edema

    (b) Intermediate-term benefits (weeks to months)
      - Decreased daily symptoms
      - Increased exercise tolerance

    - Long-term benefits (months to years): No benefit on mortality

Diuretics

- Dosing and administration considerations
  - Should be combined with an ACE inhibitor, β-blocker, and aldosterone receptor antagonist (ARA)
  - Start with a low initial dose and then double the dose and titrate according to the patient's weight and diuresis as needed
  - For a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day
  - Long-term therapy should be adjusted to maintain a euvolemic state
  - A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed
  - Loop diuretics are preferred because of their greater diuretic capabilities; also retain efficacy with decreased renal function.

Diuretics

- Monitoring:
  - Monitor and replace K (goal with CVD is ≥4.0 mEq/L)
  - Scr and renal function to avoid acute kidney injury with overdiuresis.

Diuretics and Recommended Dosing

Agent	Oral BA (%)	Initial Daily Dose	Maximal Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide	10–67	20–40 mg daily or BID	600	6–8
Bumetanide	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid	100	25–50 mg daily or BID	200	6–8

Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg

ACE inhibitors

- Place in therapy: Recommended in all patients with HF*r*EF and current or prior symptoms, unless contraindicated
- Benefits:
  (a) Decreased mortality (25%–50% relative risk reduction compared with placebo depending on severity of HF)
  (b) Decreased hospitalizations (about 30% relative risk reduction compared with placebo)
  (c) Symptom improvement
  (d) Improved clinical status
  (e) Improved sense of well-being

ACE inhibitors

- Dosing and administration considerations
  - Start low and double the dose every 1–4 weeks to target dose
  - Avoid use in
    - Patients who have experienced angioedema
    - Who are pregnant or plan to become pregnant
  - Use caution if
    - SBP is less than 80 mm Hg,
    - SCr is greater than 3 mg/dL,
    - K is greater than 5.0 mEq/L, or
    - The patient has bilateral renal artery stenosis

ACE inhibitors

- Monitoring
  - Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients
  - Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness)
  - Monitor angioedema (<1%):
    - Can switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%)
  - Monitor cough (20%):
    - Can switch to ARBs (less than 1%)

ACE Inhibitors and Recommended Dosing

Drug	Starting Dosage	Target Dosage	Maximal Dosage
Captopril	6.25 mg three times daily	50 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 mg twice daily	20 mg twice daily
Lisinopril	2.5–5 mg daily	20 mg daily	40 mg daily
Perindopril	2 mg daily	8 mg daily	16 mg daily
Ramipril	1.25–2.5 mg daily	10 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily	4 mg daily

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Angiotensin Receptor Blockers

- Place in therapy
  - (a) Recommended in patients with HF*r*EF with current or prior symptoms who are unable to take an ACE inhibitor
    - Cough
    - Angioedema
  - (b) Have not been proven superior to ACE inhibitors at target HF dosages.
- Benefits:
  - Decreased HF-related hospitalizations and decreased death from CV causes

Angiotensin Receptor Blockers

- Dosing and administration
  - Start low and double the dose every 1–4 weeks to target dose
  - Avoid use in
    - Patients who have experienced angioedema
    - Who are pregnant or plan to become pregnant
  - Use caution if
    - SBP is less than 80 mm Hg,
    - SCr is greater than 3 mg/dL,
    - K is greater than 5.0 mEq/L, or
    - The patient has bilateral renal artery stenosis

Angiotensin Receptor Blockers

- Monitoring
  - Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients
  - Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness)

Angiotensin Receptor Blockers

ARBs and Recommended Dosing

Drug	Starting Dosage	Target Dosage
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	20–40 mg twice daily	160 mg twice daily

β-blockers

- Place in therapy:
  - Recommended in all patients with HF*r*EF with current or prior symptoms unless contraindicated
- Benefits (when added to an ACE inhibitors):
  - Decreased mortality (about 35% relative risk reduction compared with placebo)
  - Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
  - Symptom improvement
  - Improved clinical status

β-blockers

- Dosing and administration considerations
  - Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HF*r*EF.
  - Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvolemic.
  - Should not be prescribed without diuretics in patients with current or recent history of fluid retention
  - Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose.
    - Aim to achieve target dose in 8–12 weeks
  - Avoid abrupt discontinuation; can precipitate clinical deterioration
  - Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

β-blockers

- Monitoring
  - BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)
    - Occurs in about 1% of patients when the β-blocker is titrated slowly
    - If these symptoms appear, lower the dose by 50%
  - Increased edema or fluid retention (monitor in 1–2 weeks)
    - 1% to 2% more common than with placebo
    - Responds to diuretic increase
  - Fatigue or weakness
    - One percent to 2% more common than with placebo
    - Usually resolves spontaneously in several weeks
    - May require dosage decrease or discontinuation

β-blockers

- β-Blockers and Recommended Dosing

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily
Carvedilol CR	10 mg daily	80 mg daily
Metoprolol succinate	12.5–25 mg daily	200 mg daily

Aldosterone Receptor Antagonists

- Place in therapy:
  - Recommended in patients with NYHA class II–IV with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists.
  - Patients with NYHA class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels
  - Recommended to reduce morbidity and mortality in patients after an MI when they have an LVEF <40% with symptoms of HF or an LVEF <40% and DM
- Benefits of spironolactone in NYHA class III and IV HF
  - Decreased mortality (30% relative risk reduction compared with placebo)
  - Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
  - Improved symptoms

Aldosterone Receptor Antagonists

- Benefits of eplerenone in NYHA class II HF
  - Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
  - Decreased death from CV causes (24% relative risk reduction compared with placebo)
  - Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
  - Decreased mortality (24% relative risk reduction compared with placebo)
- Benefits of eplerenone in left ventricular dysfunction after MI
  - Decreased mortality (15% relative risk reduction compared with placebo)
  - Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative reduction compared with placebo)

Aldosterone Receptor Antagonists

- Dosing and administration considerations
  - Should be added to ACE inhibitor (or ARB) and β-blocker therapy
  - SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women (or eGFR >30 mL/minute/1.73 m^2), and K should be less than or equal to 5.0 mEq/L.
  - In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an ARA

Aldosterone Receptor Antagonists

- ARAs and Recommended Dosing

Parameters	Eplerenone	Spironolactone
eGFR ≥ 50 mL/min/1.73 m^2 and K ≤ 5 mEq/L	25 mg daily	12.5–25 mg daily
Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR ≥ 50 mL/min/1.73 m^2	50 mg daily	25 mg daily or twice daily
eGFR 30–49 mL/min/1.73 m^2 and K ≤ 5 mEq/L	25 mg every other day	12.5 mg daily or every other day
Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR 30–49	25 mg daily	12.5–25 mg daily

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Aldosterone Receptor Antagonists

- Monitoring
  - K and SCr within 2–3 days, again at 7 days after starting therapy, monthly for first 3 months, and every 3 months thereafter.
    - If the dose of ACE inhibitor or ARB is increased, restart monitoring.
    - Hyperkalemia: bout 20% of patients.
    - Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L
  - Gynecomastia
    - Spironolactone: Reported at a rate of 10% in clinical trials
    - Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

Digoxin

- Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HF*r*EF; should be added after ACE inhibitor (or ARB) and β-blocker therapy
- Benefits
  (a) Improved symptoms
  (b) Improved exercise tolerance
  (c) Decreased hospitalizations (28% relative risk reduction compared with placebo)
  (d) No effect on mortality

Digoxin

- Dosing and administration considerations
  - For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
  - Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
  - No indication to load patients with digoxin in the setting of HF
  - Avoid abrupt discontinuation; can precipitate clinical deterioration

Digoxin

- Monitoring
  - Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9ng/mL are suggested.
    - Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
    - Risk of toxicity increases with age and renal impairment.
    - Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
    - Signs of toxicity generally include nausea, vomiting, vision changes
  - SCr should be monitored because the drug is primarily cleared renally

Hydralazine/isosorbide dinitrate

- Place in therapy
  - Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African American with NYHA class III or IV HF*r*EF
  - May be useful in patients with current or prior symptoms of HF*r*EF who are unable to tolerate an ACE inhibitor or an ARB
- Benefits
  - Decreased mortality (43% relative risk reduction compared with placebo in African American patients)
  - Reduced pulmonary congestion and improved exercise tolerance

Hydralazine/isosorbide dinitrate

- Dosing and administration considerations
  - Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses
  - Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) with a goal dose of 2 tablets three times daily
- Monitoring

(a) Headache

(b) Hypotension

(c) Drug-induced lupus (with hydralazine)

Sacubitril/valsartan

- Neprilysin inhibitor
- Place in therapy
  - Alternative to ACE inhibitors or ARBs
  - Replacement of ACE inhibitors or ARBs by sacubitril/valsartan is recommended to further reduce morbidity and mortality
- Benefits
  - Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
  - Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
  - Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)

Sacubitril/valsartan

- **Dosing and administration considerations**

(a) Initial dose

  - Not currently taking ACE inhibitor or ARB, or switching from low doses of ACE inhibitor or ARB: sacubitril 24 mg/valsartan 26 mg twice daily
  - Switching from an ACE inhibitor or ARB at a standard dosage: sacubitril 49 mg/ valsartan 51 mg twice daily

- Maintenance dose:
  - Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/ valsartan 103 mg twice daily, as tolerated.

- If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan

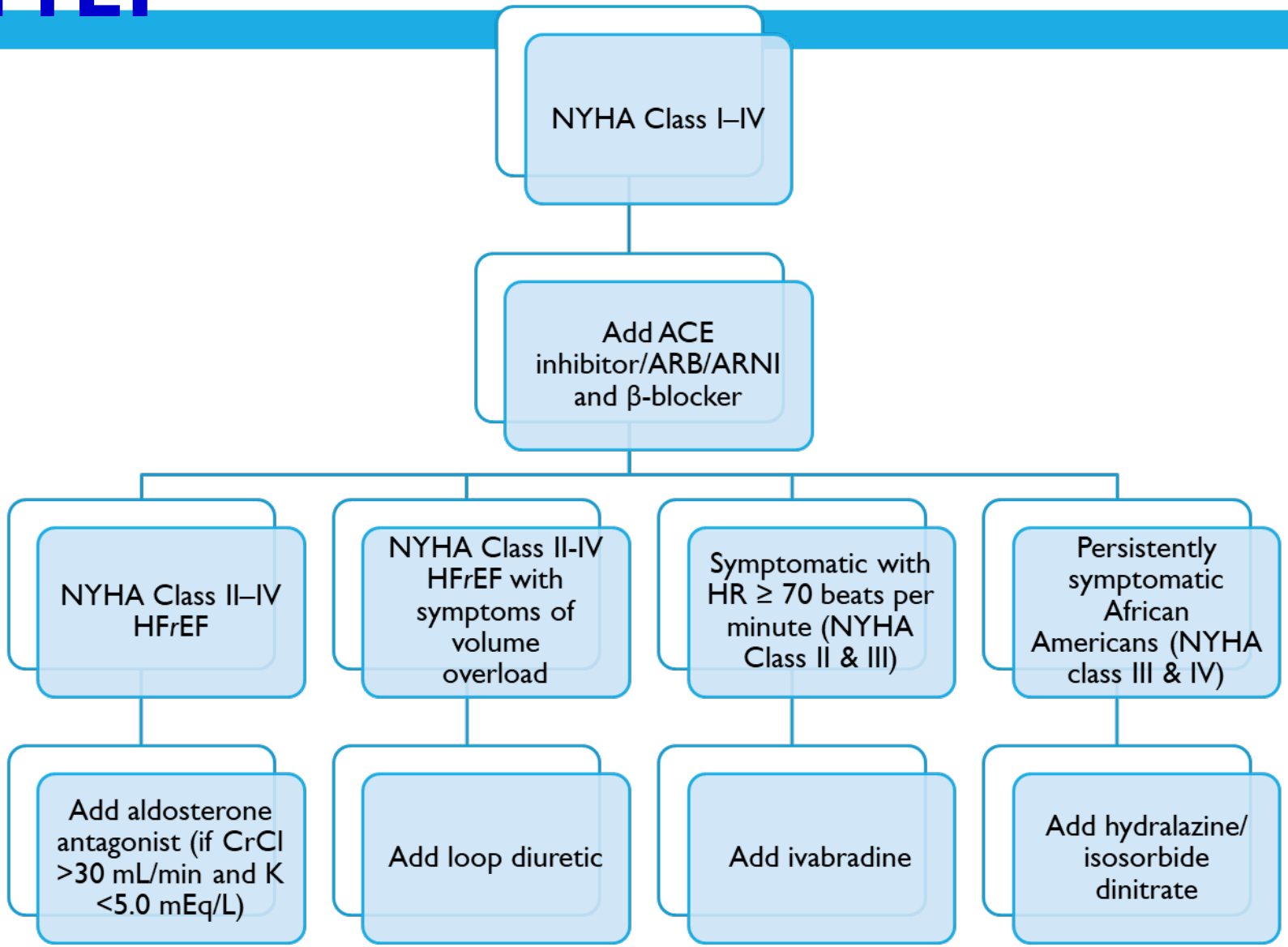
Sacubitril/valsartan

- Monitoring
  - (a) Observe for signs and symptoms of angioedema and hypotension.
  - (b) Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, DM, K supplements, azotemia)

Other medication therapies

- Anticoagulation
  - Recommended for HF with permanent, persistent, or paroxysmal AF
  - Not recommended in the absence of AF, prior stroke, or a cardioembolic source
- Antiarrhythmics:
  - Given the neutral effects on mortality, the preferred antiarrhythmics in patients with HFrEF are dofetilide (AF/atrial flutter) and amiodarone.

Algorithm for the Management HFrEF



HF*p*EF or Diastolic Dysfunction

- Clinical evidence for efficacious agents for HF*p*EF has generally been disappointing.
- (1) SBP and diastolic blood pressure (DBP) should be well controlled.
  - HTN impairs myocardial relaxation and promotes cardiac hypertrophy.
  - Goal SBP less than 130 mm Hg
- Diuretics should be used for symptom relief in volume overload
- The use of β-blockers, ACE inhibitors, and ARBs in patients with HTN is reasonable to control BP.
- Use of ARAs might be considered to decrease hospitalizations in HF*r*EF patients already on ACE inhibitors/ARBs and β-blockers.
- Control tachycardia

Acute and Advanced Heart Failure

- Patients with AHF present with symptoms of worsening fluid retention or decreasing exercise tolerance and fatigue
- Patients can be described as
  - "Wet" or "dry" depending on volume status
    - Wet": patients with volume/fluid overload (eg, edema and jugular venous distension [JVD]),
    - "Dry" refers to euvolemic patients.
  - "Warm" or "cool" based on adequacy of tissue perfusion.
    - "Warm": patients with adequate CO to perfuse peripheral tissues (and hence the skin will be warm to touch),
    - "Cool" refers to patients with evidence of hypoperfusion (skin cool to touch with diminished pulses).

Acute and Advanced Heart Failure

- Invasive hemodynamic monitoring with invasive IV lines (e.g., Swan-Ganz pulmonary artery catheters)

  - To provide objective data for assessing
    - Volume status (pulmonary capillary wedge pressure [PCWP])
      - PCWP above 18 mmHg correlates with congestion and an elevated preload
    - Perfusion (CO).
      - CI below 2.2 L/min/m^2 is consistent with hypoperfusion reduced contractility.

Acute and Advanced Heart Failure

1) **Subset I (Warm and Dry)**
   - CI *greater than* 2.2 L/min/m^2, PCWP <18 mmHg
   - Patients considered well compensated and perfused, without evidence of congestion
   - No immediate interventions necessary except optimizing oral medications and monitoring

- **Subset II (Warm and Wet)**
   - CI greater than 2.2 L/min/m^2, PCWP ≥18 mm Hg
   - Patients adequately perfused and display signs and symptoms of congestion
   - Main goal is to reduce preload (PCWP) carefully with loop
     diuretics and vasodilators

Acute and Advanced Heart Failure

3) **Subset III (Cool and Dry)**
   - CI *less than* 2.2 L/min/m^2, PCWP *less than* 18 mm Hg
   - Patients are inadequately perfused and not congested
   - Hypoperfusion leads to increased mortality, elevating death rates fourfold compared with those who are adequately perfused
   - Treatment focuses on increasing CO with positive inotropic agents and/or replacing intravascular fluids
   - Fluid replacement must be performed cautiously because patients can rapidly become congested

Acute and Advanced Heart Failure

4) **Subset IV (Cool and Wet)**
   - CI *less than* 2.2 L/min/m^2, PCWP *greater than* 18 mm Hg
   - Patients are inadequately perfused and congested
   - Classified as the most complicated clinical presentation of AHF with the worst prognosis
   - Most challenging to treat; therapy targets alleviating signs and symptoms of congestion by increasing CI as well as reducing PCWP while maintaining adequate mean arterial pressure
   - Treatment involves a delicate balance between diuretics, vasodilators, and inotropic agents
   - Use of vasopressors is sometimes necessary to maintain BP

AHF Therapy Based on Hemodynamic Subset

Subset and description	Treatment
Subset I: Warm and Dry (normal parameters) (PCWP 15–18 mmHg and CI > 2.2 L/min/m^2)	Optimize oral medications
Subset II: Warm and Wet (pulmonary or peripheral congestion) (PCWP > 18 mmHg and CI >2.2 L/min/m^2)	IV diuretics ± IV vasodilators (venous) If symptoms persist, adjunct strategies to overcome diuretic resistance may be necessary.

AHF Therapy Based on Hemodynamic Subset

Subset III: Cold and Dry (hypoperfusion ± orthostasis) (PCWP 15–18 mmHg and CI < 2.2 L/min/m^2)	If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg If PCWP ≥ 15 mm Hg, SBP <90 mm Hg, IV inotrope If PCWP ≥ 15 mm Hg, SBP ≥90 mm Hg, IV vasodilator (arterial) ±IV vasopressore if needed
Subset IV: Cold and Wet (pulmonary/peripheral congestion + hypoperfusion) (PCWP >18 mm Hg and CI < 2.2 L/min/m2)	IV diuretics + If SBP ≥90 mm Hg, IV vasodilator (arteriald) If SBP <90 mm Hg, IV inotrope ±IV vasopressore if needed

Acute Heart Failure Treatment Recommendations

- **Diuretic therapy**
  - Recommended as intravenous loop diuretics for patients with fluid overload.
  - Change to oral route on day before discharge, if possible.
  - When response to diuretics is minimal, the following options should be considered:
    - Fluid and sodium restriction
    - Initiation of increased doses or continuous infusion of loop diuretic
    - Addition of a second diuretic with a different mechanism of action (metolazone, hydrochlorothiazide, chlorothiazide)
    - Ultrafltration

Acute Heart Failure Treatment Recommendations

- **Inotropic therapy**
  - May be considered to relieve symptoms and improve end-organ function in patients with reduced left ventricular ejection fraction and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if
    - SBP (< 90 mm Hg)
    - Symptomatic hypotension despite adequate filling pressure
    - No response to or intolerance of IV vasodilators

Acute Heart Failure Treatment Recommendations

- **Vasodilator therapy**
  - May be considered in addition to IV loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension
  - May be considered in patients with persistent symptoms despite aggressive diuretics and oral drug therapy
  - When adjunctive therapy is necessary in addition to loop diuretics, intravenous vasodilators should be considered over inotropic drugs

Acute Heart Failure Treatment Recommendations

- **Loop diuretics**
  - Most widely used and most potent, effective at low CrCl (< 30 mL/min/1.73 m2)
  - Furosemide most commonly used;
    - Furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg IV or PO

Acute Heart Failure Treatment Recommendations

- **Diuretic resistance**
  - **Increase** dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide)
  - **Add** a second diuretic with a different mechanism of action
    - Hydrochlorothiazide 12.5–25 mg PO daily, metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration)
    - Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is very expensive; reserve for NPO or refractory to other alternatives
    - Continuous infusion of loop diuretic: Furosemide 0.1 mg/kg/hr IV doubled every 4–8 hr, maximum 0.4 mg/kg/hr

ISCHEMIC HEART DISEASE

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Objectives

1) Identify risk factors for the development of ischemic heart disease (IHD).
2) Differentiate between the pathophysiology of chronic stable angina and acute coronary syndromes.
3) Recognize symptoms and diagnostic criteria of IHD in a specific patient.
4) Compare and contrast the diagnostic criteria of IHD and acute coronary syndrome.
5) Design an appropriate therapeutic regimen for the management of IHD based on patient-specific information.
6) Formulate a monitoring plan to assess effectiveness and adverse effects of an IHD drug regimen

Introduction

- **Ischemic heart disease** (IHD) is also called **coronary heart disease** (CHD) or **coronary artery disease** (CAD).
- "**Ischemic**" refers to a decreased supply of oxygenated blood, in this case to the heart muscle
- Ischemic heart disease results from an imbalance between **myocardial oxygen supply** and **oxygen demand**

Introduction

- Common clinical manifestations of IHD include
  - **Chronic stable angina**
  - **Acute coronary syndromes (ACS)**
    - ✓Unstable angina (UA)
    - ✓Myocardial infarction (MI)
      - ✓Non – ST-segment elevation MI (NSTEMI)
      - ✓ST-segment elevation MI (STEMI).
- **Angina** is discomfort in the chest that occurs when the blood supply to the myocardium is compromised.

EPIDEMIOLOGY

- Leading cause of death for both men and women in the US
- Incidence of IHD is higher in middle-aged men compared to women

Risk Factors

- **Modifiable**
  - Cigarette smoking
  - Dyslipidemia
    - ✓ Elevated LDL or total cholesterol
    - ✓ Reduced HDL cholesterol
  - Diabetes mellitus
  - Hypertension
  - Physical inactivity
  - Obesity (BMI ≥30 kg/m^2)

Risk Factors

Non-modifiable

- Age ≥45 yrs for males, ≥ 55 yrs for females
- Gender (men and postmenopausal women)
- Family history of premature cardiovascular disease,

Pathophysiology

Increased Myocardial O_2 Demand:

- Increases in heart rate, left ventricular wall tension, and cardiac contractility increase the rate of **myocardial oxygen consumption**
- **Left ventricular wall tension** is a function of blood pressure, left ventricular end-diastolic volume, and ventricular wall thickness
- Physical exertion increases **heart rate**, **blood pressure**, and **cardiac contractility**, and commonly precipitates ischemia and symptoms of angina in patients with significant coronary atherosclerosis

Pathophysiology

Decreased Myocardial O_2 Supply

- Reductions in coronary **blood flow** (secondary to atherosclerotic plaques, vasospasm, or thrombus formation) and **arterial oxygen content** (secondary to hypoxia) decrease myocardial oxygen supply.
- Because the coronary arteries fill during diastole, **decreases in diastolic filling time** (e.g., tachycardia) can also reduce coronary perfusion and myocardial oxygen supply
- In chronic stable angina, **atherosclerotic plaques** are the most common cause of coronary artery narrowing and reductions in coronary blood flow.

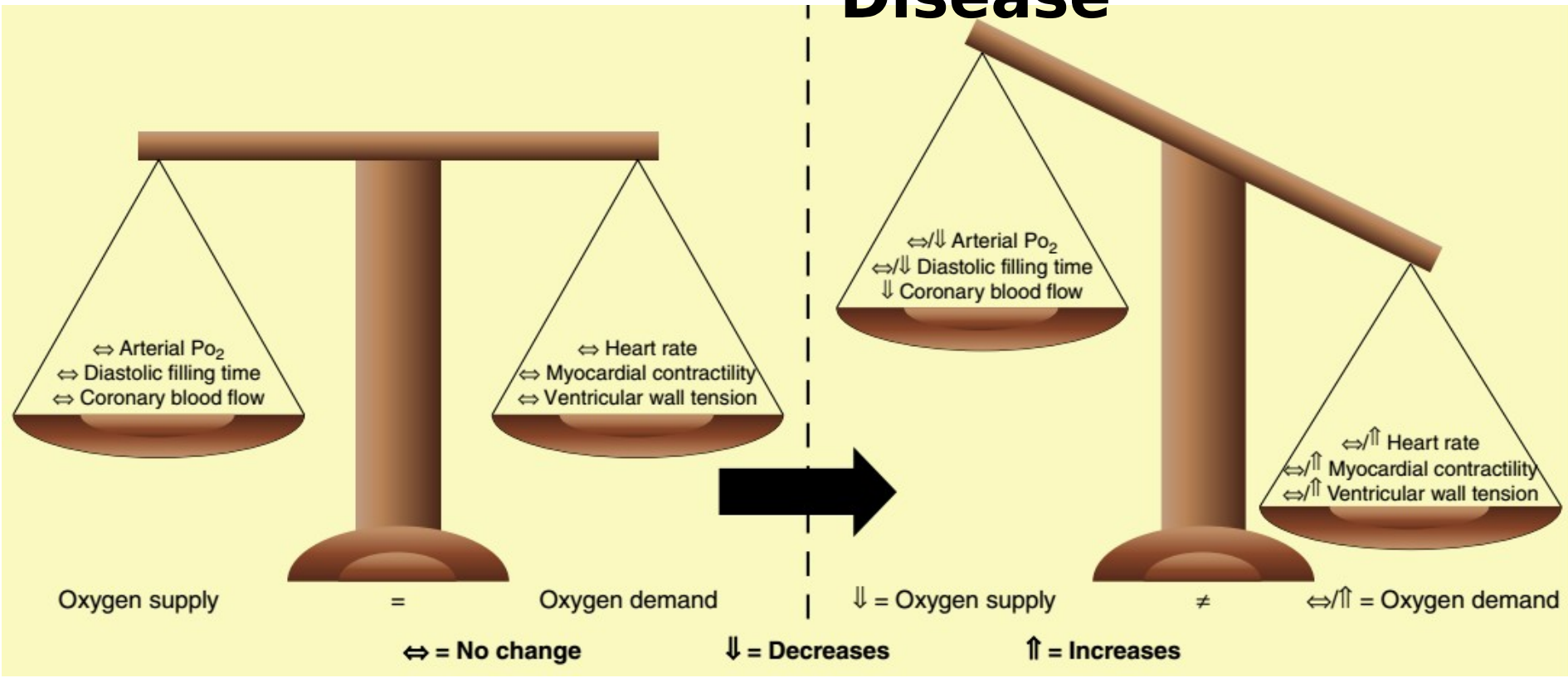
Pathophysiology

Decreased Myocardial O_2 Supply

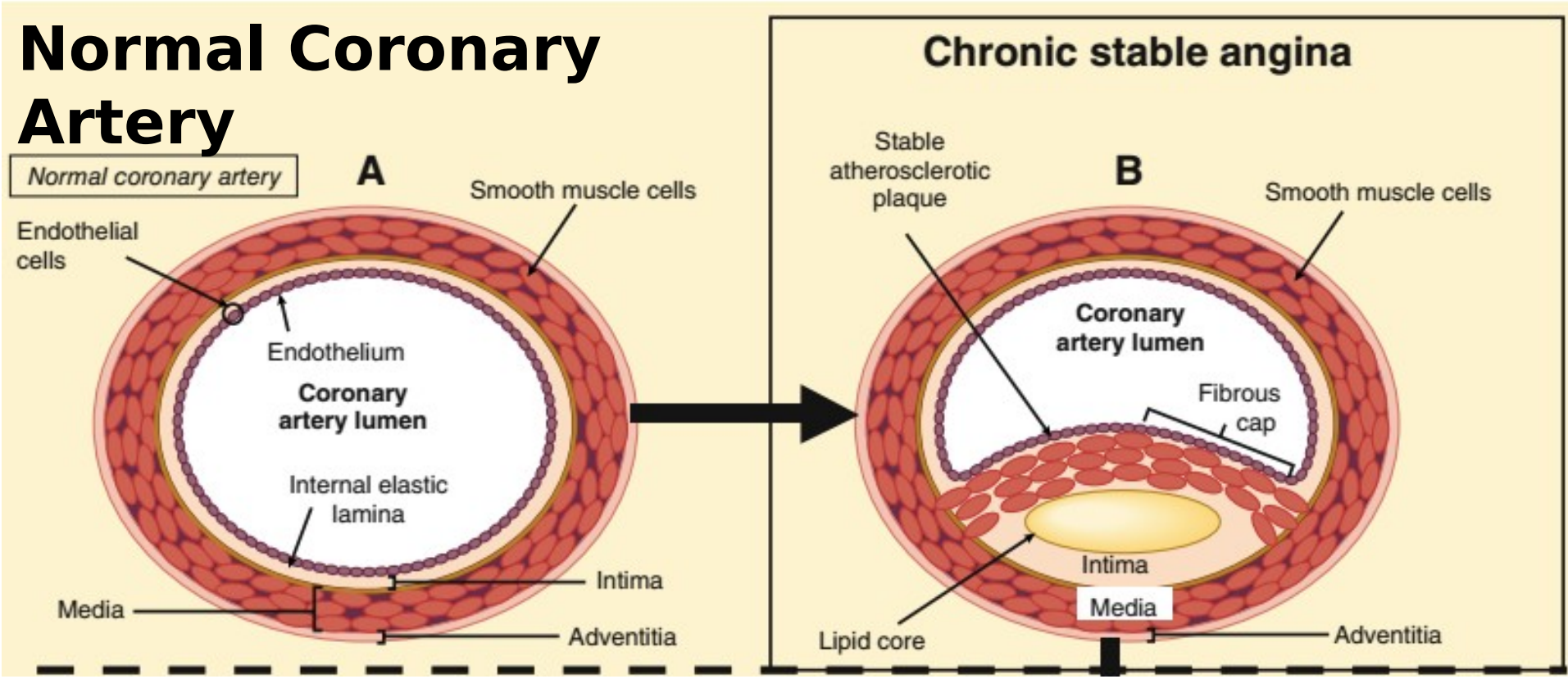
- In contrast, in ACS, disruption of an atherosclerotic plaque with subsequent **thrombus** (blood clot) formation causes abrupt reductions in coronary blood flow and oxygen supply.
- **Anemia**, **CO poisoning**, and **cyanotic congenital heart** disease are examples of conditions that reduce the oxygen-carrying capacity of the blood, potentially causing ischemia in the face of adequate coronary perfusion

Normal

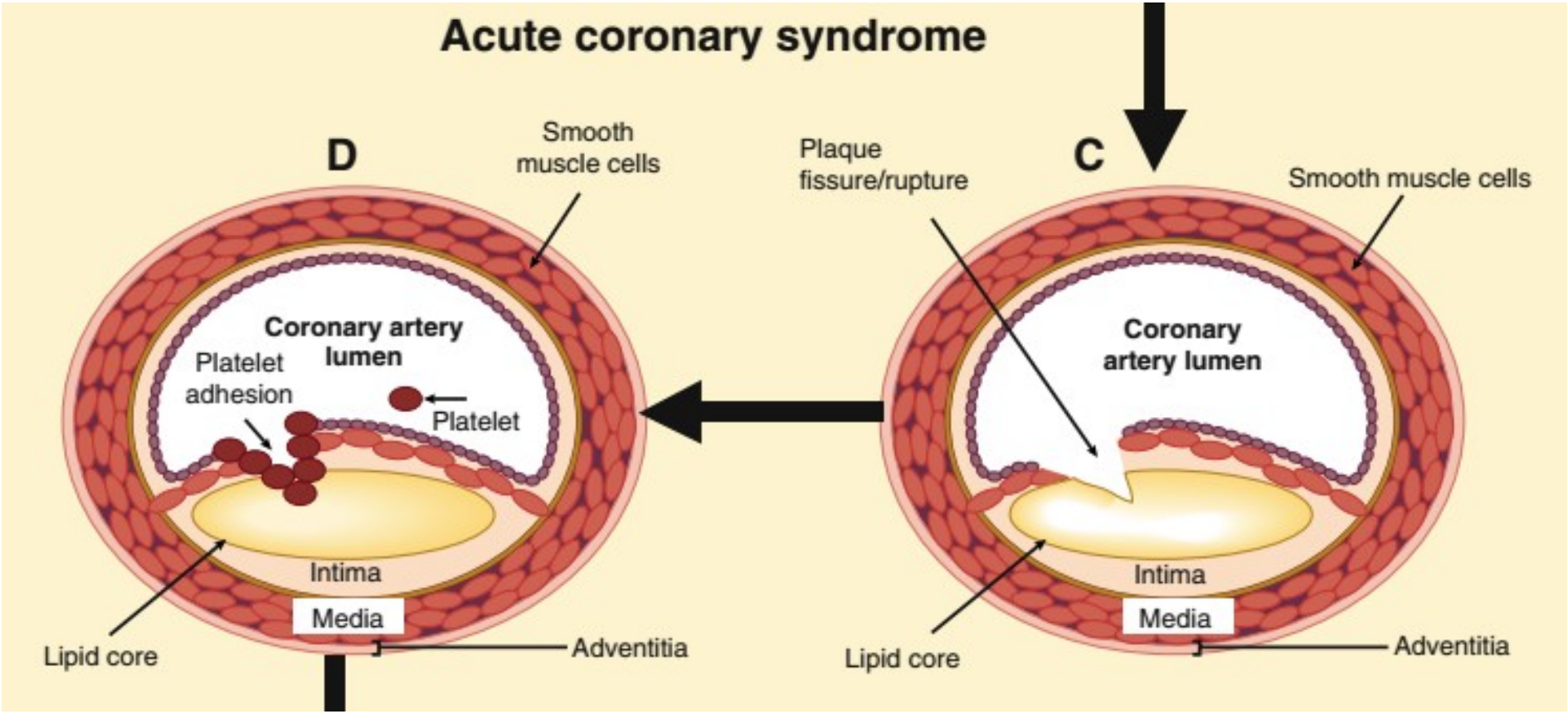
Ischemic Heart Disease



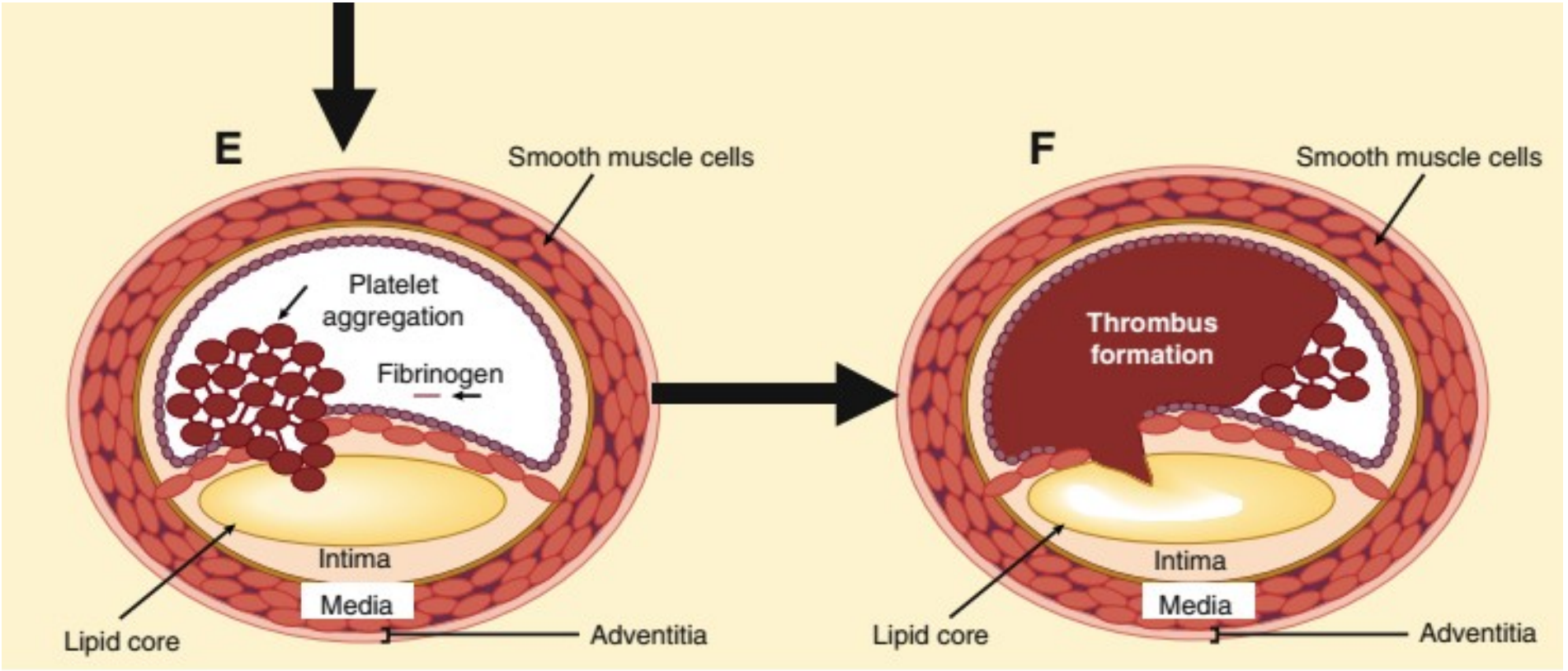
Normal Coronary Artery



In a **stable atherosclerotic plaque** the lipid core is relatively small in size and the fibrous cap is made up of several layers of smooth muscle cells.



Unstable atherosclerotic plaque has a larger lipid core, and a thin fibrous cap comprised of a single layer of smooth muscle cells with a fissure or rupture.



Platelet activation may ensue leading to platelet aggregation as fibrinogen binds platelets to one another to form a meshlike occlusion in the coronary lumen. If endogenous anticoagulant proteins fail to halt this process, platelet aggregation continues and fibrinogen is converted to fibrin, resulting in an occlusive thrombus.

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Clinical Presentation and Diagnosis

Symptoms of Angina Pectoris

- Patients typically describe **pain** as a sensation of pressure, heaviness, or squeezing in the anterior chest area.
  - Sharp pain is not a typical symptom of IHD.
- Pain may **radiate** to the neck, jaw, shoulder, back, or arm.
- Pain may be accompanied by dyspnea, nausea, vomiting, or diaphoresis

Clinical Presentation and Diagnosis

- Symptoms are often **provoked by exertion** (e.g., walking, climbing stairs, and doing yard or house work) or **emotional stress** and relieved within minutes by **rest** or **nitroglycerin**.
- Other precipitating factors include exposure to **cold temperatures** and **heavy meals**.
- Pain that occurs **at rest** (without provocation) or that is prolonged and unrelieved by nitroglycerin is indicative of an ACS.

Clinical Presentation and Diagnosis

1. **Biochemical markers** (creatine kinase [CK], CK-MB fraction, troponin I and troponin T):

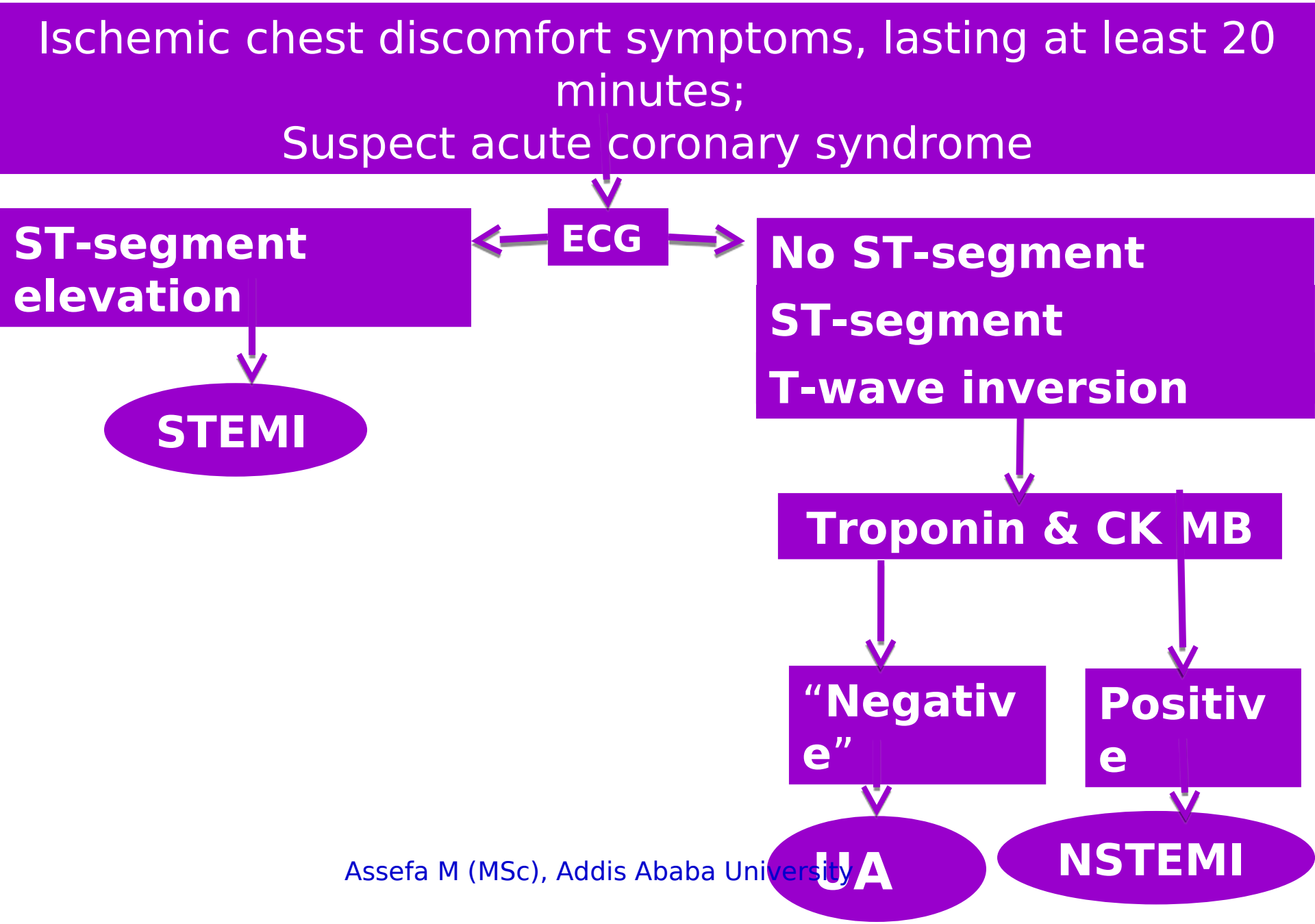
- ✓ Elevated in MI (ST-segment elevation MI and non–ST-segment elevation MI)
- ✓ Normal in chronic stable angina and unstable angina.

Clinical Presentation and Diagnosis

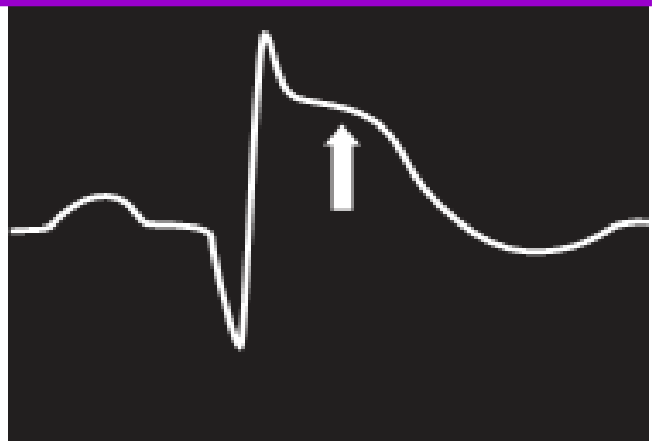
2. ECG

- Normal at rest in patients with chronic stable angina in the absence of active ischemia
- Significant Q waves indicate prior MI.
- ***ST-segment depression*** or ***T-wave inversion*** is typically observed in chronic stable angina, unstable angina, and non–STEMI, whereas ST-segment elevation occurs with **STEMI** and Prinzmetal's (variant) angina

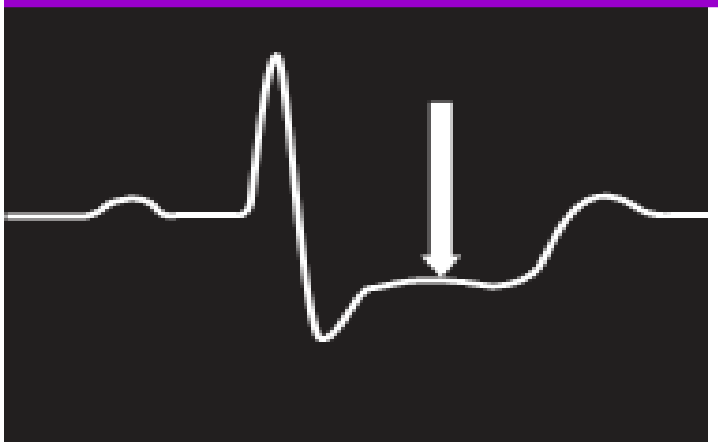
3. Coronary Angiography: detects the location and degree of coronary atherosclerosis

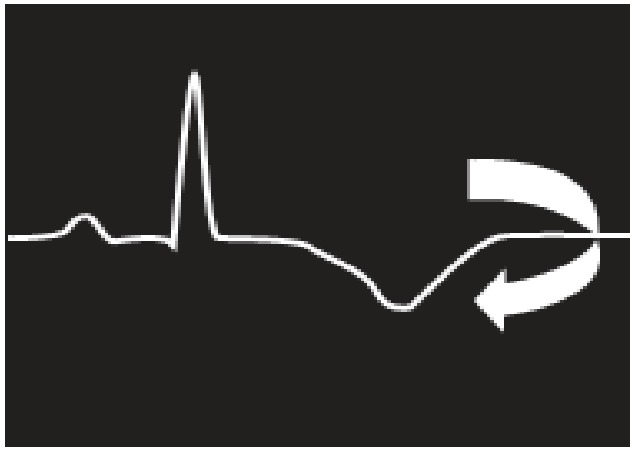

Ischemic chest discomfort symptoms, lasting at least 20 minutes;
Suspect acute coronary syndrome
ECG
ST-segment elevation
STEMI
No ST-segment
ST-segment
T-wave inversion
Troponin & CK MB
“Negative”
Positive
UA
NSTEMI

ST-segment elevation

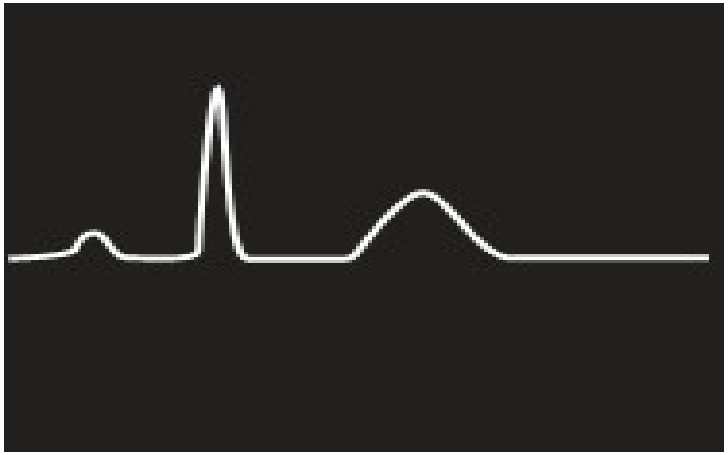


ST-segment depression





T-wave inversion



No ECG changes

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The CCS Classification System

I. Able to perform ordinary physical activity (e.g., walking and climbing stairs) **without symptoms**. Strenuous, rapid, or prolonged exertion causes symptoms.

II. Symptoms **slightly limit** ordinary physical activity. Walking rapidly or for more than two blocks, climbing stairs rapidly or climbing more than one flight of stairs causes symptoms.

III. Symptoms **markedly limit** ordinary physical activity. Walking less than two blocks or climbing one flight of stairs causes symptoms.

IV. Angina may occur **at rest**. Any physical activity causes symptoms.

Chronic Stable Angina Vs Unstable Angina

Chronic Stable Angina:

- Is due to **increases in oxygen demand**, not acute changes in oxygen supply
- Usually occurs with exertion
- Symptoms are typically reproducible and reversible.
- Patients will generally experience a similar pattern of discomfort (same quality, location, and accompanying symptoms) with a similar level of exertion with each angina attack
- Is usually relieved within minutes by rest or sublingual nitroglycerin

Chronic Stable Angina Vs Unstable Angina

Unstable Angina:

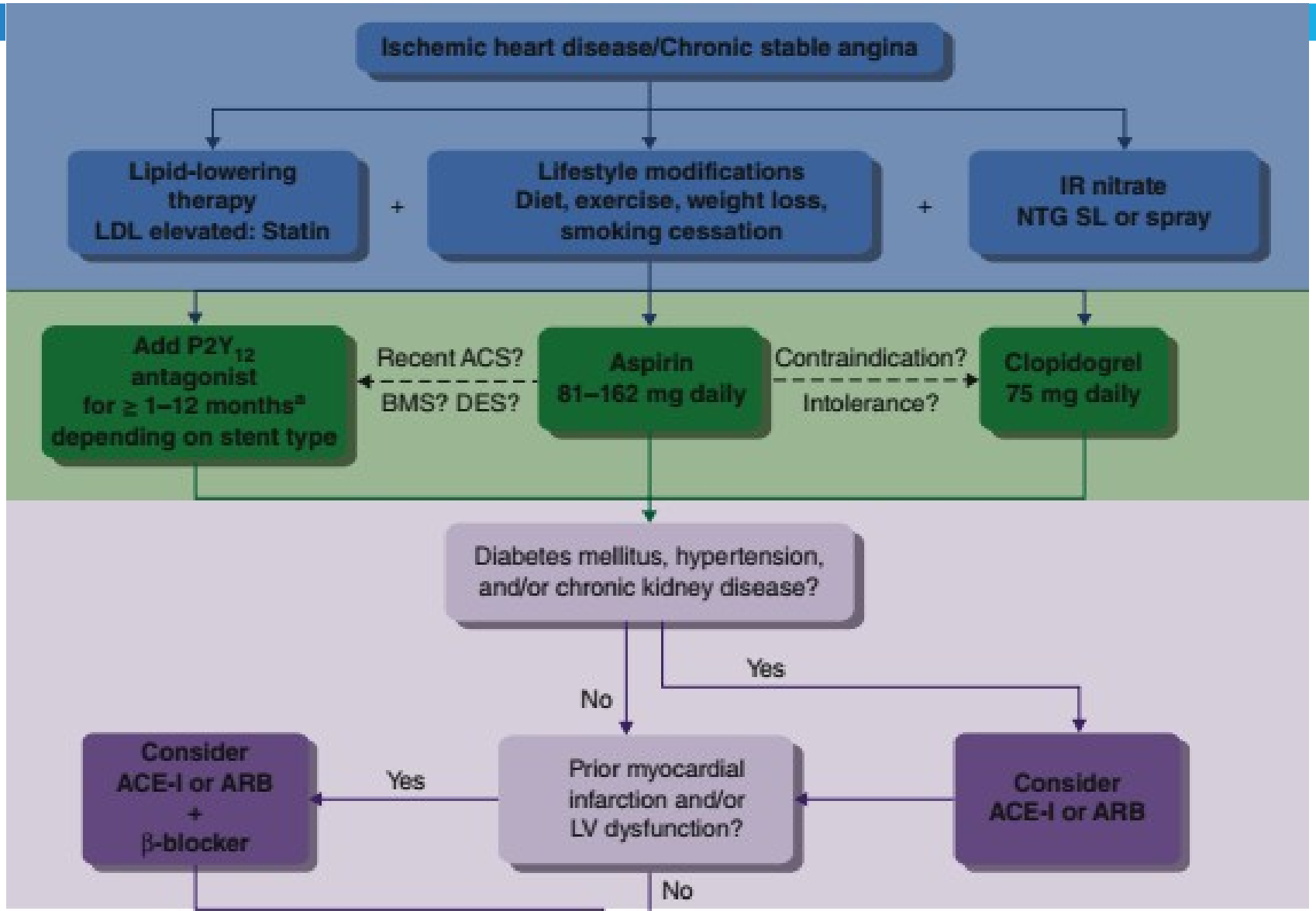
- Is due to an acute **decrease** in coronary blood flow leading to **insufficient oxygen supply**.
- Marked by prolonged symptoms (**greater than or equal to 20 minutes**) or an escalation in the frequency or severity of angina over a short period of time
- Frequently occurs at **rest** without any precipitating factors,
- May be less responsive to rest or medication.

Management of IHD/CSA

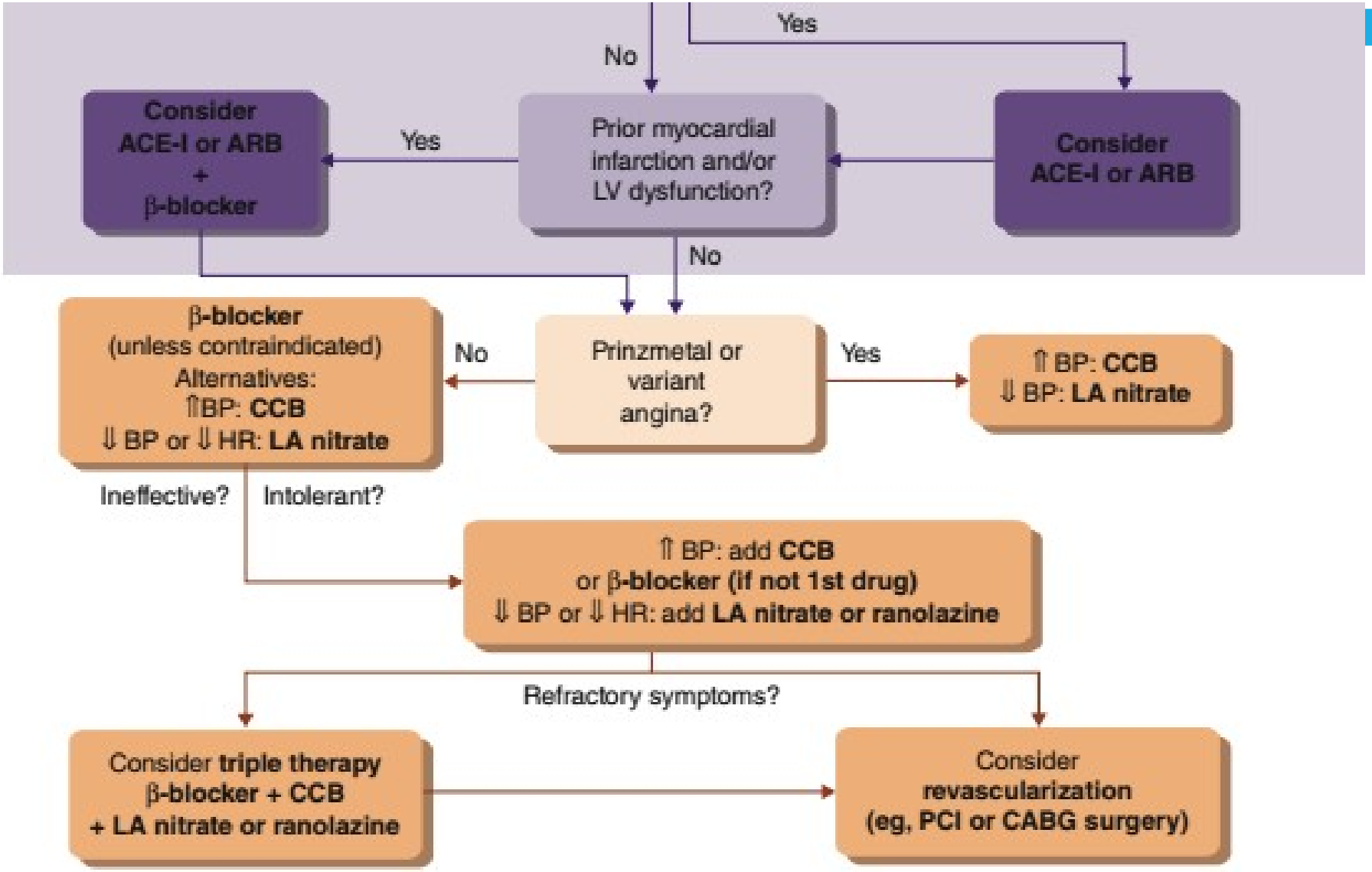
Desired Outcomes

- *The major goals for the treatment of IHD are to:*
  - *Prevent acute coronary syndrome and death*
  - *Alleviate acute symptoms of myocardial ischemia*
  - *Prevent recurrent symptoms of myocardial ischemia*
  - *Prevent progression of the disease*
  - *Reduce complications of IHD*
  - *Avoid or minimize adverse treatment effects*

Treatment Algorithm for IHD



Treatment Algorithm for IHD…



PCI

- For patients with stable IHD, optimal medical therapy is equivalent to PCI in reducing major adverse cardiac events (MACE) and is the preferred initial strategy.
- PCI is indicated when:
  (a) When optimal medical therapy fails,
  (b) Symptoms are unstable, or
  (c) Extensive coronary atherosclerosis is present (eg, greater than 70% occlusion of coronary lumen),

Prevent ACS and Death

- Antiplatelet Agents
  - Platelets play a major role in the pathophysiology of ACS.
  - Thromboxane A2 (TXA2) is a potent platelet activator.
  - **Aspirin** inhibits cyclooxygenase, an enzyme responsible for the production of TXA2, thereby inhibiting platelet activation and aggregation.
  - In patients with stable or unstable angina, aspirin has been consistently shown to reduce the risk of major adverse cardiac events, particularly MI.
  - *Aspirin doses of 75 to 162 mg daily are recommended in patients with or at risk for IHD.*
  - *If aspirin is contraindicated (eg, aspirin allergy) or is not tolerated by the patient, an alternative antiplatelet agent such as clopidogrel should be considered*

Prevent ACS and Death

- *Inhibition of the P2Y12 receptor with either a tclopidogrel, prasugrel or ticagrelor prevents platelet aggregation and is indicated in combination with aspirin in select patients with IHD.*
- Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is recommended following hospitalization for ACS and/or following PCI with stent placement to prevent ischemic events
- Clopidogrel is a prodrug that must be converted via a two-step process to its active thiol metabolite.

Prevent ACS and Death

- **Control of Risk Factors**: dyslipidemia, hypertension, and diabetes
- **Statins:** should be considered in all patients with IHD, regardless of baseline LDL cholesterol
- **ACE-I/ARBs:** should be considered in all patients with IHD, particularly those individuals who also have
  - Hypertension,
  - Diabetes mellitus,
  - Chronic kidney disease,
  - Left ventricular dysfunction,
  - History of MI

Relieve Acute Symptoms

- ***Nitroglycerin:***
  - *Should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms.*
  - At the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually, and repeated every 5 minutes up to three times or until symptoms resolve.
  - Sublingual nitroglycerin may be used to prevent effort- or exertion-induced angina.
  - In this case, the patient should use sublingual nitroglycerin 2 to 5 minutes prior to an activity known to cause angina, with the effects persisting for approximately 30 minutes

Prevent Recurrent Ischemic Symptoms

- **β-blockers** are the preferred initial therapy to prevent symptoms of angina in patients with IHD because of their potential cardioprotective effects
- **Calcium channel blockers** are recommended as alternative treatment in IHD when β-blockers are contraindicated or not tolerated
- **Long-Acting Nitrates**: treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or CCB

Prevent Recurrent Ischemic Symptoms

Long-Acting Nitrates

- Nitrate products are available in both oral and transdermal formulations for chronic use.

- **Oral**_
  - ✓ Nitroglycerin extended-release capsules
  - ✓ Isosorbide dinitrate tablets
  - ✓ Isosorbide dinitrate slow-release capsules
  - ✓ Isosorbide mononitrate tablets
  - ✓ Isosorbide mononitrate extended-release tablets
- **Transdermal**
  - ✓ Nitroglycerin extended-release film

Prevent Recurrent Ischemic Symptoms

Long-Acting Nitrates

- The major limitation of nitrate therapy is the development of **tolerance** with continuous use.
- The loss of anti-anginal effects may occur within the first 24 hours of continuous nitrate therapy
- The most effective method to avoid tolerance and maintain the anti-anginal efficacy of nitrates is to allow a daily nitrate-free interval of at least 8 to12 hours
- Therefore, the nitrate-free interval should occur when the patient is **least likely to experience angina.**

Prevent Recurrent Ischemic Symptoms

Long-Acting Nitrates

- Treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or calcium channel blocker or a combination of the two.
- β-Blockers attenuate the increase in sympathetic tone and heart rate that occurs during nitrate therapy.
- Common adverse effects of nitrates include postural hypotension, flushing, and headache secondary to venodilation.

Prevent Recurrent Ischemic Symptoms

Nitrate Dosing for Chronic Use

Formulation	Dose	nitrate-free interval
Nitroglycerin XR	2.5 mg TID	10 – 12-hour
Isosorbide dinitrate	5–20 mg BID to TID	At least 14 hours
Isosorbide dinitrate slow release	40 mg QD to BID	at least 18 hours
Isosorbide mononitrate	5–20 mg BID	taken 7 hours apart
Isosorbide mononitrate XR	30–120 mg QD	

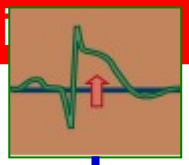
Management of ACS

- Short-term desired outcomes in a patient with ACS are:
  - (a) Early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA);
  - (b) Prevention of death and other MI complications;
  - (c) Prevention of coronary artery reocclusion;
  - (d) Relief of ischemic chest discomfort; and
  - (e) Resolution of ST segment and T-wave changes on the ECG

Ischemic chest discomfort symptoms, lasting at least 20 minutes; Suspect acute coronary syndrome

ECG with 10 min

ST-segment elevati



NST-segment elevation

ST-segment depressio n



T-wave inversio n



No ECG chang es

Initiate reperfusion therapy in appropriate candidates (fibrinolysis or primary PCI)

Serial troponin as confirmatory; results not needed before reperfusion therapy is initiated; continuous ST-segment monitoring

Initiate adjunctive ST-segment elevation ACS pharmacotherapy

Risk stratification; multi-lead continuous ST-segment monitoring; obtain serial troponin

Initiate pharmacotherapy for NSTE-ACS based upon risk

Low risk

Stress test to evaluate likelihood of CAD

- stress test

+ stress test

Moderate & high risk

PCI or CABG)

Non-cardiac chest pain syndrome

ST-segment-elevation MI

Oxygen (if O_2 saturation < 90%), aspirin,
SL NTG, IV NTG, morphine sulfate

PCI capable facility

Primary PCI (FMC-device ≤ 90 minutes)

Dual antiplatelet therapy with ASA and:
1)Clopidogrel or
2)Ticagrelor or
3)Prasugrel
4)+/– GPI in select patients receiving UFH and P2Y12 inhibitor

Anticoagulant with either:
1)IV UFH
2)IV bivalirudin

1) Transfer to PCI capable facility for primary PCI within 120 minutes.
2) Immediate transfer for cardiogenic shock or failed fibrinolysis.
3) Transfer for PCI 3–24 hrs after successful fibrinolysis in stable patients

Non-PCI capable facility

Fibrinolysis within 30 minutes of arrival (When PCI not available within 120 minutes)

Dual antiplatelet therapy with ASA and clopidogrel 300 mg

Anticoagulant with either:
1)IV UFH
2)IV bolus, then SC enoxaparin
3)IV bolus, then SC fondaparinux

Late hospital care/2⁰ prevention:
1)ASA indefinitely
2)P2Y12 inhibitor
3)β-blocker within 24 hours if no CI
4)High intensity statin as early as possible

Reperfusion Strategies for STEMI

- ***PCI***
  - *Early reperfusion therapy with primary PCI of the infarct artery within 90 minutes from time of hospital presentation is the reperfusion treatment of choice for patients with STEMI who present within 12 hours of symptom onset*
  - Lower mortality rate with primary PCI as compared with fibrinolysis
  - More than 90% of occluded infarct-related coronary arteries are opened with primary PCI compared with fewer than 60% with fibrinolytics
  - Intracranial hemorrhage (ICH) and major bleeding risks from primary PCI are lower than the risks of severe bleeding events following fibrinolysis

Reperfusion Strategies for STEMI

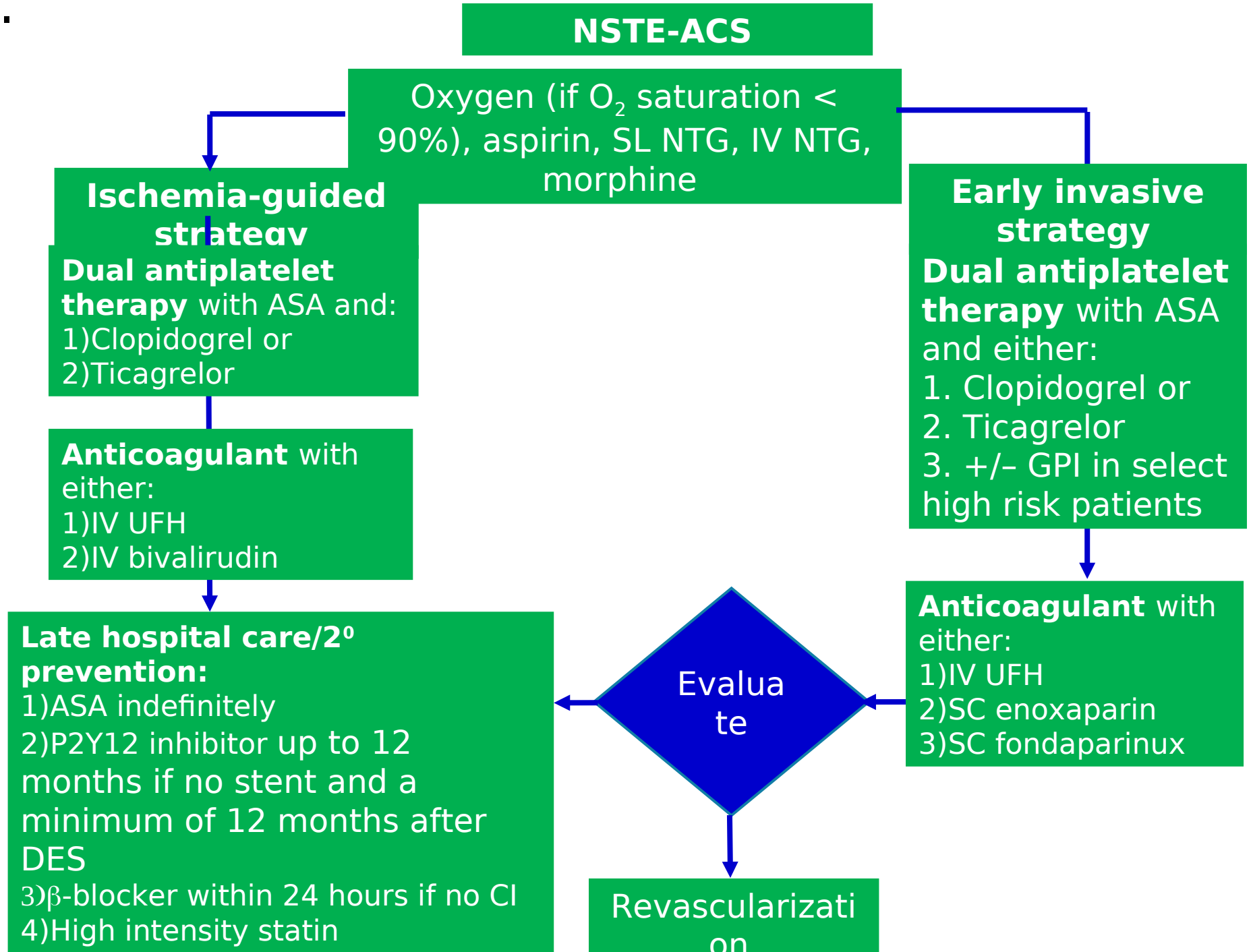
- ***Fibrinolytic Therapy***
  - Administration of a fibrinolytic agent is indicated in patients with STEMI who present to the hospital within 12 hours of the onset of chest discomfort
  - The use of fibrinolytics between 12 and 24 hours after symptom onset should be limited to patients with ongoing ischemia
  - It is recommend that the fibrinolytic agent be administered within 30 minutes of arrival
  - More fibrin-specific agents such as alteplase, reteplase, or tenecteplase is preferred over a nonfibrin-specific agent such as streptokinase.
  - Fibrinolytic therapy is not indicated and should not be used in patients with NSTE-ACS

Reperfusion Strategies for STEMI

- ***Fibrinolytic Therapy***
  - Indications
    1) Ischemic chest discomfort at least 20 minutes in duration but 12 hours or less since symptom onset **and** ST-segment elevation
    2) Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset **and** ST-segment elevation

Reperfusion Strategies for STEMI

- ***Fibrinolytic Therapy***
  - **Absolute Contraindications**
    1) Active internal bleeding (not including menses)
    2) Previous intracranial hemorrhage at any time; ischemic stroke within 3 months (except acute ischemic stroke within 4.5 hours)
    3) Known intracranial neoplasm
    4) Known structural cerebral vascular lesion (eg, arteriovenous malformation)
    5) Suspected aortic dissection
    6) Significant closed head or facial trauma within 3 months
    7) Intracranial or intraspinal surgery within 2 months
    8) Severe uncontrolled hypertension (unresponsive to emergency therapy)
    9) For streptokinase, prior treatment within the previous 6 months


NSTE-ACS
Oxygen (if O_2 saturation < 90%), aspirin, SL NTG, IV NTG, morphine
Ischemia-guided strategy
Dual antiplatelet therapy with ASA and:
1)Clopidogrel or
2)Ticagrelor
Anticoagulant with either:
1)IV UFH
2)IV bivalirudin
Late hospital care/2⁰ prevention:
1)ASA indefinitely
2)P2Y12 inhibitor up to 12 months if no stent and a minimum of 12 months after DES
3)β-blocker within 24 hours if no CI
4)High intensity statin
Evalua te
Revascularizati on
Early invasive strategy
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor
3. +/– GPI in select high risk patients
Anticoagulant with either:
1)IV UFH
2)SC enoxaparin
3)SC fondaparinux

Risk Stratification

- Patients with STEMI are at the highest risk of death; therefore, immediate reperfusion strategies should be initiated
  - Target time to initiate reperfusion treatment is
    - within 30 minutes of hospital arrival for fibrinolytics (eg, alteplase, reteplase, and tenecteplase) and
    - within 90 minutes from presentation for primary PCI
- Based on the risk assessment, a management strategy is chosen for NSTE ACS:
  - An invasive strategy, which involves coronary angiography, or
  - An ischemia-guided strategy

Early Invasive Therapy for NSTE-ACS

- For patients with NSTE-ACS at an elevated risk for death or MI, including those with a high risk score
- Patients with refractory angina, hemodynamic instability or electrical instability
- Dual Antiplatelet Therapy (DAPT)
  - All patients undergoing PCI should receive ASA therapy indefinitely.
  - A P2Y12 inhibitor antiplatelet (clopidogrel, prasugrel, or ticagrelor) should be administered concomitantly with ASA for at least 12 months following PCI for a patient with ACS
  - A longer duration of P2Y12 inhibitor therapy for patients
    receiving a drug-eluting stent (DES)

Ischemia-Guided Therapy for NSTE-ACS

- Recommended for patients with a low risk score, normal ECGs, and negative troponin tests who are without recurrence of chest discomfort
- Also preferred in patients with extensive comorbidities

Early Pharmacologic Therapy

- *All patients should receive within the first day of hospitalization, and preferably in the ED*

1) **Oxygen**:
   - Supplemental oxygen to patients with ACS with:
     - Arterial oxygen saturation less than 90%,
     - Respiratory distress, or
     - Other high-risk features of hypoxemia.

Early Pharmacologic Therapy

2) Initial Antiplatelet/ Anticoagulant Therapy

- **Aspirin**:
  - STEMI, NSTE-ACS
- **Clopidogrel**
  - NSTE-ACS, added to aspirin
  - STEMI, added to aspirin.
  - In patients with aspirin allergy
- **Prasugrel**
  - PCI in STE and NSTE-ACS, added to aspirin
- **Ticagrelor**
  - PCI in STEMI and NSTE-ACS, added to aspirin

Early Pharmacologic Therapy

Antiplatelet	NSTE-ACS Ischemia Guided	NSTE-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
P2Y12 receptor antagonist	Clopidogrel Ticagrelor	Clopidogrel Prasugrel a Ticagrelor a	Clopidogrel Prasugrel Ticagrelor	Clopidogrel
GP IIb/IIIa inhibitor	Greatest benefit when given to patients and high-risk features (e.g., elevated troponin) not adequately			

Early Pharmacologic Therapy

- **Anticoagulant Therapy**
  - UFH:
    - STEM undergoing PCI and for those patients treated with fibrinolytics
    - NSTE-ACS, class I recommendation in combination with antiplatelet therapy for ischemia-guided or early invasive approach PCI
    - Continue for 48 hours or until the end of PCI
  - Enoxaparin
    - STEMI: in patients receiving fibrinolytics and for primary PCI
    - NSTE ACS: for conservative or invasive approach.
  - Bivalirudin
    - NSTE-ACS: for invasive strategy.
    - PCI in STEM
  - Fondaparinux
    - STEMI: receiving fibrinolytics
    - NSTE-ACS: for invasive or conservative approach
  - Glycoprotein IIb/IIIa receptor inhibitors (Abciximab): NSTE-ACS ischemia guided

Early Pharmacologic Therapy

3) Nitrates

- STEMI and NSTE-ACS
- Sublingual nitroglycerin (0.3 mg to 0.4 mg) every 5 minutes for up to 3 doses
- Intravenous nitroglycerin: for patients with persistent ischemia, HF, HPN.
- Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor,
  - Within 24 hours of sildenafil or vardenafil, or
  - Within 48 hours of tadalafil.

Early Pharmacologic Therapy

4) Analgesic Therapy

- **Morphine sulfate IV**: STEMI and NSTE-ACS
  - For patients whose chest pain persists despite treatment with maximally tolerated anti-anginal drugs
  - 1–5 mg IV every 5–30 min
- NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS
  - Because of the increased risk of MACE associated with their use

Early Pharmacologic Therapy

5) Beta-Adrenergic Blockers

- STEMI and NSTE-ACS
- Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following:
  a) Signs of HF,
  b) Evidence of low-output state,
  c) Increased risk for cardiogenic shock, or
  d) Other contraindications to beta blockade
    a) PR interval >0.24 second,
    b) 2nd or 3rd degree heart block without a cardiac pacemaker,
    c) active asthma, or reactive airway disease.

a) In patients with concomitant stabilized HF, and reduced systolic function: use sustained-release metoprolol succinate, carvedilol, or bisoprolol

Early Pharmacologic Therapy

5) Additional Therapies

- **Cholesterol Management**
  - Reduce the risk of CV death, recurrent MI, stroke, and the need for revascularization
  - High-intensity statin therapy should be initiated or continued in all patients with ACS
- **ACE Inhibitors/ARBs**
  - To prevent cardiac remodeling and ultimately development of HF
  - Used cautiously in the first 24 hours to avoid renal dysfunction or hypotension
  - ARBs: for those patients with ACEIs intolerance

Early Pharmacologic Therapy

5) **Additional Therapies**

- **Calcium Channel Blockers**
  5) Nondihydropyridine calcium channel blocker (CCB) (e.g., verapamil or diltiazem)
  6) Used for relief of continued ischemia despite β-blocker and nitrate therapy, vasospastic angina, additional need for BP lowering (ie, amlodipine), or in patients with contraindications to β-blockers.
  7) In patients who do not have any of the following:
     - Clinically significant LV dysfunction
     - Increased risk for cardiogenic shock
     - PR interval greater than 0.24 second, or
     - Second - or third-degree atrioventricular block

Secondary Prevention Following MI

- The long-term goals following ACS are to:
  - (a) Control modifiable CHD risk factors;
  - (b) Prevent the development of HF;
  - (c) Prevent new or recurrent MI and stroke;
  - (d) Prevent death, including sudden cardiac death; and
  - (e) Prevent stent thrombosis following PCI.

Secondary Prevention Following MI

- *All patients should receive long-term treatment with*
  - *ASA:* 81 mg daily indefinitely
  - *A β-blocker: for 3 years (if no HF), indefinitely (if with HF)*
  - *An ACE inhibitor:* in all patients
  - *A statin for secondary prevention of death, stroke, or recurrent infarction*
- *A P2Y12 inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided treatment strategy.*

Outcome Evaluation

- *To determine the efficacy of nonpharmacologic and pharmacotherapy for CSA, STEMI and NSTE-ACS, monitor patients for:*
  - *(a) relief of ischemic discomfort;*
  - *(b) return of ECG changes to baseline; and*
  - *(c) (c) absence or resolution of HF signs and symptoms*
- Monitoring parameters for recognition and prevention of adverse effects from ACS pharmacotherapy
  - *hypotension and bleeding*

ARRHYTHMIAS

Electrophysiology

- The heart functions via both **mechanical** and **electrical** activity
- The mechanical activity of the heart refers to **atrial** and **ventricular contraction**, the mechanism by which blood is delivered to tissues

Mechanisms of Cardiac Arrhythmias

- In general, cardiac arrhythmias are caused by
  (1) Abnormal impulse formation;
  (2) Abnormal impulse conduction; or
  (3) Both

Cardiac Arrhythmias

- Deviation from the normal rhythm of the heart
- Classified into two broad categories:
  - **Supraventricular:** those occurring above the ventricles
  - **Ventricular:** those occurring in the ventricles

Cardiac Arrhythmias

- The names of specific arrhythmias are composed of two words;
  - The first word indicates the **location** of the electrophysiologic abnormality resulting in the arrhythmia (sinus, AV node, atrial, or ventricular),
  - The second word describes the **arrhythmia** in terms of whether it is abnormally slow (**bradycardia**) or fast (**tachycardia**), or the type of arrhythmia (block, fibrillation, or flutter).

Sinus Bradycardia

- Sinus bradycardia is an arrhythmia that originates in the SA node, defined by a **sinus rate less than 60 bpm.**
- Sinus bradycardia occurs as a result of **fibrotic tissue in the SA node**, which replaces normal SA node tissue.

Sinus Bradycardia

- Treatment:
  - Nonpharmacologic Therapy
    - Implantation of a permanent pacemaker
    - D/C medications that may cause sinus bradycardia,
  - Pharmacologic
    - **Atropine**: 0.5 mg IV every 3 to 5 minutes with maximum total dose of 2 mg
    - **Epinephrine** (2 to 10 mcg/minute, titrate to response) and/or
    - **Dopamine** (2 to 10 mcg/kg/minute)

AV Nodal Blockade

- AV nodal blockade occurs when conduction of electrical impulses through the AV node is impaired to varying degrees.
- AV nodal blockade is classified into three categories.

1. First-degree AV block

- All impulses initiated by the SA node that have resulted in atrial depolarization are conducted through the AV node;
  - The impulses are conducted **more slowly than normal through the AV node**, resulting in prolongation of the PR interval, greater than 0.2 seconds

AV Nodal Blockade

2. Second-degree AV block:

- Some of the impulses initiated by the SA node are not conducted through the AV node.
- This often occurs in a regular pattern; for example, every third or fourth impulse generated by the SA node may not be conducted.

AV Nodal Blockade

3. Third-degree AV block

- Also referred to as "**complete heart block**"
- None of the impulses generated by the SA node are conducted through the AV node.
- This results in "**AV dissociation**," during which the atria continue to depolarize normally as a result of normal impulses initiated by the SA node;
  - However, the ventricles initiate **their own depolarizations**, because no SA node–generated impulses are conducted to the ventricles.

Treatment

- Second-or third-degree AV nodal blockade requires treatment, because bradycardia usually results in symptoms.
- Administration of **atropine**
  - Unresponsive to atropine: **epinephrine** (2 to 10 mcg/minute, titrate to response) and/or **dopamine** (2 to 10 mcg/kg/minute)

Atrial Fibrillation

- AF is an irregularly irregular supraventricular rhythm with no discernible, consistent atrial activity (P waves).
- Ventricular rate is usually 120 -180 bpm and the pulse is irregular
- Has the following ECG characteristics
  - The RR intervals follow no repetitive pattern. They have been labeled as “irregularly irregular.”
  - There are no distinct P waves
  - Atrial rate greater than 300 beats per minute
- Prevalence
  - Most common arrhythmia: 2.2 million Americans
  - Prevalence increases with age.
    - The prevalence of AF increases with advancing age; roughly 8% of patients between the ages of 80 and 89 years have AF
  - Common comorbidity in patients with valvular heart disease or HF

ECG



Etiologies of AF

- Hypertension
- Coronary artery disease
- Heart failure
- Diabetes
- Hyperthyroidism
- Rheumatic heart disease
- Diseases of the heart valves:
  - Mitral stenosis or regurgitation
  - Mitral valve prolapse
- Acute myocardial infarction
- Obesity
- Sleep apnea
- Pericarditis
- Amyloidosis
- Myocarditis
- Pulmonary embolism
- Idiopathic

Etiologies of AF

- Drugs:
  - Adenosine
  - Albuterol
  - Alcohol
  - Alendronate
  - Dobutamine
  - Enoximone
  - Ipratropium bromide
  - Methylprednisolone
  - Milrinone
  - Mitoxantrone
  - Paclitaxel
  - Propafenone
  - Theophylline
  - Verapamil
  - Zoledronic acid

Pathophysiology

- *AF may be caused by both abnormal impulse formation and abnormal impulse conduction*
- AF is triggered by electrical impulses generated within the pulmonary veins
- These impulses initiate the process of reentry within the atria, and AF is believed to be sustained by multiple reentrant wavelets operating simultaneously within the atria.
- AF leads to electrical remodeling of the atria
  - Therefore, it is often said that "atrial fibrillation begets atrial fibrillation"; that is, AF causes atrial electrophysiologic alterations that further promote AF

Pathophysiology

- A substantial amount of the atrial electrical activity occurring during AF is conducted through the AV node into the ventricles, resulting in ventricular rates ranging from 100 to 200 beats/min
- AF is associated with substantial morbidity and mortality.
- This arrhythmia is associated with a risk of ischemic stroke of approximately 5% per year
- The risk of stroke is increased two to seven fold in patients with AF compared to patients without this arrhythmia.
- AF is the cause of roughly one of every six strokes
- Patients with AF are also at increased risk for systemic thromboembolism
- AF is associated with a threefold increase in the risk of HF as a result of tachycardia-induced cardiomyopathy

Clinical Presentation

Symptoms

- Some patients have no symptoms.
- Potential symptoms that may be present to some degree include the following:
  (a) Palpitations
  (b) Chest pain
  (c) Dyspnea
  (d) Fatigue
  (e) Lightheadedness
- At worst, a thromboembolic event will occur or symptoms of HF may be present

Clinical Presentation

- **Classification**

a. **Paroxysmal**: Spontaneous self-termination within 7 days of onset
b. **Persistent**: Lasting more than 7 days
c. **Long-standing persistent**: Continuous duration of more than 12 months
d. **Permanent**: Present all the time, unable to return to SR using pharmacologic or nonpharmacologic options
e. **Nonvalvular**: The absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Management

The goals of individualized therapy for AF are:

(a) *Ventricular rate control;*

(b) *Termination of AF and restoration of sinus rhythm ("cardioversion" or "conversion to sinus rhythm");*

(c) *Maintenance of sinus rhythm, or reduction in the frequency of episodes of paroxysmal AF; and/or*

(d) *Prevention of stroke and systemic thromboembolism*

Management

1) Ventricular rate control

- Ventricular rate control can be achieved by inhibiting the proportion of electrical impulses conducted from the atria to the ventricles through the AV node
- If patients have a rapid ventricular rate, AV nodal blockade is necessary
- To reduce symptoms and possibly prevent tachycardia-induced *cardiomyopathy*.
- Goal HR: resting HR less than 80 beats/minute

Ventricular rate control

i. **β-Blockers**

- Any agent with β-blockade can be used and dosed to the goal HR.
- Labetalol or carvedilol if additional α_1-blockade is desirable (e.g., HTN)
- Effective for controlling exercise-associated HR increases
- Can be considered in patients with stable HFrEF (only carvedilol, metoprolol succinate, or bisoprolol)
- Avoid in patients with Wolff-Parkinson-White syndrome

Ventricular rate control

ii. **Non-DHP CCBs: Verapamil or diltiazem**

- Avoid use if there is concomitant **systolic dysfunction**.
- May be preferred over β-blocker in patients with **asthma** or severe **chronic obstructive pulmonary disease**
- Effective for controlling exercise-associated HR increases
- Avoid in patients with Wolff-Parkinson-White syndrome.
- Verapamil, IV: 0.075–0.15-mg/kg bolus over 2 minutes. If no response after 30 min, may give an additional 10 mg, then 0.005 mg/kg/min continuous infusion
  - PO: 180–480 mg daily (extended release)
- Diltiazem: 0.25-mg/kg bolus over 2 minutes, then 5–15 mg/hour continuous infusion

Ventricular rate control

iii. Digoxin

- Often **ineffective alone** for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
- Can be included in regimen if patient has HF*r*EF
- May be effective if additional HR control is needed when a patient is already receiving a β-blocker, diltiazem, or verapamil
- Avoid in patients with Wolff-Parkinson-White syndrome.
- IV: 0.25 mg every 2 hours, up to 1.5 mg over 24 hours
- PO maintenance: 0.125–0.25 mg once daily

Ventricular rate control

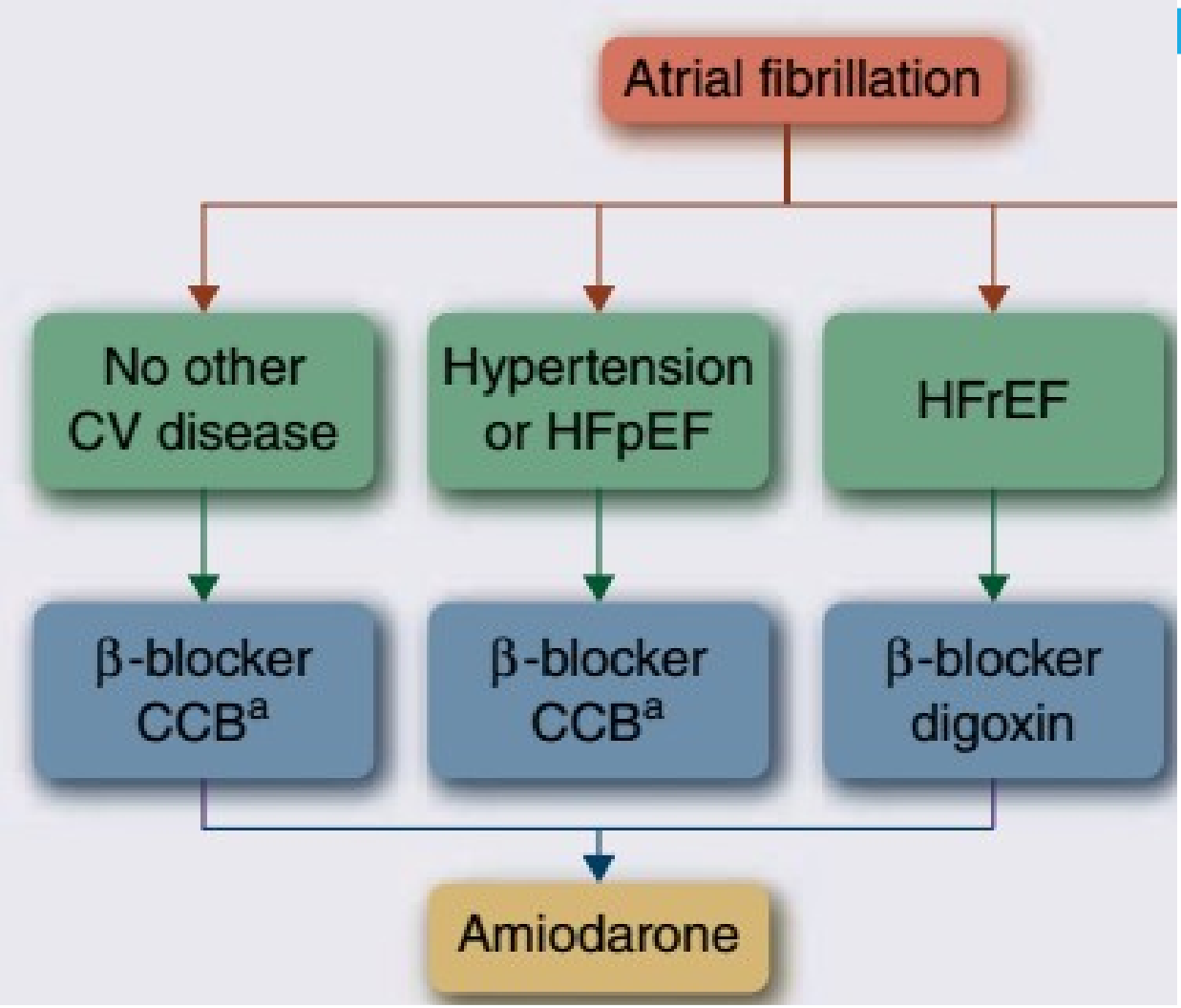
iv. Amiodarone

- May be used for rate control in patients with HF who do not have an accessory pathway
- May be used for rate control in patients who are refractory to other therapies such as β-blockers, non-DHP CCBs, and digoxin
- IV: 300 mg over 1 hour, then 10–50 mg/hour over 24 hours via continuous infusion
- Oral maintenance: 100–200 mg po once daily

Ventricular rate control

- In patients who present to the emergency department (ED) with an episode of symptomatic persistent AF or paroxysmal AF for which intervention is desired, ventricular rate control is usually initially achieved using IV drugs
- An IV CCB or β-blocker is preferred for ventricular rate control in patients with normal LV function because ventricular rate control can often be achieved within several minutes.
- In patients with HFrEF, IV diltiazem and verapamil should be avoided, as these drugs confer negative inotropic effects and may exacerbate HFrEF
- In patients with HFrEF, an IV β-blocker may be administered, but only following stabilization of acute decompensated HF, due to the potential or acute HF exacerbation.
  - IV digoxin is also a therapeutic option for patients with HFrEF.
- Patients with paroxysmal or permanent AF require long-term rate control with oral medications,

Ventricular rate control



[a]When administered intravenously, diltiazem is generally preferred over verapamil because of a lower risk of severe hypotension

Management

2) Rhythm control

- Maintaining SR offers no advantage over controlling the ventricular rate.
- However, in specific patients

i. Cardioversion in AF

2) If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
3) Without anticoagulation (thrombi caused by decreased or stagnant blood flow in the atria)
   - AF for more than 48 hours = 15% rate of atrial thrombus.
   - AF for more than 72 hours = 30% rate of atrial thrombus

- Thrombi present plus cardioversion = 91% stroke rate.

Rhythm Control

- Ensure safe cardioversion by either:
  (a) Transesophageal echocardiogram (TEE) to visualize the atria, or
  (b) Three or more weeks of therapeutic anticoagulation (INR greater than 2.0 if warfarin is selected)
- Hemodynamically Unstable AF
- Emergent conversion to sinus rhythm is necessary using direct current cardioversion (DCC)
- Hemodynamic instability: the presence of any one of the following:
  (a) Acutely altered mental status;
  (b) Hypotension (SBP < 90 mm Hg) or other signs of shock;
  (c) Ischemic chest discomfort; and/or
  (d) Acute HF

Rhythm Control

ii. ***Oral antiarrhythmic*** agents to induce or maintain SR

a) Class Ic antiarrhythmics: 50% efficacy

- ✓ Flecainide and propafenone
- ✓ For patients without structural heart disease
- ✓ Concomitant AV nodal blocking agent (β-blocker or non-DHP CCB) typically required
- ✓ Contraindicated in patients with structural heart disease

Rhythm Control

b) Class III antiarrhythmics

1) Amiodarone: 85%–95% efficacy
   - Oral loading dose required (e.g., 400 mg 2 or 3 times per day for 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose)
   - May use in patients with HF
   - Monitoring: LFT, TFT, CXR, ECG, Pulmonary FT, ophthalmic exam, skin, neuro, GI

2) Sotalol: 50%–60% efficacy
   - Recommended starting dose is 80 mg twice daily (unless CrCl less than 60 mL/minute), then once daily
   - Monitor: ECG, RFT, electrolytes (K, Mg)
   - Contraindicated: uncontrolled HF; CrCl less than 40 mL/minute; QT interval greater than 450 milliseconds; and second- or third-degree AV block or sick sinus syndrome

Rhythm Control

3) Dofetilide: 50%–60% efficacy
   - May use in patients with HF
   - Starting dose is selected based on renal function
4) Dronedarone: 21%–25% efficacy
   - Amiodarone analog lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone
   - Dose: 400 mg twice daily

Management

3) Antithrombotic therapy

- The average annual stroke rate is 5% per year without anticoagulation.
- Risk stratification and treatment determination is based on the CHA_2DS_2-VASc score

Risk Stratification for Antithrombotic Therapy in AF

- CHA_2DS_2-VASc Score

Risk Factor	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 yr	2
Diabetes	1
Stroke, TIA, thromboembolism	2
Vascular disease	1
Age 65–74 yr	1
Sex category (female)	1

NB:

- For use in patients with nonvalvular atrial fibrillation.
- Maximum point value is 9

Recommendations for Antithrombotic Therapy

- Based on CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score = 0	CHA_2DS_2-VASc Score = 1	CHA_2DS_2-VASc Score ≥ 2
Reasonable to omit antithrombotic therapy	No antithrombotic therapy or treatment with an OAC or aspirin may be considered	OAC

Antithrombotic therapy

1) Dabigatran

- Direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF;
- Demonstrated superiority to warfarin for efficacy
- Dose:
  - (a) CrCl greater than 30 mL/minute: 150 mg twice daily
  - (b) CrCl 15–30 mL/minute: 75 mg twice daily
  - (c) CrCl less than 15 mL/minute: No dosing recommendations available
  - (d) Swallow capsules whole (do not break, crush, or chew).

Antithrombotic therapy

2) Rivaroxaban

- Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF;
- Demonstrated non-inferiority compared with warfarin for efficacy
- Dose
  2) CrCl greater than 50 mL/minute: 20 mg/day with evening meal
  3) CrCl 15–50 mL/minute: 15 mg/day with evening meal
  4) CrCl less than 15 mL/minute: Avoid use
  5) Can be administered by nasogastric tube or gastric feeding tube (crush tablets and suspend in 50 mL of water). Tablets can also be crushed and mixed in applesauce

Antithrombotic therapy

3) Apixaban

- Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF
- Demonstrated superiority over warfarin for efficacy
- Dose
  - 5 mg twice daily unless:
  - In patients with at least two of the following characteristics (age 80 years or older, body weight of 60 kg or less, or SCr of 1.5 mg/dL or greater) the recommended dose is 2.5 mg twice daily.
  - CrCl less than 15 mL/minute, no specific recommendations
  - End-stage renal disease maintained on hemodialysis, 5 mg twice daily. In patients with end-stage renal disease maintained with hemodialysis who are 80 years and older and/or weigh 60 kg or less, 2.5 mg twice daily

Antithrombotic therapy

3) Edoxaban

- Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF;
- Demonstrated non-inferiority compared with warfarin for efficacy
- Dose
  - (a) Dosage is 60 mg once daily in patients with CrCl of >50mL/minute
  - (b) CrCl 15–50 mL/minute: Reduce dose to 30 mg once daily.
  - (c) CrCl less than 15 ml/min: Avoid use.
  - (d) There are no data on administering edoxaban by feeding tubes or with crushing the medication to mix with other foods or liquids

Antithrombotic therapy

3) Warfarin

- Inhibits vitamin K–dependent clotting factors II, VII, IX, X.
- Also inhibits anticoagulant proteins C and S. Racemic mixture of R- and S-isomers:
  - S-isomer more potent vitamin K antagonist
  - S-isomer metabolized primarily by CYP2C9
  - R-isomer metabolized primarily by CYP3A4
- Dosing is based on what is needed to achieve an INR goal of 2–3 for patients with non-valvular AF.
  - For patients with mitral stenosis, prosthetic heart valves, prior thromboembolism, or persistent atrial thrombus on TEE, an INR goal of 2.5–3.5 or even higher may be indicated.

Antithrombotic therapy

3) Warfarin

- Initial starting dose is usually 5 mg/day.
  - Lower starting dose (2–3 mg/day) should be considered in patients with the following: advanced age, low body weight, drug interactions, malnourishment, HF, hyperthyroid state, low albumin, or liver disease.
  - Adjusting dose: Watch for trends; remember that the INR seen today is the result of the doses given in the past 4–5 days. It takes 5–7 days to reach full effect, given the half-life of factor II.
    - Half-lives of vitamin K–dependent clotting factor VII, 6 hours; factor IX, 24 hours; factor X, 36 hours; factor II, 72 hours
  - If INR is out of therapeutic range, increase or decrease cumulative weekly warfarin dose by 5%–20% depending on INR; if INR is high, hold one or two doses and resume at a lower dose

Antithrombotic therapy

3) Warfarin

- If INR was previously stable or therapeutic and single out-of-range INR is 0.5 or less above or below therapeutic range, the current dose can be continued; recheck INR within 1–2 weeks
- In general, no need to adjust if INR is within 0.1 of goal (but monitor more closely)
- Place in therapy: May be optimal for patients with severe renal impairment, mechanical heart valves, and valvular AF or for those who are stable on warfarin or are not otherwise candidates for direct oral anticoagulant therapy
- Antidote: Vitamin K

Antithrombotic therapy

3) Warfarin

- Bleeding: incidence 2.4%–29%, life threatening 2%–8% (epistaxis, hematuria, GI hemorrhage, bleeding gums).
- Easy bruising often occurs with therapeutic INR.
- Risk of intracranial hemorrhage increased with INR greater than 4

STROKE

Learning Objectives

1) Differentiate types of cerebrovascular disease: transient ischemic attack, ischemic stroke, and hemorrhagic stroke.
2) Identify modifiable and non-modifiable risk factors associated with ischemic stroke and hemorrhagic stroke.
3) Explain the pathophysiology of ischemic stroke and hemorrhagic stroke.
4) Describe the clinical presentation of transient ischemic attack, ischemic stroke, and hemorrhagic stroke.
5) Indicate treatment options for acute ischemic stroke.
6) Determine whether fibrinolytic therapy is indicated in a patient with acute ischemic stroke.
7) Formulate strategies for primary and secondary prevention of acute ischemic stroke.
8) Evaluate treatment options for acute hemorrhagic stroke.

Introduction

- **Stroke:** Injury or death of brain tissue due to oxygen deprivation; usually due to an interruption of blood flow
  - Also referred to as “Brain Attack” or “Cerebrovascular Accident” (CVA)
- **Transient Ischemic Attack (TIA):** A neurologic deficit that lasted less than 24hrs (usually few minutes)
  - This abrupt onset of a neurologic deficit in stroke/TIA is attributable to a focal vascular cause

Definition

- Clinically **stroke** is a sudden onset non convulsive neurologic deficit characterized by the rapid appearance (usually over minutes) of a focal deficit of brain function, most commonly a **hemiplegia** with or without signs of focal higher cerebral dysfunction (such as aphasia), hemisensory loss, visual field defect or brain-stem deficit
- In stroke the evidence of brain dysfunction (neurologic deficit) lasts for at least 24h or more

Epidemiology

- Stroke is the third most common cause of death in the world after ischemic heart disease and cancer, and is the most common cause of severe physical disability
  - The incidence rises steeply with age
  - The incidence is rising in many developing countries
  - About **one-fifth** of patients with an acute stroke will die within a month of the event, and at least **half** of those who survive will be left with physical disability

Risk factors

Non-modifiable

i) **Age**: Stroke risk doubles each decade after 55 years.

ii) **Race**: Risk for African Americans > whites.

iii) **Sex**: Risks are greater for men than for women

iv) **Low birth weight**: Odds of stroke for those with birth weights <2500 g are twice has high as the odds for those weighing >4000 g.

v) **Family history**: Parental history increases risk; some coagulopathies (e.g., protein C and S deficiencies, factor V mutations) are inherited

Risk factors

- **Modifiable**
  a) **Diabetes** mellitus increases risk 1.8 – 6-fold
  b) **Hypertension** increases risk 1.4 – 8-fold; 32% risk reduction with control
  c) **Smoking** increases risk 1.9-fold; 50% risk reduction in 1 year,
  d) **Oral contraceptives**
     - ✓ With less than 50 mcg of estrogen double risk of stroke;
     - ✓ With more than 50 mcg of estrogen increase risk 4.5-fold;
  e) **Postmenopausal hormone therapy** increases risk 1.4-fold
  f) **Atrial fibrillation** increases risk 2.6–4.5-fold; 68% risk reduction with warfarin

Risk factors

- **Modifiable**
  - g) Coronary heart disease increases risk 1.55-fold (women) to 1.73-fold (men).
  - h) Symptomatic carotid stenosis increases risk 2-fold
  - i) Dyslipidemia: High total cholesterol increases risk 1.5-fold; low HDL cholesterol (less than 35 mg/dL) increases risk 2-fold;
  - j) Obesity (especially abdominal body fat) increases risk 1.75–2.37-fold
  - k) Physical inactivity increases risk 2.7-fold
  - l) Pregnancy increases risk 2.4-fold over nonpregnant women; the risk remains elevated for the first 6 weeks postpartum.

Risk factors

- **Less well documented:**
  - i) Alcohol abuse (5 or more drinks a day),
  - ii) drug abuse (cocaine, amphetamines, and heroin),
  - iii) hypercoagulability,
  - iv) periodontal disease,
  - v) inflammation and infection,
  - vi) sleep-disordered breathing (sleep apnea and snoring),
  - vii) metabolic syndrome, and
  - viii) migraine with aura

Risk Factors

- **Ethiopia**

1. Established hypertension 65.6%
2. Cardiac disease 22.7%
3. Established diabetes 11.7%
4. TIA
5. Previous stroke
6. Atrial fibrillation

Pathophysiology Classification
(Ethiopia*)

Ischemic - 87% (43%*)

- **Thrombotic:** 25%
- **Embolic:** 75%
  - ✓ Cardioembolic: 20%
  - ✓ Artery to artery: 15%
  - ✓ Cryptogenic: 30%
  - ✓ Others: 10%

Hemorrhagic - 13% (57%*)

- Intraparenchymal (10%)
- Subarachnoid
- Subdural
- Epidural

Ischemic Stroke

- Occurs when a cerebral artery is blocked by a clot or other foreign matter causing **ischemia** (inadequate blood supply to tissue)
- **Cerebral ischemia** is caused by a reduction in blood flow that lasts longer than several seconds.
- Neurologic symptoms are manifest within seconds because neurons lack **glycogen**, so energy failure is rapid.
- If the cessation of flow lasts for more than a few minutes ischemia progresses to **infarction** (death of tissues).

Ischemic Stroke

- When blood flow is quickly restored, brain tissue can recover fully and the patient's neurologic signs and symptoms resolve within 24 h: this is called a **transient ischemic attack (TIA).**
- If the neurologic signs and symptoms last for >24 hr stroke has occurred
- Classified as: Embolic Stroke or Thrombotic Stroke

Embolic Stroke

1. Artery-Artery

- Thrombus is formed on the plaque and it embolizes to the distal artery
- Common source is carotid bifurcation, other sites: internal carotid a, prox vertebral a, subclavian a, basilar a, posterior cerebral a.
- Plaque structure ulcerate & embolize to occlude distally

Embolic Stroke

2. Cardioembolic Stroke

- Cardiac diseases associated are AF, MI, prosthetic valve, rheumatic heart disease, cardiomyopathy
- Usually to the middle cerebral a (MCA), posterior cerebral a (PCA), or one of their branches, rarely to anterior cerebral a (ACA).

Thrombotic Stroke

- Large vessels thrombosis: Atherosclerosis is the commonest pathology of vascular obstruction
- Small vessel thrombosis (Lacunar stroke):
  - These are vessel measuring 30-300 micm
  - Atherothrombotic and lipohyalinotic pathologies are the cause of the ischemia in lacunar stroke & major risk factors are age and hypertension

Intracranial Hemorrhage

- **Intracranial hemorrhage** is caused by bleeding directly into or around the brain;
  - It produces neurologic symptoms
    - By producing a mass effect on neural structures,
    - From the toxic effects of blood itself, or
    - By increasing intracranial pressure.

Intracranial Hemorrhage

- Hemorrhagic stroke or/& intracranial bleeding can be
  - ✓ Intraparenchymal hemorrhage (hypertensive or related to other cause of hemorrhage)
  - ✓ Subarachnoid hemorrhage
  - ✓ Epidural hemorrhage
  - ✓ Subdural hemorrhage
  - ✓ Intraventricular hemorrhage
  - ✓ Cerebellar hemorrhage

Clinical Presentation and Diagnosis

General

- The patient may not be able to reliably report the history owing to cognitive or language deficits.
- A reliable history may have to come from a family member or another witness.

Symptoms

- The patient may complain of weakness on one side of the body, inability to speak, loss of vision, vertigo, or falling.
- Stroke patients may complain of headache; however, with hemorrhagic stroke, the headache can be severe.

Clinical Presentation and Diagnosis

- **Signs**
  - Hemiparesis or monoparesis occur commonly, as does hemisensory deficit.
  - Patients with vertigo and double vision are likely to have posterior circulation involvement.
  - Aphasia is seen commonly in patients with anterior circulation strokes.
  - Patients may also suffer from dysarthria, visual field defects, and altered levels of consciousness.

Clinical Presentation and Diagnosis

- **Diagnostic Tests**
  - A computed tomography (CT) scan of the head: identifying that a hemorrhage has occurred.
  - The CT scan may take 24 hours (rarely longer) to reveal the area of infarction.
  - Magnetic resonance imaging (MRI): reveal areas of ischemia earlier and with better resolution than a CT scan.
  - Carotid doppler studies
  - ECG, Echo

Management of Ischemic Stroke

Desired Treatment Outcomes

- **Short-term goals**
  - Reducing secondary brain damage by **re-establishing and maintaining adequate perfusion** to marginally ischemic areas of the brain and to protect these areas from the effects of ischemia (i.e., neuroprotection).
- **Long-term goals**
  - **Prevention of a recurrent stroke** through reduction and modification of risk factors and by use of appropriate treatments.

General Approach to Treatment

- All patients should have a brain CT scan or MRI scan
  - To differentiate an ischemic stroke from a hemorrhagic stroke, as the treatment will differ accordingly and **thrombolytic** (fibrinolytic) therapy must be avoided until a hemorrhagic stroke is ruled out
- Identification of the time and manner of stroke onset is an important determinant in treatment.
- The time the patient was last without symptoms is used as the time of stroke onset.

General Approach to Treatment

Supportive Measures

- Oxygen
- Volume status and electrolytes should be corrected
- Blood glucose should be corrected, as both hyperglycemia and hypoglycemia may worsen brain ischemia.
  - ✓Hypoglycemia → bolus with 50% dextrose
  - ✓Hyperglycemia → subcutaneous insulin (<300 mg/dL)
- Febrile: acetaminophen
- DVT prophylaxis: Heparin 5000 units sc q8hr

Primary prevention

- Reduction in risk factors
  - Control of hypertension,
  - Smoking cessation,
  - Control of diabetes,
  - Cholesterol reduction
- Treatment of atrial fibrillation: up to 70% of cases are inappropriately treated.

Thrombolytic Therapy

Alteplase (tPA)

- In carefully selected patients, alteplase is effective in limiting the infarct size and protecting brain tissue from ischemia and cell death by restoring blood flow.
- Treatment must be given **within 4.5 hours** of the onset of symptoms and offers no benefit if given beyond this time period
- Dose of 0.9 mg/kg (max 90 mg) is recommended; the first 10% is given as an IV bolus and the remainder is infused over 1 hour

Criteria for Alteplase Use

Inclusion Criteria

- 18 years of age or older
- Clinical diagnosis of ischemic stroke causing a measurable deficit
- Time of symptom onset well established to be less than 4.5 hours before treatment would begin

Criteria for Alteplase Use

Exclusion Criteria

1. Evidence of IC hemorrhage on CT scan of the brain
2. Only minor or rapidly improving stroke symptoms
3. Active internal bleeding
4. Known bleeding diathesis, including but not limited to
   i) Platelet count less than 100 × 10^3/mL;
   ii) Heparin within 48 hours with an elevated aPTT; or
   iii) Current oral anticoagulant use (e.g., warfarin) or recent use with an elevated PT (greater than 15 seconds) or INR (greater than 1.7)
5. Intracranial surgery, serious head trauma, or previous stroke within 3 months

Criteria for Alteplase Use

- **Exclusion Criteria**
  6. History of GI or urinary tract hemorrhage within 21 days
  7. Major surgery or serious trauma within 14 days
  8. Lumbar puncture within 7 days
  9. SBP greater than 185 mm Hg or DBP greater than 110 mm Hg at the time of treatment

Thrombolytic Therapy

- Avoided (for 24 hours after the infusion of alteplase):
  - **Antiplatelet agents**,
  - **Anticoagulants**, and
  - **Invasive procedures** such as the insertion of a central line or the placement of a naso-gastric tube
- **Bladder catheterization** should also be avoided for 30 minutes post-infusion.

Thrombolytic Therapy

- The major adverse effects of thrombolytic therapy are bleeding, including intracerebral hemorrhage and serious systemic bleeding.
- Mental status changes and a severe headache may indicate an intracerebral hemorrhage.
- Signs of bleeding include easy bruising; hematemesis; guaiac-positive stools; black, tarry stools; hematoma formation; hematuria; bleeding gums; and nosebleeds

ASPIRIN

- Early aspirin therapy is recommended in most patients with acute ischemic stroke within the first 24 to 48 hours after stroke onset and should be continued for at **least 2 weeks**.

Prevention of Acute Ischemic Stroke

Secondary Prevention

1) **Aspirin**: Aspirin is typically considered to be the first-line secondary prevention agent for ischemic stroke and decreases the risk of subsequent stroke by approx. **25%** in both men and women with previous transient ischemic attacks or stroke.
2) **Warfarin**: In patients with atrial fibrillation, long-term anticoagulation with warfarin is recommended and is effective in both primary and secondary prevention of stroke

Secondary Prevention

3) **Ticlopidine**: Ticlopidine is slightly more beneficial in stroke prevention than aspirin in both men and women.
4) **Clopidogrel:** is slightly more effective than aspirin
5) **ER Dipyridamole plus Aspirin**: 25 mg aspirin and 200 mg ER dipyridamole.
   - More effective than either treatment alone
6) **Blood Pressure Management**
   - In patients with a previous history of stroke or TIA, a diuretic and an ACE-I are recommended

Treatment of Acute Hemorrhagic Stroke

- Surgical
- Medical
  - ✓ Protecting airway
  - ✓ Managing BP before and after aneurysm Rx
  - ✓ Preventing rebleeding
  - ✓ Seizure - prophylactic **phenytoin**
  - ✓ Vasospasm – nimodipine
    - ✓ 60 mg every 4 hours for 21 days),

Monitoring

- Patients with acute stroke should be monitored intensely for
  - the development of neurologic worsening (recurrence or extension),
  - complications (thromboembolism or infection), or
  - adverse effects from pharmacologic or nonpharmacologic interventions.

Monitoring

Drug	Adverse Effect	Monitoring Parameters	Comments
tPA	Bleeding	Neurologic exam	Every 15 minutes × 1 hour; every 0.5 hour × 6 hours; every 1 hour × 17 hours; every shift after
ASA	Bleeding		Daily
Clopidogrel	Bleeding		Daily
ERDP-ASA	Headache, bleeding		Daily
Warfarin	Bleeding	INR, Hb/Hct	Daily
Dabigatran	Bleeding		Daily

ERDP-ASA, extended-release dipyridamole plus aspirin; Hb/Hct, hemoglobin/hematocrit.

Quiz-1

1. Which is not contraindication for tPA?

   A. IC hemorrhage B. Active internal bleeding

   C. Head trauma D. Menstruation

2. Thrombolytic therapy is indicated for hemorrhagic stroke within 4.5 hours of the onset of symptoms

   A. True B. False

3. For a patient with AF, HFrEF, and Asthma; ventricular rate control is effectively achieved with:

   A. BB B. Non-DHP-CCB C. Digoxin D. Amiodarone

4. Antithrombotic activity of warfarin starts after 5 days of the first dose. Why?

5. All patients with stroke should have a brain CT scan or MRI scan before treatment is initiated. Why?

HYPERLIPIDEMIA

Objectives

- Identify the common types of lipid disorders
- Identify the statin-benefit groups and intensity of statin therapy
- Determine a patient’s atherosclerotic CVD risk and corresponding treatment goals
- Describe components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for dyslipidemias.

Definitions

- Abnormal levels of lipids in blood
  - **Hyperlipidemia**: ↑TG & cholesterol
  - **Hypertriglyceridemia**: ↑TG
  - **Hypercholesterolemia**: ↑cholesterol
  - **Hyperlipoproteinemia**: ↑lipoprotein (LDL & VLDL)
  - **Low HDL**
- Normal values in mg/dl:
  - Total cholesterol<200, LDL<100, HDL: 40-60, TG<150

Classification of Total, LDL, and HDL-C, and Triglycerides

Total Cholesterol	
<200 mg/dL (<5.17 mmol/L)	Desirable
200–239 mg/dL (5.17–6.20 mmol/L)	Borderline high
≥240 mg/dL (≥6.21 mmol/L)	High
LDL Cholesterol	
<100 mg/dL (<2.59 mmol/L)	Optimal
100–129 mg/dL (2.59–3.35 mmol/L)	Near or above optimal
130–159 mg/dL (3.36–4.13 mmol/L)	Borderline high
160–189 mg/dL (4.14–4.90 mmol/L)	High
≥190 mg/dL (≥4.91 mmol/L)	Very high
HDL Cholesterol	
<40 mg/dL (<1.03 mmol/L)	Low
≥60 mg/dL (≥1.55 mmol/L)	High
Triglycerides	
<150 mg/dL (<1.70 mmol/L)	Normal
150–199 mg/dL (1.70–2.25 mmol/L)	Borderline high
200–499 mg/dL (2.26–5.64 mmol/L)	High
≥500 mg/dL (≥5.65 mmol/L)	Very high

HDL, high-density lipoproteins; LDL, low-density lipoproteins.

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

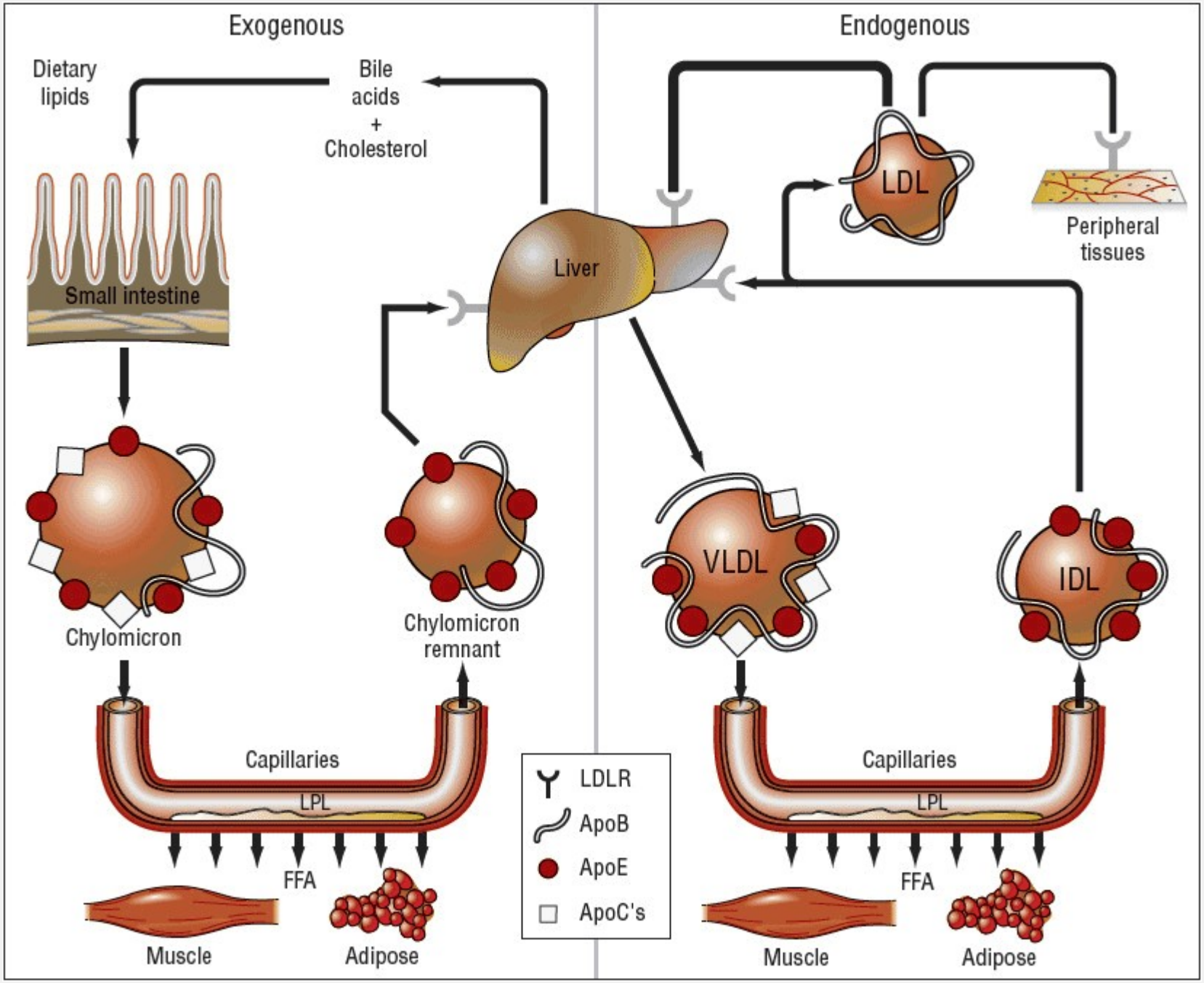
- Lipids are an essential component of several biological processes.
- The major plasma lipids are cholesterol, TGs, and phospholipids.
- Cholesterol serves as a structural component of cell wall membranes and is a precursor for the synthesis of steroid hormones and bile acids.
- TGs, the esterified 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


Exogenous
Endogenous
Dietary lipids
Bile acids + Cholesterol
Small intestine
Liver
LDL
Peripheral tissues
Chylomicron
Chylomicron remnant
VLDL
IDL
Capillaries
LPL
FFA
Muscle
Adipose
LDLR
ApoB
ApoE
ApoC's
Capillaries
LPL
FFA
Muscle
Adipose

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

Etiology

- **Hypercholesterolemia:** Hypothyrodism, obstructive liver diseases, nephrotic syndrome, drugs (e.g. progestin, thiazides, BBs, PIs)
- **Hypertriglyceridemia**: obesity, DM, lipodystrophy, pregnancy, acute hepatitis, SLE, drugs (e.g. alcohol, BB, thiazides, estrogen, glucocorticoids, bile acid resins.)
- **Low HDL**: malnutrition, obesity, drugs (e.g. progestin)

Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia

Type	Lipoprotein Elevation
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL (LDL_1)
IV	VLDL
V	VLDL + chylomicrons

Lipoprotein Disorders

Lipid Phenotype	Plasma Lipid Levels (mg/dL [mmol/L])	Lipoproteins		Clinical Signs
		Elevated	Phenotype	
Isolated Hypercholesterolemia				
Familial hypercholesterolemia	Heterozygotes TC = 275–500 (7.1–12.9)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease at 30–50 years
	Homozygotes TC >500 (>12.9)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease in childhood
Familial defective ApoB-100	Heterozygotes TC = 275–500 (7.1–12.9)	LDL	IIa	
Polygenic hypercholesterolemia	TC = 250–350 (6.5–9)	LDL	IIa	Usually asymptomatic until vascular disease develops; no xanthomas
Isolated Hypertriglyceridemia				
Familial hypertriglyceridemia	TG = 250–750 (2.8–8.5)	VLDL	IV	Asymptomatic; may be associated with increased risk of vascular disease
Familial LPL deficiency	TG >750 (>8.5)	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitits, abdominal pain, hepatosplenomegaly
Familial ApoC-II deficiency	TG >750 (>8.5)	Chylomicrons, VLDL	I, V	As above
Hypertriglyceridemia and Hypercholesterolemia				
Combined hyperlipidemia	TG = 250–750 (2.8–8.5); TC = 250–500 (6.5–12.9)	VLDL, LDL	IIb	Usually asymptomatic until vascular disease develops; familial form may also present as isolated high TG or an isolated high LDL cholesterol
Dysbetalipoproteinemia	TG = 250–750 (2.8–8.5); TC = 250–500 (6.5–12.9)	VLDL, IDL; LDL normal	III	Usually asymptomatic until vascular disease develops; may have palmar or tuboeruptive xanthomas

Clinical Presentation

- **Symptom**s: None to severe chest pain, palpitations, sweating, anxiety, shortness of breath, loss of consciousness or difficulty with speech or movement, abdominal pain, sudden death
- **Signs**: None to severe abdominal pain, pancreatitis, eruptive xanthomas, peripheral polyneuropathy, high blood pressure, BMI>30 kg/m^2 or waist size >40 inches in men (>35 inches in women)
- **Lab:** Elevations in total cholesterol, LDL, TGs, Low HDL

Screening

- Determine lipoprotein profile after fasting for 9 to 12 hours.
- All adults greater than 20 years of age should be screened at least every years using a fasting blood sample to obtain a lipid profile (total C, LDL C, HDL C, and TG).
- Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has a total cholesterol greater than 240 mg/dL

Management

- **Initiate therapeutic lifestyle changes if LDL is above goal**
  - ✓ Dietary restrictions of cholesterol and saturated fats
  - ✓ Regular exercise and weight reduction.
  - ✓ Consumption of plant stanols/sterols (which competitively inhibit incorporation of cholesterol into micelles) and dietary fiber

Management

Determine the Presence of Major Risk Factors for ASCVD

Risk Factor	Definition
Age (years)	Male ≥45; Female ≥55
Family Hx of premature CHD events	Male 1st-degree relative at < 55 years Female 1st-degree relative at < 65 years
Hypertension	SBP ≥140 mm Hg DBP ≥90 mm Hg
HDL cholesterol	< 40 mg/dL
Cigarette smoking	Within the past month

ASCVD Risk Assessment and Treatment Goals

- **Very high risk**
  - ASCVD
    - ✓ MI or other ACS
    - ✓ Coronary or other revascularization procedures
    - ✓ Transient ischemic attack
    - ✓ Ischemic stroke
    - ✓ Atherosclerotic peripheral arterial disease
    - ✓ Other documented atherosclerotic diseases
  - DM (type 1 or 2)
    - ✓ ≥ 2 other major ASCVD risk factors or
    - ✓ Evidence of end-organ damage
  - ✓ **Goal cholesterol**: non-HDL≤100 mg/dL, LDL ≤70 mg/dL

ASCVD Risk Assessment and Treatment Goals

- **High Risk**
  - ≥ 3 major ASCVD risk factors
  - DM (type 1 or 2)
    - 0–1 other major ASCVD risk factors and
    - No evidence of end organ damage
  - CKD stage 3 or 4
  - LDL ≥ 190 mg/dL (severe hypercholesterolemia)
  - ≥ 10% ASCVD risk
  - **Cholesterol Goal**
    - ✓ Non-HDL = < 130 mg/dL (goal: <130)
    - ✓ LDL = < 100 mg/dL (goal: < 70)

ASCVD Risk Assessment and Treatment Goals

- **Moderate Risk**
  - Two major ASCVD risk factors
  - Consider drug therapy
    - Non-HDL = ≥ 160 mg/dL (goal: <130)
    - LDL = ≥ 130 mg/dL (goal: <100)
- **Low Risk**
  - 0–1 major ASCVD risk factor
  - Consider drug therapy
    - Non-HDL = ≥ 190 mg/dL (goal: <130)
    - LDL = ≥ 160 mg/dL (goal: 100)

Pharmacotherapy

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins
Cholestyramine, colestipol, and colesevelam	↑ LDL catabolism ↓ cholesterol absorption	↓ cholesterol	↓ LDL ↑ VLDL
Niacin	↓ LDL and VLDL ↓ synthesis	↓ triglyceride and ↓ cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ triglyceride and cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism; inhibit LDL synthesis	↓ cholesterol	↓ LDL
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ cholesterol	↓ LDL

Pharmacotherapy

- **Hypercholesterolemia**
  - **Statins**: highest effect and pt acceptance (DoC)
  - **Niacin**: most desirable effect but higher SE
  - **BAR** and **ezetmibe** add on drug but inconvenient
  - **Fibrates** not recommended for LDL lowering only
- **Low HDL**
  - Use **statins** if LDL high.
  - If high TG use combination therapy- **niacin**, **fibrates**

Pharmacotherapy

Hypertriglyceridemia

- **Fibrates** are DoC,
- Niacin most effective but most SE.
- Statins for combination with fibrates.
- Avoid BAR

Mixed hyperlipidemia

- Statins and niacin both are effective but statins are more tolerated.

Pharmacotherapy

Statins

- Statins are the medications of choice to treat high LDL cholesterol because of:
  - ✓ Their ability to substantially reduce LDL cholesterol,
  - ✓ Ability to reduce morbidity and mortality from atherosclerotic disease,
  - ✓ Convenient once-daily dosing, and
  - ✓ Low risk of side effects.
- Check baseline CK

Pharmacotherapy

- Four major statin benefit groups
  1. Patients with clinical atherosclerotic cardiovascular disease (**ASCVD**).
     - ASCVD includes CHD, stroke or transient ischemic attack, and PAD.
  2. Patients with an **LDL-C** of 190 mg/dL or greater
  3. Patients with **DM** age 40–75 years with an LDL-C of 70–189 mg/dL and without ASCVD
  4. Patients age 40–75 years with an LDL-C of 70–189 mg/dL and an estimated 10-year **ASCVD risk** of 7.5% or greater without DM or ASCVD

Risk assessment for primary prevention

- Pooled cohort equation to estimate 10-year ASCVD risk
  - (a) Assists with identifying higher-risk patients for statin therapy
  - (b) Can be used in patients with type 1 and type 2 DM in primary prevention to guide the intensity of statin therapy
  - (c) Should not be used for patients with clinical ASCVD or an LDL-C greater than 190 mg/dL already on statin therapy

Pharmacotherapy

- General approach to initiating statin therapy

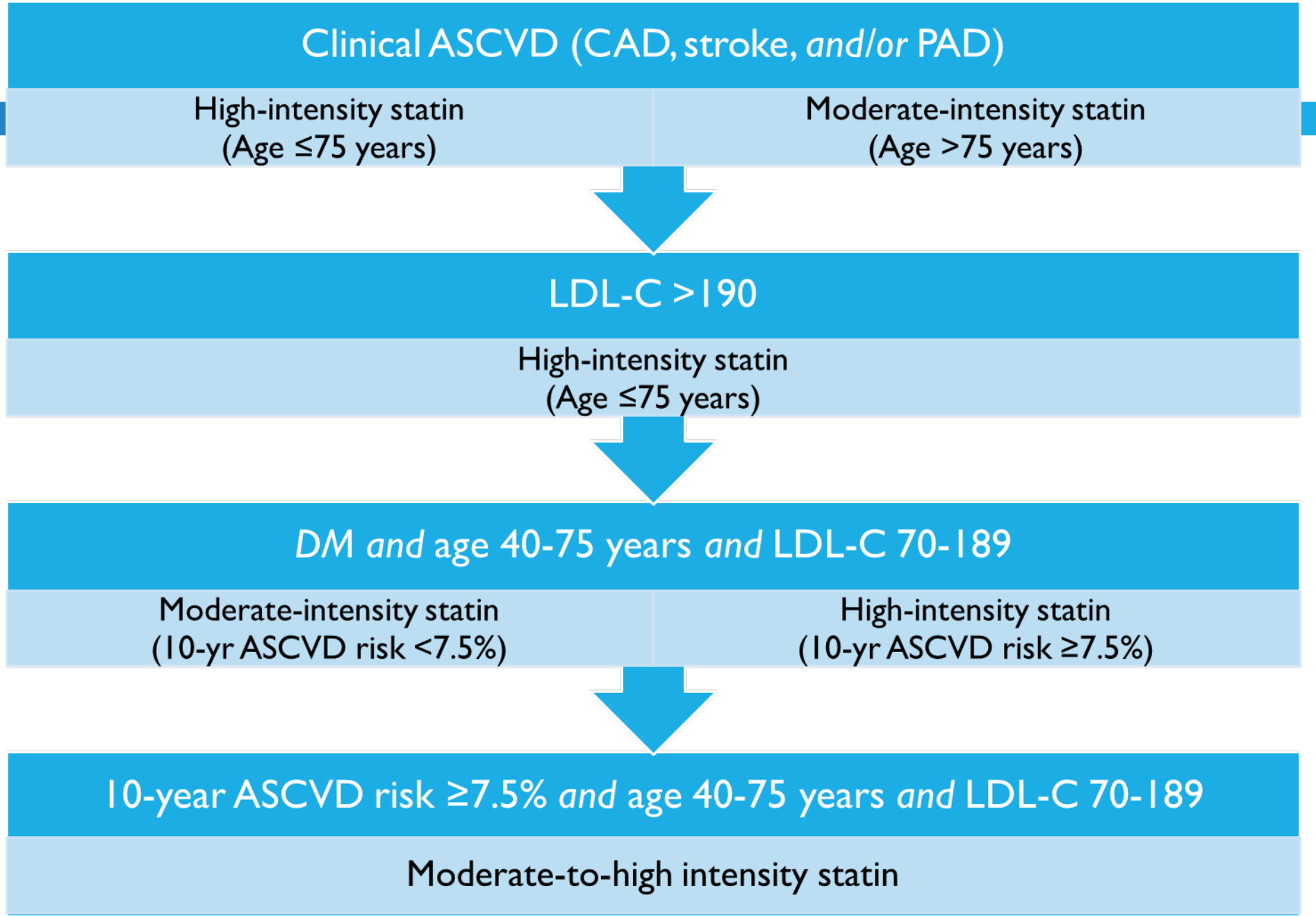
1. Check labs
   (a) Fasting lipid panel.
      - If LDL-C is higher than 190 mg/dL, evaluate for secondary causes.
      - If TG 500 mg/dL or higher, treat hypertriglyceridemia

   (b) Alanine aminotransferase (ALT)
      - Evaluate patients with unexplained ALT >3x ULN

   - Hemoglobin A1c
   - Creatinine kinase (if indicated)
   - Evaluate for secondary causes or conditions that may affect statin safety

(a) Initiate statin therapy based on statin benefit groups

Statin Recommendation for CVD Prevention



Relative LDL-C-Lowering Efficacy of Statins

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Simva	% in LDL
---	20-40	1	20	10-20	---	10	30
10	80	2	40	40	---	20	38
20	---	4	80	80	5	40	41
40	---	---	---	---	10	---	47
80	---	---	---	---	20	---	55
	---	---	---	---	40	---	63

Denotes high-intensity statin; lowers LDL-C by ≥ 50%

Denotes moderate-intensity statin; lowers LDL-C by 30% to < 50%

Denotes low-intensity statin; lowers LDL-C by < 30%

Pharmacotherapy

- **Treatment of Elevated Triglycerides**
  - ✓ Patients with serum triglycerides exceeding 500 mg/dL are at increased risk of **pancreatitis**.
  - ✓ Goal of therapy should be to reduce triglycerides to less than 150 mg/dL
  - ✓ Once triglycerides are < 500 mg/dL, the primary focus of intervention should once again be on LDL cholesterol.
  - ✓ Niacin, fibrates, and fish oils are the most effective agents in patients with hypertriglyceridemia.

Adverse Effects & CIs

- **Statins:** Atorvastatin, fluvastatin, lovastatin, lovastatin ER, pravastatin, rosuvastatin, simvastatin
  - ✓ Headache, dyspepsia, myositis, hepatotoxicity
  - ✓ CI in active liver disease
- **Nicotinic acid:** niacin ER, niacin
  - ✓ flushing, dyspepsia, itching, headache, nausea, fatigue, rash, PU, hyperglycemia, hyperuricemia, hepatitis,

    CI: in active liver disease and gout

Adverse Effects & CIs

- **BAR-** Cholestyramine, Colesevelam, Colestipol

  - ✓ Indigestion, bloating, nausea, constipation, abdominal pain, flatulence. May increase TG**.**

- **Fibrates –** Fenofibrate, Gemfibrozil

  - ✓ Gallstones**,** dyspepsia, rash, urticaria, hair loss, myalgias, fatigue, headache, impotence, and anemia.
  - ✓ CI: in severe liver and renal diseases**.**

VENOUS THROMBOEMBOLISM

Introduction

- Manifested as:
  - Deep vein thrombosis (DVT) and/or
  - Pulmonary embolism (PE)
- Results from clot formation within the venous circulation,
  - Most commonly the legs,
  - Others: the arms, and in the mesenteric and cerebral veins

Risk Factors

1. **Age**: 1 in 100,000 in adolescents, 1 in 100 in old age
2. **History of VTE**: Strongest known risk factor
3. **Venous stasis**
   - Major medical illness (e.g., CHF, status post-MI)
   - Major surgery (e.g., general anesthesia >30 minutes)
   - Paralysis and immobility (e.g., plaster casts, status post-stroke, spinal cord injury)
   - Polycythemia vera
   - Obesity
   - Varicose veins

Risk Factors

4. Vascular injury

- Major orthopedic surgery (knee and hip replacement)
- Trauma (especially fractures of the pelvis, hip, or leg)
- Indwelling venous catheters

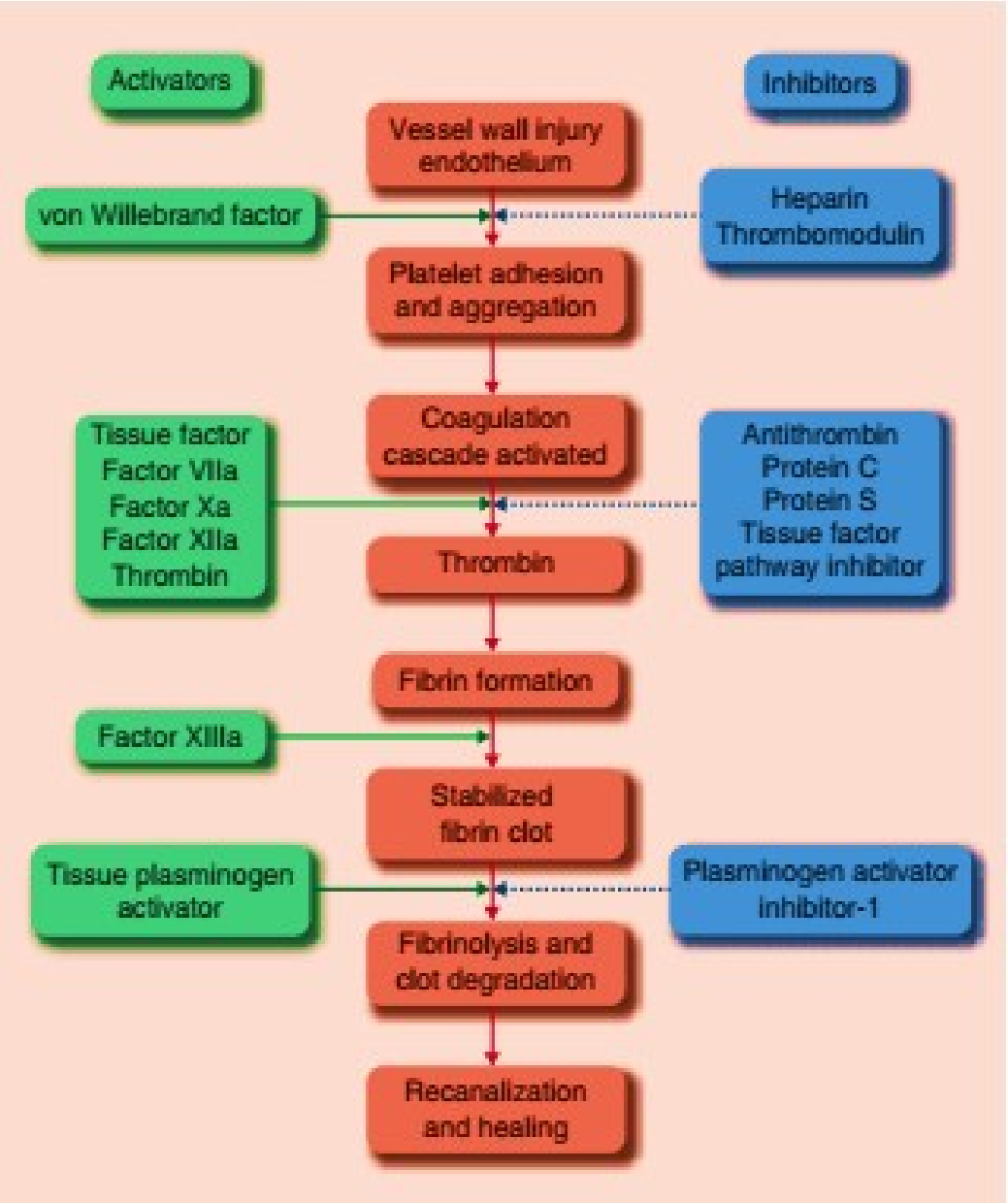
5. Hypercoagulable states

4. Malignancy
5. Genetics
6. Nephrotic syndrome
7. Pregnancy/postpartum

Drug therapy

- Estrogen-containing contraception
- Estrogen replacement therapy
- Selective estrogen receptor modulators (tamoxifen)
- Heparin-induced thrombocytopenia

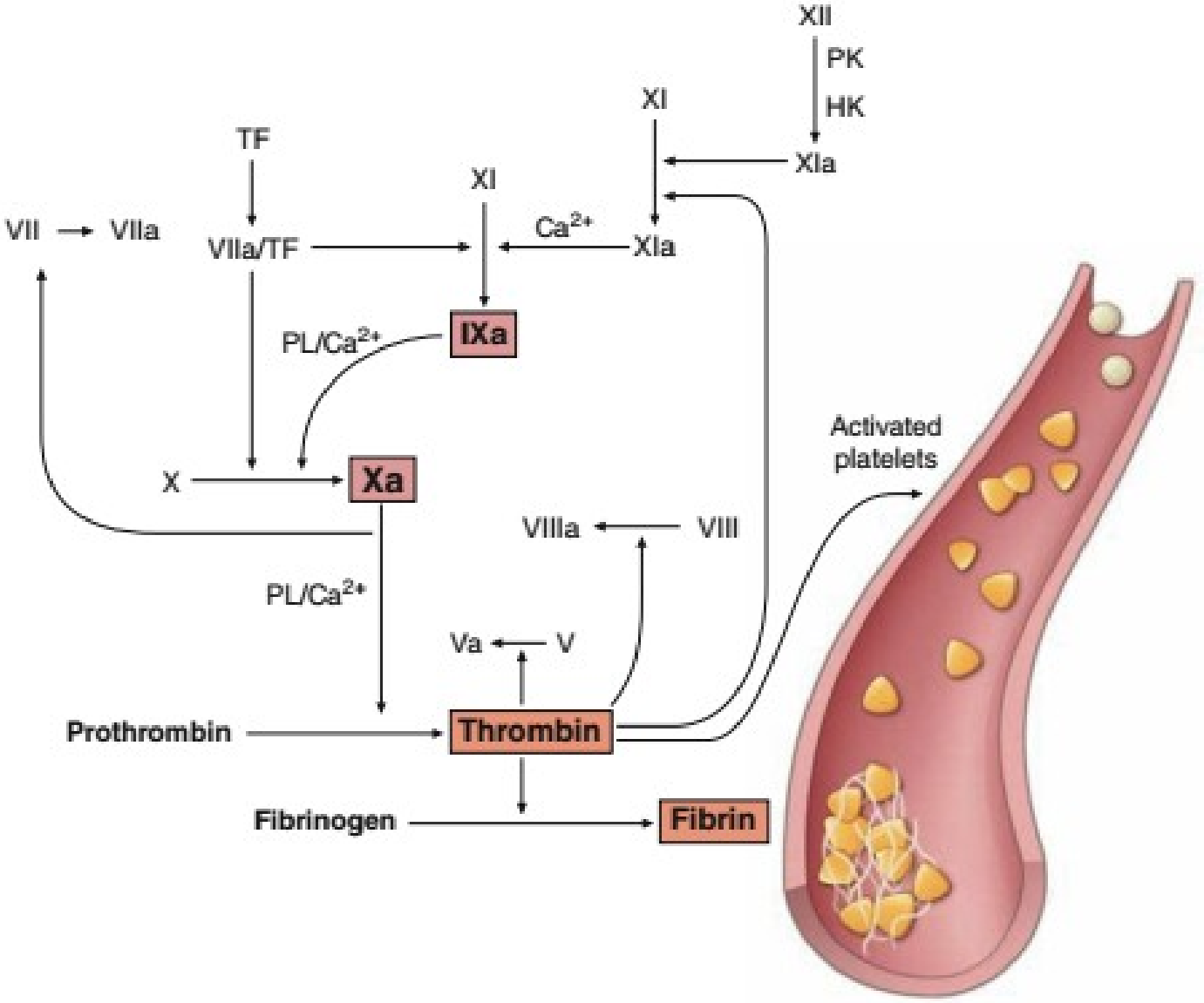
Pathophysiology



Pathophysiology

- When a vessel is **injured**, a dynamic interplay between thrombogenic (activating) and antithrombotic (inhibiting) forces result in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss
- A disruption of this delicate system of **checks** and **balances** may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed
- Vascular injury exposes the subendothelium.
- Platelets adhere to the subendothelium, using glycoprotein (GP) Ib receptors found on their surfaces and facilitated by von Willebrand factor (vWF).
- This causes platelets to become activated, releasing a number of procoagulant substances that stimulate circulating platelets to expose GP IIb and IIIa receptors and allow platelets to adhere to one another, resulting in platelet aggregation.
- The damaged vascular tissue releases tissue factor that activates the **extrinsic pathway** of the coagulation cascade

Summary of Coagulation Pathways



Clinical Presentation and Diagnosis

DVT

General

- Identifiable risk factors
- Immediate death from PE

Symptoms

- Leg swelling, pain and warmth

Signs

- Dilated superficial veins
- Palpable cord
- Homan's sign

- **Lab tests:**
  - CBC
  - PT, INR, aPTT
  - RFT
  - LFT
- **Diagnostic tests**
  - US:
    - non invasive,
    - may not visualize small clots in distal veins
  - Venography:
    - Gold standard

Clinical Presentation and Diagnosis

PE

General

- Identifiable risk factors of DVT
- Most develop symptoms of DVT before PE
- Immediate death from PE

Signs

- Tachypnea, diaphoretic
- Distended veins
- Cyanotic, hypotensive
- Hypoxic (pulse oximetry)
- Shock

- **Symptoms**
  - ✓ Cough, chest pain,
  - ✓ Chest tightness, SOB,
  - ✓ Palpitation
  - ✓ Hemoptysis
- Lab tests:
  - CBC, ESR, AST, LDH
  - ECG
- Diagnostic **tests**
  - o CT scan
  - o Pulmonary angiography: gold

Modified Wells Criteria for Probability of DVT

Clinical feature	Score
Tenderness along entire deep vein system	1.0
Swelling of the entire leg	1.0
Greater than 3 cm difference in **calf circumference**	1.0
Pitting **edema**	1.0
Collateral **superficial veins**	1.0
Risk factors present:	
• Active cancer	1.0
• Prolonged immobility or paralysis	1.0
• Recent surgery or major medical illness	1.0
Alternative diagnosis likely (ruptured Baker cyst, rheumatoid arthritis, superficial thrombophlebitis	−2.0

Score ≥3 = high probability; 1–2 = moderate probability; ≤0 = low probability

Pretest Probability of PE

Clinical feature	Score
Deep vein thrombosis suspected	
• Clinical features of deep vein thrombosis	3.0
• Recent prolonged immobility or surgery	1.5
• Active cancer	1.0
• History of deep vein thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Resting heart rate >100 beats/min	1.5
No alternative explanation for acute shortness of breath or chest pain	3.0

Score ≥6 = high probability; 2–6 = moderate probability; ≤1.5 = low probability

Prevention and Treatment of VTE

Prevention

- Given that VTE is often clinically silent and potentially fatal, prevention strategies have the greatest potential to improve patient outcomes.

- The goal of an effective VTE prophylaxis is

  - To identify all patients at risk,
  - Determine each patient’s level of risk, and
  - Select and implement regimens that provide sufficient protection for the level of risk

Nonpharmacologic Prophylaxis

- **Ambulation** as soon as possible following surgery
- Graduated compression stockings (GCS)

Pharmacologic Prophylaxis

- For hospitalized general surgical and medical patients
  - **UFH** 5000 Units every 12 or 8 hours,
  - **LMWH:**
    - **Enoxaparin:** 40 mg SC daily,
    - **Dalteparin** 2500 to 5000 Units SC daily, or
  - **Fondaparinux** 2.5 mg SC daily.
  - **Fondaparinux > enoxaparin/dalteparin > UFH**

Pharmacologic Prophylaxis

- For patients following major orthopedic surgery
  - **UFH**: 5000 Units every 12 or 8 hours
  - **LMWH**:
    - **Enoxaparin** 30mg SC BID or 40 mg SC daily
    - **Dalteparin** 5000 Units SC daily
  - **Fondaparinux**: 2.5 mg SC daily
  - Adjusted dose **warfarin** (maintain an INR between 2 and 3)
  - **Rivaroxaban**: 10 mg PO daily
  - **Apixaban**: 2.5 mg PO daily
    - Rivaroxaban/apixaban > LMWH > UFH/warfarin

Pharmacologic Prophylaxis

Duration of Prophylaxis

- Should be given throughout the period of risk.
- For patients who have undergone total knee replacement, total hip replacement, or hip fracture repair:
  - Prophylaxis is recommended for a minimum of
    10 to 14 days

Treatment

- Goal
- Immediate goal
  - Prevention of propagation or local extension of the clot,
  - Prevention of embolization,
  - Prevention of hemodynamic collapse,
  - Prevention of death.
- Long-term goal
  - Prevention of **complications** such as PTS, pulmonary hypertension, and recurrent VTE

Treatment

General Treatment Principles

Acute (5 – 10 days)	• Fast-acting parenteral or • DOAC
Long-term (3 months)	• Warfarin, or • DOAC
Extended (beyond 3 months)	• Warfarin, or • DOAC

Treatment

General Treatment Principles

- Patients with **cancer** and women who are **pregnant**, the **LMWHs** are the preferred agents during long-term and extended treatment phases due to better safety or efficacy
- The treatment of VTE should initially include a **rapid-acting injectable anticoagulant** (UFH, LMWH, fondaparinux) or **a rapidly acting DOAC** (eg, apixaban, rivaroxaban).
- If warfarin is used for oral anticoagulation, it should be initiated on the **same day** as the parenteral anticoagulant, and the parenteral agent should be overlapped for a minimum of 5 days and until the INR is greater than or equal to 2 for at least 24 hours.
- Anticoagulation therapy should be continued for a **minimum of 3 months**. However, the duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding

Treatment

- **Acute Phase Treatment of VTE**

1. Parenteral Anticoagulants

a) UFH

- ✓ IV: 80 units/kg (or 5000 units) I.V. push followed by continuous infusion of 18 units/kg/hour (or alternatively 1000 units/hour)
- ✓ SC: 17,500 units (250 units/kg) given every 12 hours (after an initial 5000 unit IV bolus dose)

b) LMWHs

c) **Enoxaparin**: 1.5 mg/kg SC once daily *or* 1 mg/kg SC twice daily;
if CrCl < 30 mL/min: 1 mg/kg SC once daily

d) **Dalteparin**: 200 units/kg SC once daily *or* 100 units/kg SC twice daily

Factor Xa Inhibitor

- ✓ **Fondaparinux**:
  1. Body weight < 50 kg: 5 mg SC once daily
  2. Body weight 50–100 kg: 7.5 mg SC once daily
  3. Body weight > 100 kg: 10 mg SC once daily

Treatment

- **Acute Phase Treatment of VTE**

2. Direct Oral Anticoagulants

2. **Apixaban**: 10 mg PO twice daily for the initial 7 days, then 5 mg po twice daily
3. **Rivaroxaban**: 15 mg PO **twice** daily for the initial 21 days, then 20 mg PO **daily**

Treatment

- **Prevention of Recurrence VTE**

1.Direct Oral Anticoagulants

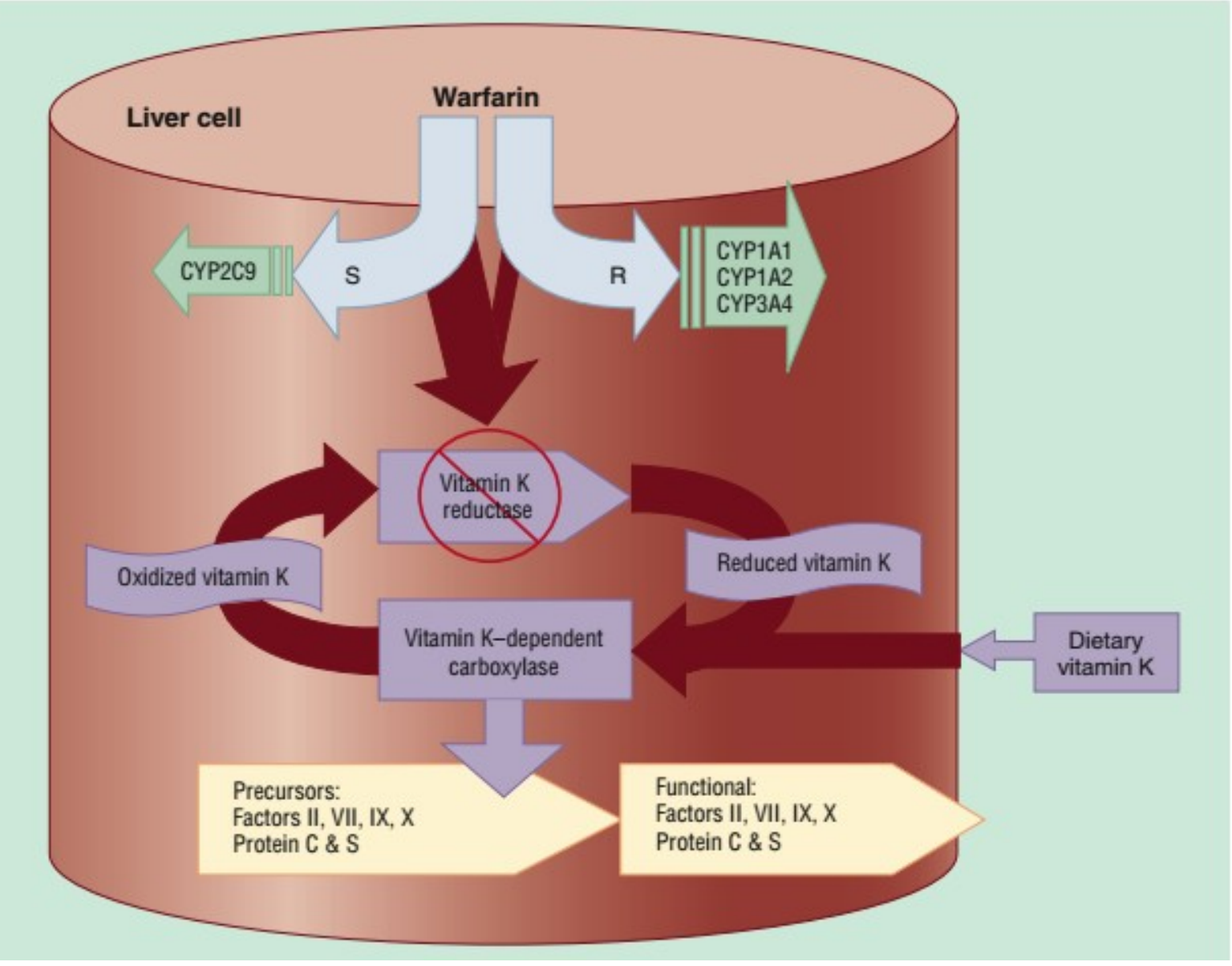
a) Rivaroxaban: 20 mg once daily

b) Apixaban: 2.5 mg BID

2.Warfarin: start with 5 mg daily

⇒ Adjust dose based on INR

Warfarin


Liver cell
Warfarin
CYP2C9
S
R
CYP1A1
CYP1A2
CYP3A4
Vitamin K reductase
Oxidized vitamin K
Reduced vitamin K
Vitamin K–dependent carboxylase
Dietary vitamin K
Precursors:
Factors II, VII, IX, X
Protein C & S
Functional:
Factors II, VII, IX, X
Protein C & S

Warfarin

- Warfarin has been the primary oral anticoagulant used
- Warfarin exerts its anticoagulant effect by inhibiting production of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as the anticoagulant proteins C and S.
- Warfarin has no effect on circulating coagulation factors that have been previously formed, and its therapeutic antithrombotic activity is delayed for 5 to 7 days, and potentially longer in slower metabolizers.
- This delay is related to half-lives of the clotting factors: 60 to 100 hours for factor II (prothrombin), 6 to 8 hours for factor VII, 20 to 30 hours for factor IX, and 24 to 40 hours for factor X.
- Proteins C and S, the **natural anticoagulants**, are inhibited more rapidly due to their shorter half-lives, 8 to 10 hours and 40 to 60 hours, respectively.
- Reductions in the concentration of natural anticoagulants before the clotting factors are depleted can lead to a paradoxical hypercoagulable state during the first few days of warfarin therapy.

Warfarin

- Warfarin does not follow linear kinetics.
  - Small-dose adjustments can lead to large changes in anticoagulant response.
  - The dose of warfarin is determined by each patient's individual response to therapy and the desired intensity of anticoagulation.
- Goal or target INR for each patient is based on the indication for warfarin therapy.
- For treatment and prevention of VTE, the INR target is 2.5 with an acceptable range of 2 to 3
- INR should be monitored:
  - **Every 2 to 3 days** during the first week of therapy.
  - **Weekly** for the first 1 to 2 weeks
  - **Every 4 to 6** weeks thereafter

Warfarin

- In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or fondaparinux) should be overlapped with warfarin for a minimum of 5 days and until the INR is greater
than 2 and stable.
- This is important because the full antithrombotic effect will not be reached until 5 to 7 days or even longer after initiating warfarin therapy.
  - The typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week,
- Adjustments in the maintenance warfarin dose should be determined based on the total weekly dose and by reducing or increasing the weekly dose by increments of 5% to 25%.

Monitoring

- **Risk factors for major bleeding while taking anticoagulation therapy**
  - Anticoagulation intensity (INR > 5, aPTT > 120 seconds)
  - Initiation of therapy (first few days and weeks)
  - Unstable anticoagulation response
  - Age older than 65 years
  - Concurrent antiplatelet drug use
  - Concurrent nonsteroidal anti-inflammatory drug or aspirin use
  - History of gastrointestinal bleeding
  - Recent surgery or trauma
  - High risk for fall/trauma
  - Heavy alcohol use
  - Renal failure
  - Cerebrovascular disease
  - Malignancy

Evaluation of Therapeutic Outcomes

- Initial duration of warfarin therapy to effectively treat an acute first episode of VTE for all patients is 3 months
- For 3 months:
  - Reversible risk factor (e.g., surgery, plaster cast immobilization of a leg, or hospitalization)
- Continuing anticoagulation therapy beyond the initial 3 months;
  - The presence of active cancer
  - Idiopathic

SHOCK

Definition

- **Shock** is a syndrome of impaired tissue perfusion usually, accompanied by hypotension.
- If left untreated, impairment of tissue perfusion eventually leads to cellular dysfunction, organ damage and death
- ***Systemic inflammatory response syndrome*** (SIRS) is the umbrella term to describe any acute, overwhelming inflammatory response, independent of cause.
- It is usually a late manifestation of hypovolemic shock, is uncommon in cardiogenic shock, and is the hallmark of
septic shock

Classification

- **Hypovolemic Shock**: secondary to a reduction in intravascular volume
- **Cardiogenic Shock**: from an abnormality of cardiac function where there is an inability to maintain CO unrelated to hypovolemia
- **Distributive Shock**: characterized by overt loss of vascular tone causing acute tissue hypoperfusion.
  - Numerous events (anaphylaxis, neurogenic causes, sepsis) can initiate distributive shock.
  - ***Septic shock*** is characterized by a profound vasodilatory response and resultant decrease in blood pressure.

Causes

- The most common causes of shock are situations that result in a reduction of intravascular volume, myocardial pump failure, or increased vascular resistance.
- Common causes of hypovolemia in surgical patients are postoperative bleeding, third spacing, and temperature-related vasodilation.
- The most common cause of cardiogenic shock is left ventricular dysfunction and necrosis as a result of acute myocardial infarction

Who are at Risk?

- Immunocompromised patients
- Patients with infection
- Neonates
- Elderly
- AIDS patients
- Alcoholics
- Childbearing women
- Those undergoing surgery
- Those who have experienced trauma

Hemodynamic Findings

	Hypovolemic	Cardiogenic	Distributive (Septic)
HR	↑	↑	↑
BP	↓	↓/↑	↓
CO	↓	↓	↑
Preload	↓	↑	↓/↑
Afterload	↑	↑	↓

Clinical Findings in Shock

- SBP < 90 mmHg, or a > 40 mmHg decrease from baseline
- Tachycardia (HR > 90 beats/minute)
- Tachypnea (RR > 20 breaths/minute)
- Cutaneous vasoconstriction: cold, clammy, mottled skin
- Mental confusion: agitation, stupor, coma
- Oliguria (urine output < 20 mL/hour)
- Elevated blood lactate levels leading to metabolic acidosis
- Decreased venous oxygen saturation

Goals of Therapy

- **Hypovolemic Shock:** correction of inadequate tissue perfusion and oxygenation, and limiting secondary insults.
- **Cardiogenic Shock**: HR should be <125 beats/minute and urine output should be at least 0.5 mL/kg/hour.
  - The goal is to optimize preload increase contractility and reduce afterload if the blood pressure permits.
- **Septic Shock**.
  - Eradicating the precipitating infection,
  - Optimize delivery of oxygen to tissues
  - Control abnormal use of oxygen and anaerobic metabolism by reducing the tissue oxygen demand.

Treatment

- Treatment requires addressing the **underlying cause** of shock and early, aggressive measures to maintain adequate perfusion to vital organs.
- The type of treatment for shock required depends on the etiology.

Treatment

- **Hypovolemic Shock**.
  - Infusion of **IV fluids** is critical.
  - Inotropic agents and vasopressors are generally not indicated in initial treatment of hypovolemic shock (if fluid therapy is adequate)
- **Cardiogenic Shock**.
  - Hypovolemia should always be evaluated first.
  - Inotropic support is directed at establishing or maintaining a reasonable arterial pressure and ensuring adequate tissue perfusion by improving CO.
  - Optimizing preload to improve CO is crucial.

Treatment

Septic Shock.

- Management is directed at eradication of the source of infection, hemodynamic support and control of tissue hypoxia, and inhibition/attenuation of the initiators and mediators of sepsis.
- Initial hemodynamic therapy for septic shock is administration of IV fluid
- **Norepinephrine** is the preferred initial vasopressor in septic shock not responding to fluid administration
  - It has strong α1-agonist activity and less potent β1-agonist effects
- **Dobutamine** is used in low CO states despite adequate fluid resuscitation pressures

Inotropic and Vasopressor Agents

	α1	α2	β1	β2	D
Dobutamine					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	+++	+++	0
Dopamine					
1–3 mcg/kg/min	0	0	+		++ ++
3–10 mcg/kg/min	0	0	++++	++	++ ++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0

Evaluation of Therapeutic Outcomes

- Vital signs, urine output, mental status, and physical examination.
- Electrolytes and renal function tests (BUN and serum creatinine); CBC to assess possible infection

RESPIRATORY DISORDERS

Chapter Three



ASTHMA





Definition

- A syndrome characterized by airflow obstruction
- Relieved spontaneously or with **BD** ± **Corticosteroids**
- Chronic inflammatory disease of airways
- ↑ responsiveness of tracheobronchial tree
- **Physiologic manifestation**: AW narrowing which is usually reversible
- **Clinical manifestations**: **a triad of paroxysms of cough, dyspnea and wheezing**

Disease Pattern

- **Episodic**: acute exacerbations interspersed with symptom-free periods
- **Chronic**: daily AW obstruction which may be mild, moderate or severe ± superimposed acute exacerbations
- **Life-threatening*:*** slow-onset or fast-onset (fatal within 2 hours)

Prevalence

- All ages, predominantly early life with *peak age of 3 years*
- 50% of Dx <10 year, 85% of Dx < 40 year
- 2:1 male:female majorly in childhood; equalize in adults
- Asthma is both common and frequently **complicated** by the effects of smoking on the lungs

Mortality

- Deaths from asthma are *uncommon*
- Risks for death:
  - Poorly controlled disease with frequent use of bronchodilator inhalers
  - Lack of corticosteroid therapy
  - Previous admissions to the hospital with near-fatal asthma

Etiology

- **Allergic/atopic/early onset asthma***:* rhinitis, urticaria, eczema, (+) skin tests, ↑IgE, (+) response to provocation tests with aeroallergens.
- **Idiosyncratic/non-atopic/intrinsic asthma/late onset asthma*:*** no allergic diseases, (-)skin tests, normal IgE, symptoms when upper resp infection, sx lasting days or months and usually have more severe, persistent asthma.
- **Mixed group**: usually onset later in life

Risk Factors

Endogenous Factors

- Genetic predisposition
- Atopy
- Air way hyperresponsiveness
- Gender

Environmental Factors

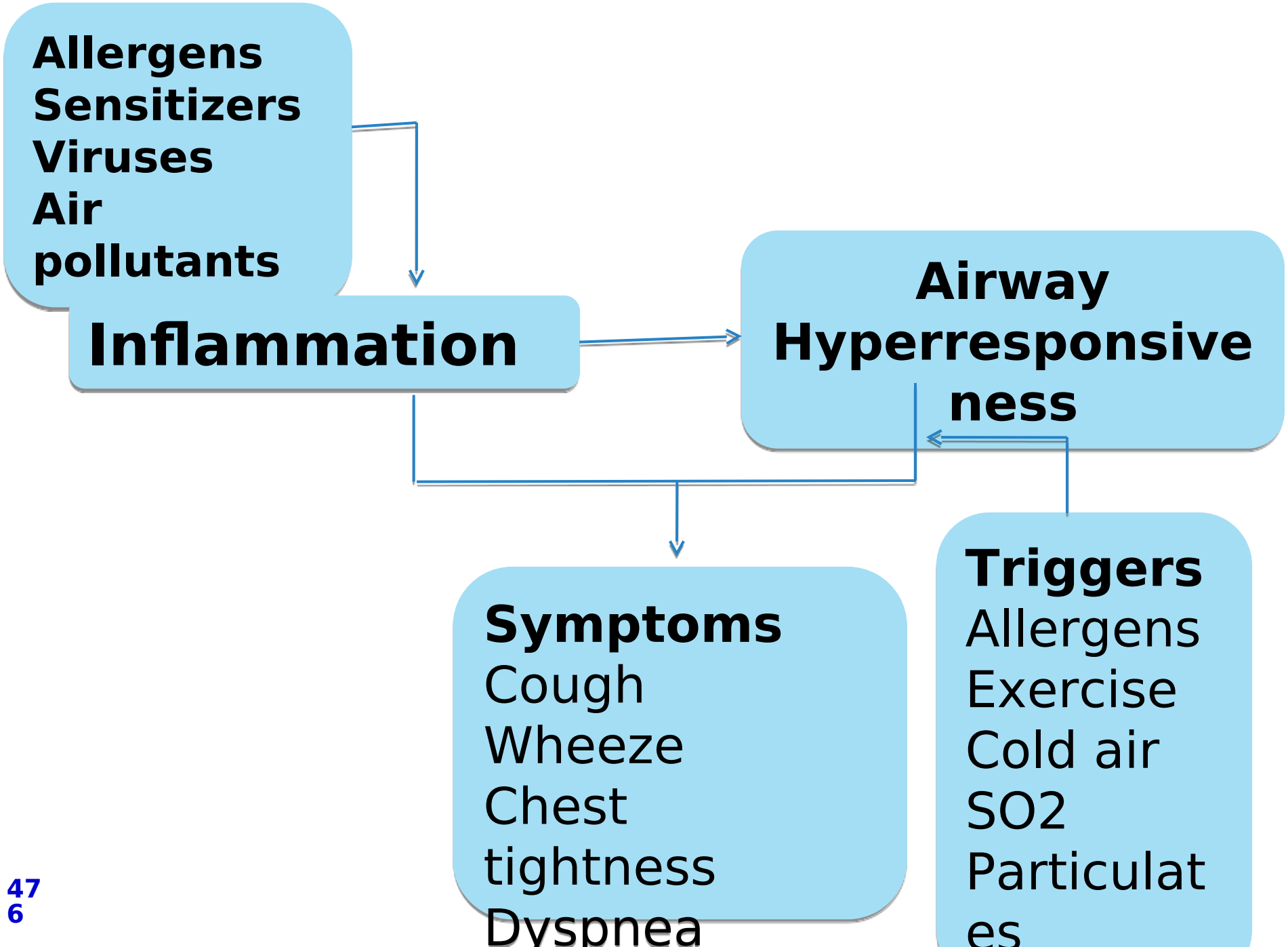
- Indoor allergens
- Outdoor allergens
- Occupational sensitizers
- Passive smoking
- Respiratory infections
- Obesity

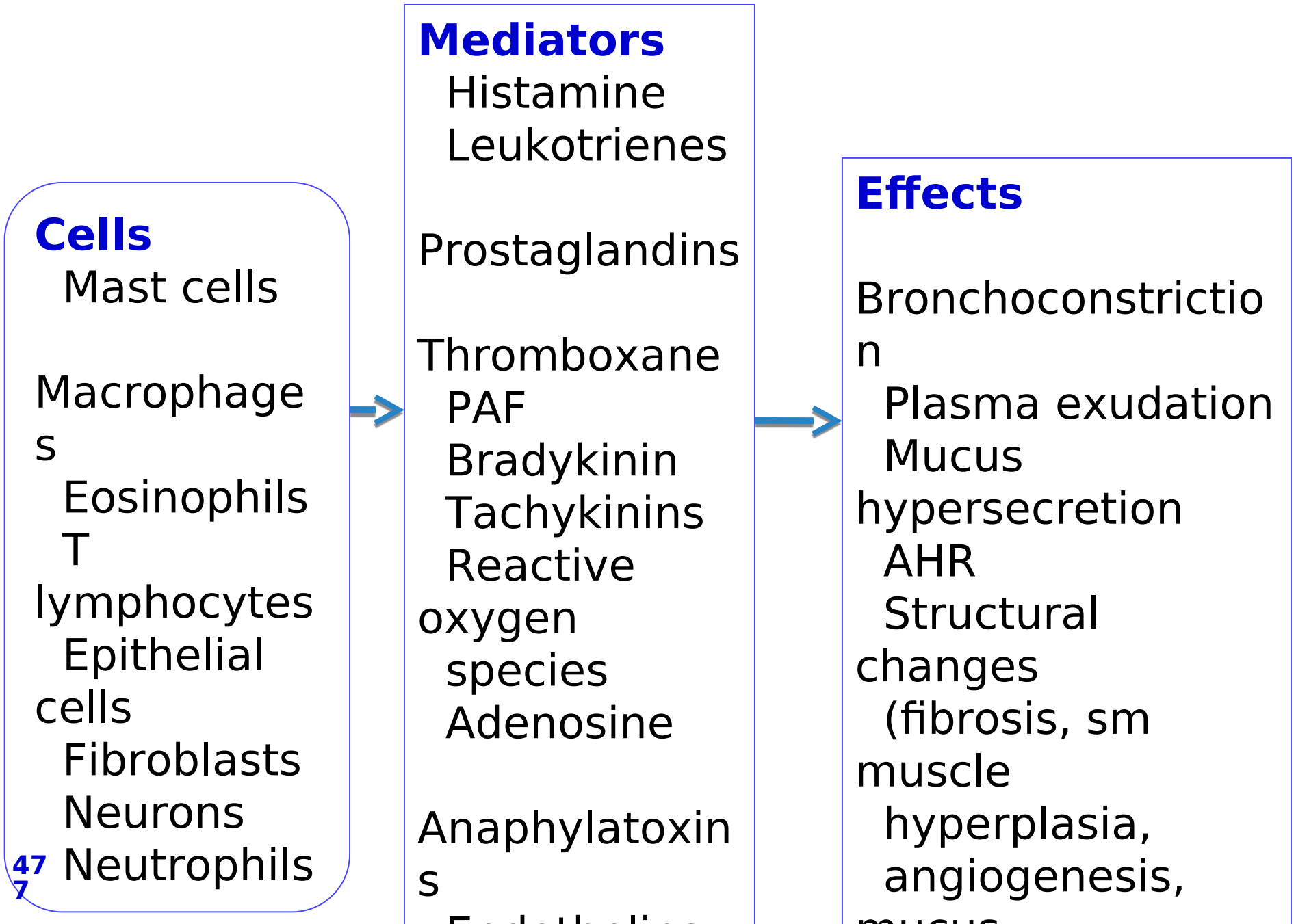
Asthma Triggers

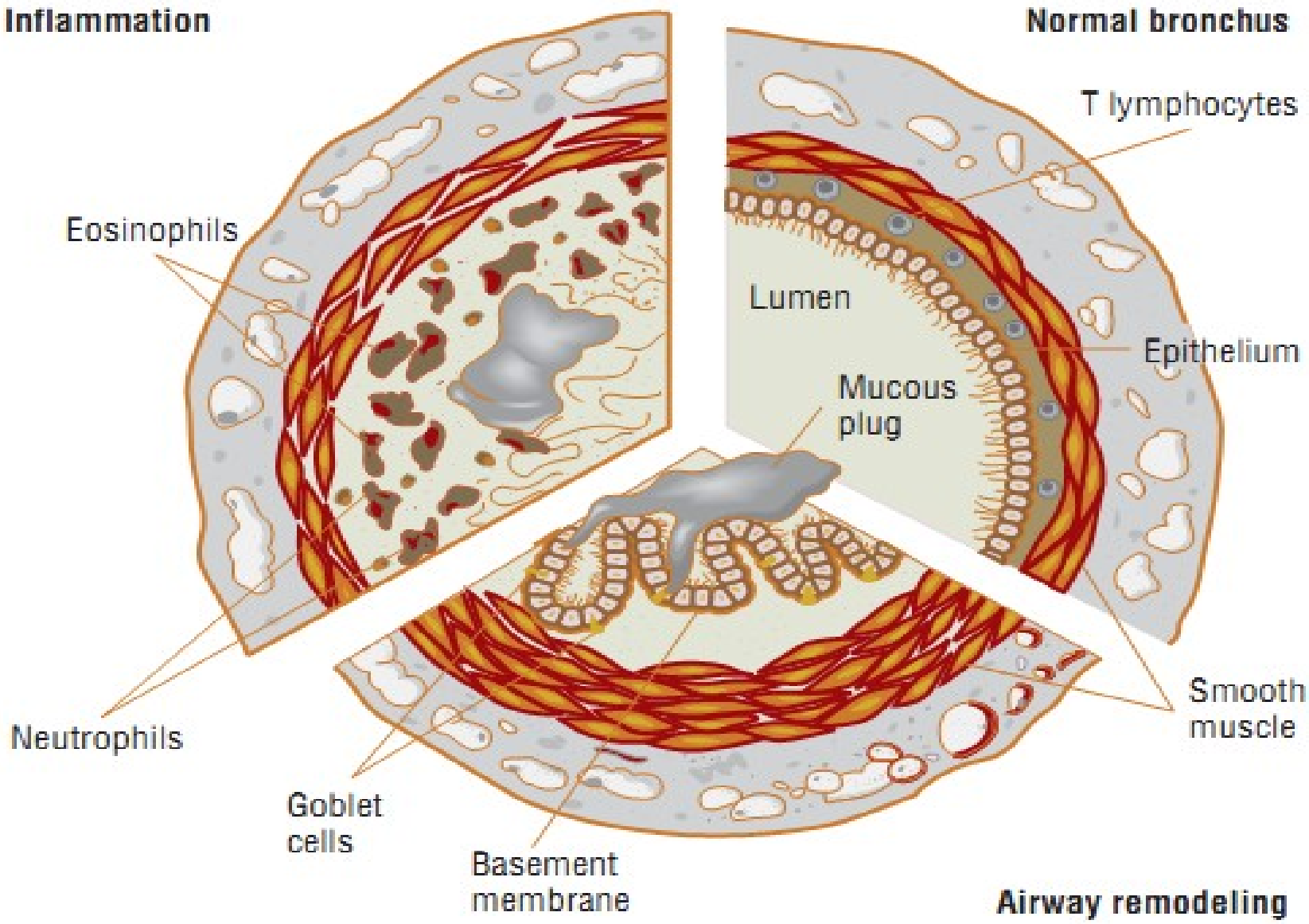
Respiratory infection	RSV, rhinovirus, influenza, parainfluenza, mycoplasma pneumonia
Allergens	Airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores
Environment	Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke, wood smoke
Emotions	Anxiety, stress, laughter
Exercise	Particularly in cold, dry environments
Drugs / preservatives	Aspirin, NSAIDs, sulfites, benzalkonium chloride, nonselective β-blockers
Occupational stimuli	Bakers (flour dust); farmers (hay mold); spice and enzyme workers; printers (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)

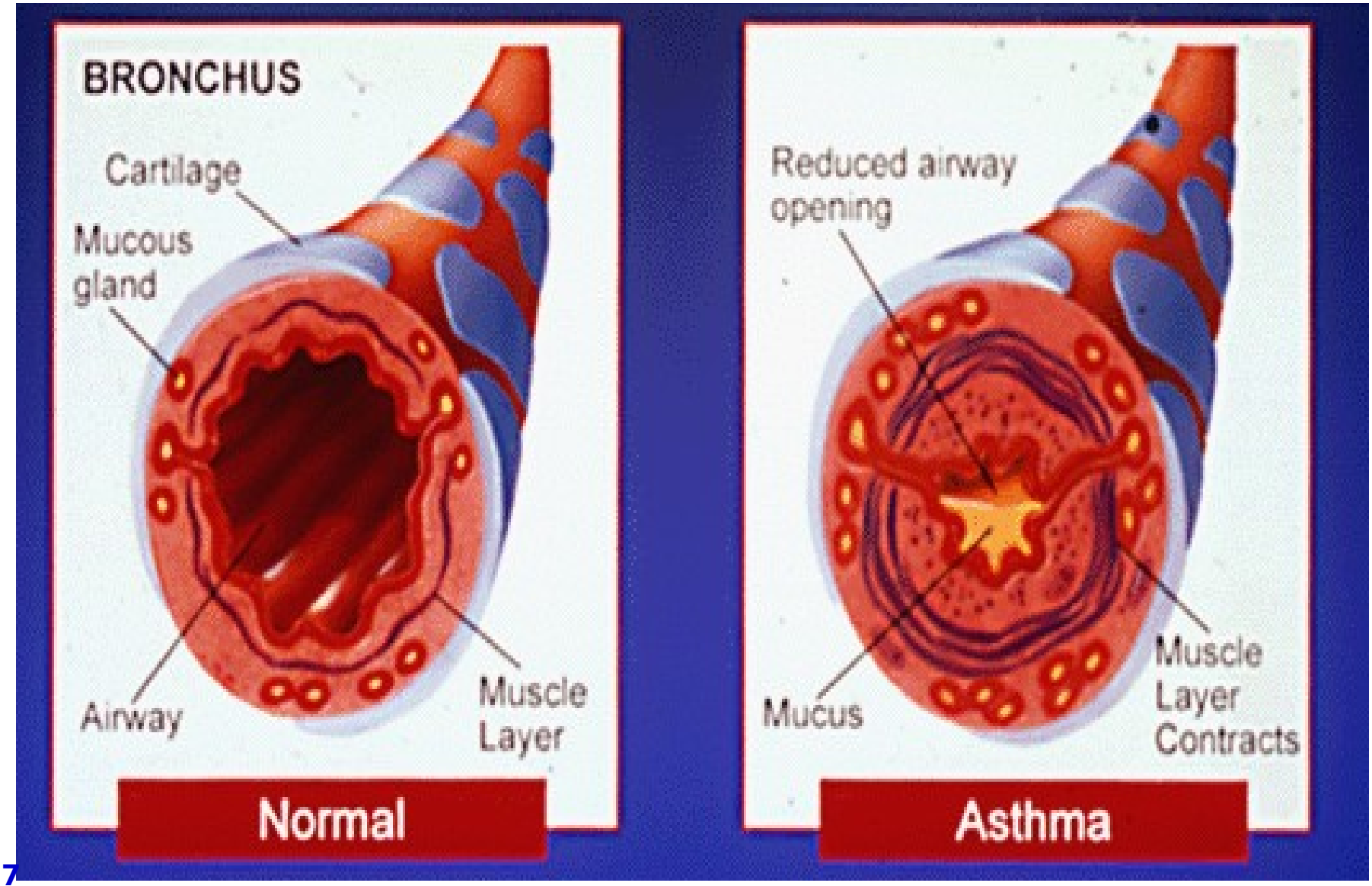
Pathophysiology

- Airway inflammation
- Bronchial hyperresponsiveness (BHR)
- Airflow obstruction
  - Bronchospasm, edema, mucus hypersecretion
- Airway remodeling
- Mediated by eosinophils, T cells, mast cells, macrophages, epithelial cells, fibroblasts, bronchial smooth muscle cells


Allergens
Sensitizers
Viruses
Air pollutants
Inflammation
Airway Hyperresponsiveness
Symptoms
Cough
Wheeze
Chest tightness
Dyspnea
Triggers
Allergens
Exercise
Cold air
SO2
Particulates


Cells
Mast cells
Macrophages
Eosinophils
T lymphocytes
Epithelial cells
Fibroblasts
Neurons
Neutrophils
Mediators
Histamine
Leukotrienes
Prostaglandins
Thromboxane
PAF
Bradykinin
Tachykinins
Reactive oxygen species
Adenosine
Anaphylatoxins
Effects
Bronchoconstriction
Plasma exudation
Mucus hypersecretion
AHR
Structural changes (fibrosis, sm muscle hyperplasia, angiogenesis,


Inflammation
Normal bronchus
T lymphocytes
Eosinophils
Lumen
Epithelium
Mucous plug
Smooth muscle
Neutrophils
Goblet cells
Basement membrane
Airway remodeling


BRONCHUS
Cartilage
Mucous gland
Airway
Muscle Layer
Normal
Reduced airway opening
Mucus
Muscle Layer Contracts
Asthma

Pathophysiology

- **Reduction in AW diameter**→↑AW resistance → ↓FeV and flow rates →hyperinflation →↑work of breathing →altered respiratory muscle function and elastic recoil →abnormal ventilation
- **Vascular congestion** and edema of bronchial walls → abnormal perfusion

Diagnosis : Clinical

- **Episodic asthma**:
  - Paroxysms of wheeze, dyspnoea and cough, asymptomatic between attacks.
- **Acute severe asthma**:
  - Upright position, use accessory resp muscles, can’t complete sentences in one breath,
  - Tachypnea > 25/min, tachycardia > 110/min, PEF < 50% of pred or best,
  - Chest hyperresonant, prolonged expiration, breath sounds decreased, inspiratory and expiratory rhonchi.

Diagnosis: Clinical

- **Life-threatening Features**:
  - PEF < 33% of pred or best, silent chest, cyanosis, bradycardia, hypotension, feeble respiratory effort, exhaustion, confusion, coma, PaO_2 < 60, PCO_2 normal or increased, acidosis
- **Chronic Asthma**:
  - Dyspnea on exertion, wheeze, chest tightness and cough on **daily basis**, usually at night and early morning;
  - Intercurrent acute severe asthma (exacerbations) and productive cough (mucoid sputum),
  - Recurrent respiratory infection,

Diagnosis: Physiologic

- Demonstration of variable airflow obstruction with reversibility by means of FEV1 and PEF measurement (spirometer and peak flow meter).

1. **FEV1** < 80% of pred – **PEF** < 80% of pred.
2. **Reversibility**: A good bronchodilator response is a 12% or 200ml improvement in FEV1 15 min after inhalation of 200µg salbutamol (2 puffs)

Diagnosis: Physiologic

3. Provocation studies: **AHR**

a) **Exercise:** A 15% drop in FEV1 post exercise indicates exercise induced asthma.

b) **Metacholine challenge**: A 20% reduction in FEV1 at metacholine concentrations < 8mg/ml indicates bronchial hyperreactivity.

- This is expressed as a PC20 value of e.g., 0.5mg/ml (= a 20% reduction in FEV1 at 0.5mg/ml metacholine).

Diagnosis : Radiology

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

Management Asthma

- **Desired Outcomes**
- Chronic Asthma
  - (1) Prevent chronic and troublesome symptoms;
  - (2) Maintain normal or near normal pulmonary function;
  - (3) Maintain normal activity levels, including exercise and other physical activities;
  - (4) Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations;

Acute Severe Asthma

(1) Correct significant hypoxemia;

(2) Rapidly reverse airflow obstruction; and

(3) Reduce the likelihood of recurrent severe airflow obstruction

Acute Severe Asthma

1. **Immediate Rx**: **O_2** 40-60% via mask or cannula + **β_2 agonist** (salbutamol 5mg) via nebulizer + **Prednisone** tab 30-60mg **and/or hydrocortisone** 200mg IV. With life threatening features add 0.5mg **ipratropium** to nebulized β_2 agonist + **Aminophyllin** 250mg IV over 20 min **or salbutamol** 250µg over 10 min.
2. **Subsequent Rx**: **Nebulized *β_2*** agonist 6 hourly + **Prednisone** 30-60mg daily **or hydrocortisone** 200mg 6 hourly IV + 40-60% **O_2**.

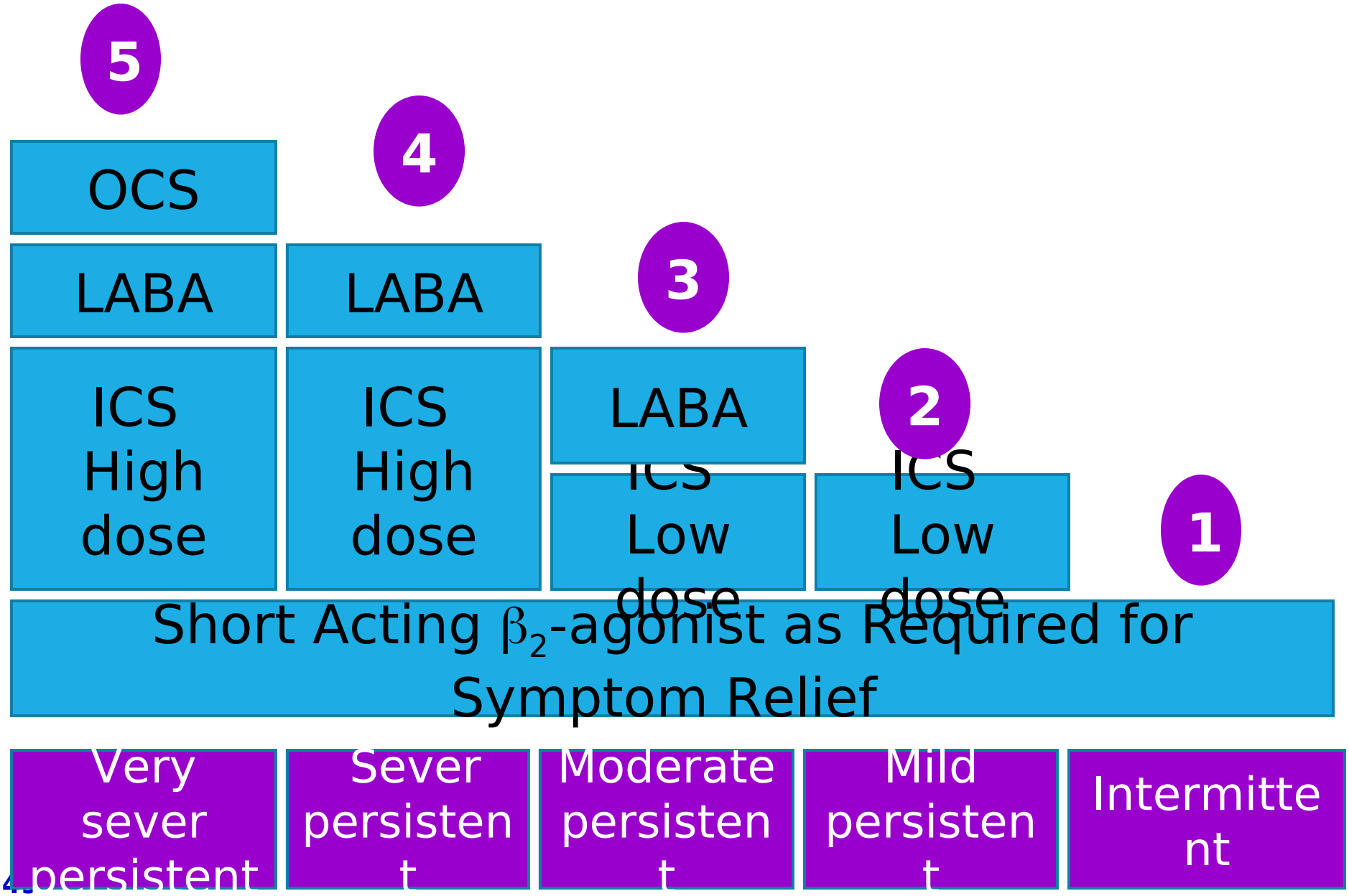
Acute Severe Asthma

- **No improvement after 15-30 min**: Nebulized β_2 agonist every 15-30 min + **Ipratropium**.
- **Still no improvement**: **Aminophyllin infusion** 750mg/24H (small pt), 1 500mg/24H (large pt), **or** alternatively **salbutamol infusion**.
- **Monitor Rx**: Aminophyllin blood levels + PEF after 15-30 min + oxymetry (maintain $SaO_2 > 90$) + repeat blood gases after 2 hrs if initial PaO2 < 60, PaCO2 normal or raised and patient deteriorates.
- **Deterioration**: ICU, intubate, ventilate + muscle relaxant.

Chronic Asthma

- **Nonpharmacologic Treatment**
  - Environmental control
  - Manage comorbid conditions
  - Self-management skills
    - ✓ Recognize early signs of deterioration
  - Education
    - ✓ Asthma, role of medications, inhalation technique, environmental control, reinforce every visit

Components		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤twice/mnth	3-4 times/month	> Once per week but not nightly	Often 7 times/week
	SABA use for symptom control	≤2 days/week	>2 days/week but not > once per day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function (Normal FEV_1/FVC: age 8-19 y 85%; 20-39 y 80%; 40-59 y 75%; 60-80 y 70%)	FEV_1 >80% FEV_1/FVC normal	FEV_1 >80% FEV_1/FVC normal	FEV_1 60-80% FEV_1/FVC reduced 5%	FEV_1 <60% FEV_1/FVC reduced > 5%
Risk		**Intermittent**	**Persistent**		
	Exacerbations	0-2/year	>2 in 1 year →		
Recommended		Step 1	Step 2	Step 3 and	Step 4 or 5


5
4
3
2
1
OCS
LABA
LABA
LABA
ICS High dose
ICS High dose
ICS Low dose
ICS Low dose
Short Acting β_2-agonist as Required for Symptom Relief
Very sever persistent
Sever persistent
Moderate persistent
Mild persistent
Intermittent

Inhaled Corticosteroids (ICS)

- Use: cornerstone of chronic asthma therapy
  - Improve lung function
  - Reduce severe exacerbations
  - Only therapy shown to reduce risk of asthma death
- Low systemic activity
- Response delayed for several weeks
- Products: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, ciclesonide

ICS

Corticosteroid	Low dose	Medium dose	High Dose
Beclomethasone	80 – 240 μg	240 – 480 μg	>480 μg
Budesonide	180 – 600 μg	600 – 1200 μg	>1200 μg
Flunisolide	320 μg	320 – 640 μg	> 640 μg
Fluticasone	88 – 264 μg	264 – 440 μg	> 440 μg
Memetasone	220 μg	440 μg	>440 μg

ICS

- Adverse effects: dose dependent
  - Systemic effects can occur at high doses
  - Oropharyngeal candidiasis
  - Dysphonia

LABAs

- Use: preferred adjunct/ICS combination
  - Adults & most children
  - Better control than increasing ICS dose alone
- Not for quick relief
- Provide long lasting bronchodilation (≥ 12 hours)
- Products
  - Formoterol
  - Salmeterol

LABAs

- Systemic side effects: dose dependent
- *Not to be used as monotherapy*
  - Increased risk of severe, life threatening exacerbation & asthma related death
  - Preliminary data suggest concomitant ICS may prevent/decrease risk

Methylxanthines

- Mechanism: bronchodilation
  - Nonselective *phosphodiesterase* inhibitor
    - Isoenzyme III: airway smooth muscle
    - Isoenzyme IV: inflammatory cell regulation
  - Competitively inhibit adenosine
  - Stimulate catecholamine release
- Use declined due to risk for toxicity
  - Alternative/adjunct therapy

Methylxanthines

- Routine serum concentration monitoring
  - Significant bronchodilation by 5 mcg/mL
  - Most will not have toxic symptoms when <15 mcg/ml
- Much potential for interactions
  - CYP-450 1A2, 3A3 metabolism

Factors Affecting Theophylline Clearance

Decreased Clearance	% Decrease
Cimetidine	-25 to -60
Macrolides	-25 to -50
Allopurinol	-20
Propranolol	-30
Quinolones	-20 to -50
Interferon	-50
Thiabendazole	-65
Ticlopidine	-25
Zileuton	-35
Systemic viral illness	-10 to -50

Increased Clearance	% Increase
Rifampin	+53
Carbamazepine	+50
Phenobarbital	+34
Phenytoin	+70
Charcoal-broiled meal	+30
High-protein diet	+25
Smoking	+40
Sulfinpyrazone	+22
Moricizine	+50
Aminoglutethimide	+50

Methylxanthines

- Signs of toxicity: nausea/vomiting, tachycardia, jitteriness, difficulty sleeping, tachyarrhythmias, seizures

Mast Cell Stabilizer

- Mechanism
  - Inhibit neurally mediated bronchoconstriction
- Improvement in 1 to 2 weeks
- Alternative to initial ICS therapy but not as effective
- **Cromolyn**
  - MDI or nebulizer

Leukotriene Modifiers

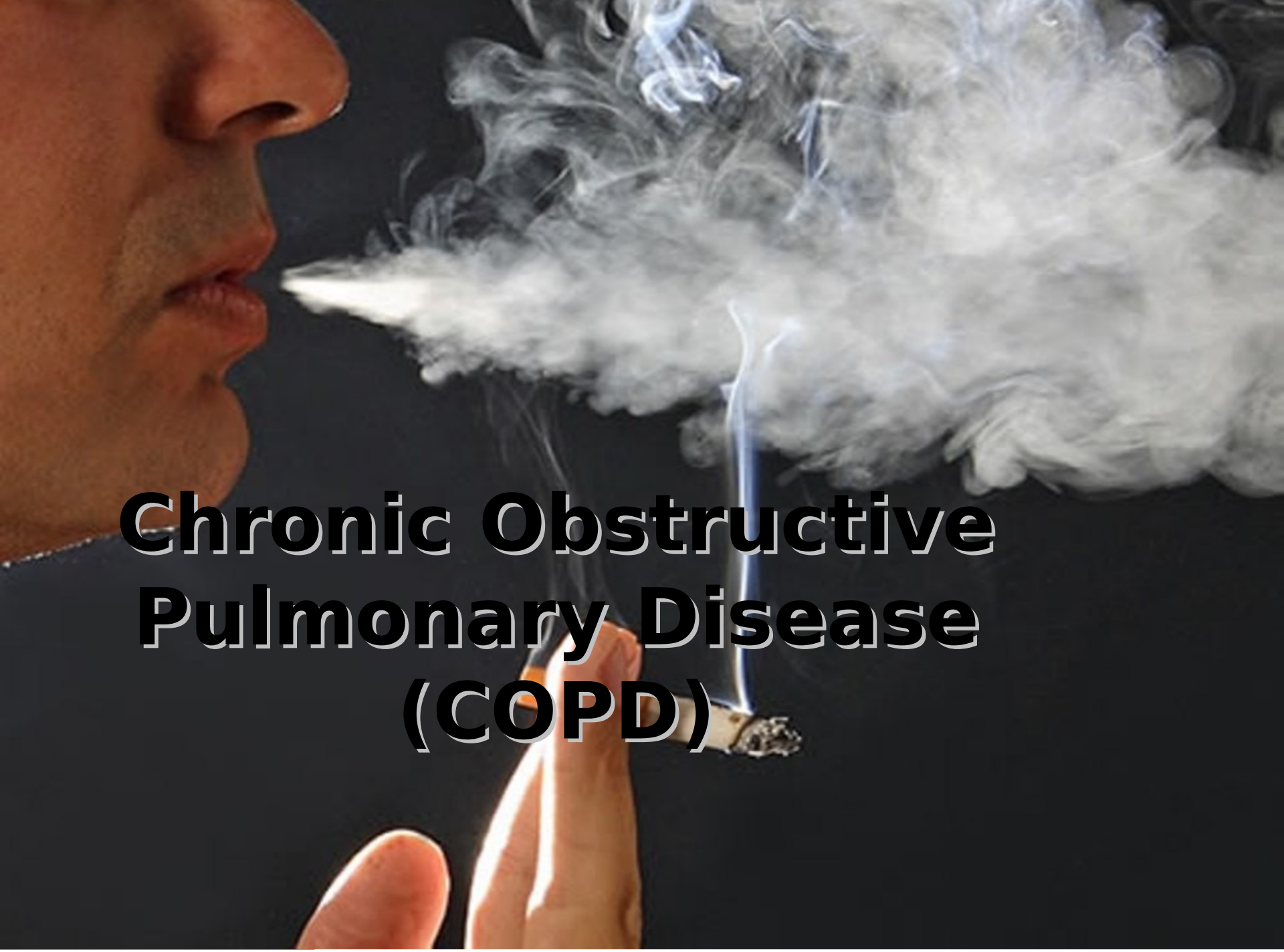
- Leukotriene receptor antagonists (LTRA)
  - Zafirlukast
  - Montelukast
- 5-lipoxygenase inhibitor
  - Zileuton
- Use: alternative/adjunct therapy
  - Less effective than ICS
  - Oral dosage form
- Adverse effects
  - Hepatic dysfunction

Anti-IgE: Omalizumab

- Mechanism: recombinant anti-IgE antibody
  - Prevents binding of IgE to mast cells & basophils
    - Decreases release of mediators following allergen exposure
- Use
  - Allergic asthma not well controlled by corticosteroids
  - ***≥ 12 years old***
  - Severe persistent asthma

Anti-IgE: Omalizumab

- Dosage/administration
  - Subcutaneous every 2 to 4 weeks
  - Dosage based on serum IgE level & weight
- Adverse effect
  - Anaphylaxis
    - 70% occur within 2 hours
    - may occur up to 24 hours after injection



Chronic Obstructive Pulmonary Disease (COPD)

COPD

- Definition: a disease state characterized by airflow limitation that is **not fully reversible**
- COPD is the **fourth leading cause of death** in the US
- COPD includes:
  - **Emphysema*:*** an anatomically defined as **destruction and enlargement of the lung alveoli,** but without obvious fibrosis
  - **Chronic Bronchitis**: chronic or recurrent excess **mucus secretion with cough** that occurs on most days for at least 3 months of the year for at least 2 consecutive years when other causes of cough have been excluded.

RISK FACTORS

Exposures	Host Factors
Environmental tobacco smoke	Genetic predisposition (α_1-antitrypsin)
Occupational dusts and chemicals	Airway hyperresponsiveness
Air pollution	Impaired lung growth

Risk Factors

- Cigarette smoking
  - ⇒ Accounts for 85% to 90% of case of COPD
  - ⇒ Pa[illegible]nd, smoking ex[illegible]



Risk Factors

- Imbalance between aggressive and protective defense systems in the lungs (**proteases** and **antiproteases**).
- The protective *antiprotease* **α_1-antitrypsin** (AAT) inhibits several *protease* enzymes, including **neutrophil elastase**.
- Protect cells, especially those in the lung, from destruction by elastase.
- AAT is a plasma protein that is synthesized in hepatocytes

Risk Factors

- In the presence of unopposed protease activity, elastase attacks **elastin**, which is a major component of alveolar walls.
- A **hereditary deficiency** of α_1-antitrypsin (AAT) results in an increased risk for premature development of emphysema.

Pathophysiology

- COPD is characterized by chronic inflammatory changes that lead to **destructive changes** and the development of chronic airflow limitation.
- Inflammatory process is wide spread which involves **airways**, pulmonary **vasculature**, and **lung parenchyma**.

Pathophysiology

- On exposure to noxious particles and gases (tobacco smoke) → inflammatory cells (neutrophils, macrophages and CD_8^+ lymphocytes) release a variety of chemical mediators (tumor necrosis factor-α, interleukin (IL-8), and leukotriene (LTB4)→ capillary permeability, mucus production → edema, air flow obstruction

Pathophysiology

Oxidative Stress

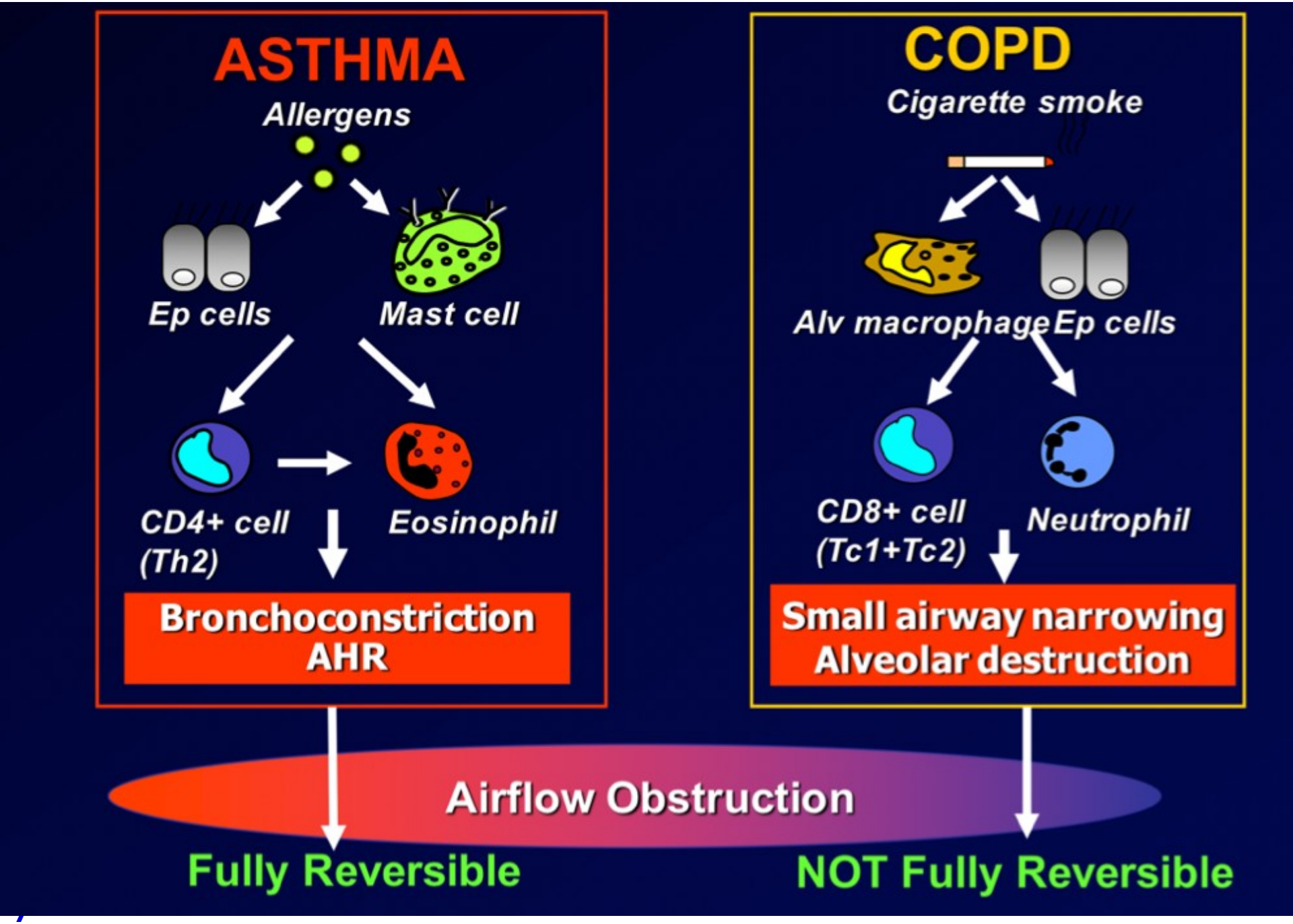
- Increased **oxidants** generated by cigarette smoke **react** with and **damage** various proteins and lipids → cell and tissue damage.
- Oxidants also promote **inflammation** directly and exacerbate the protease-antiprotease imbalance by inhibiting antiprotease activity

Pathophysiology

- Imbalance between aggressive and protective defense systems in the lungs (proteases and antiproteases).
- In the inherited form of emphysema, there is an **absolute deficiency of AAT**.
- In cigarette smoking-associated emphysema,
  - Increased protease activity or
  - Reduced activity of antiproteases.
    - Oxidative stress reduces antiprotease (or protective) activity

Features of Inflammation in COPD Compared with

	COPD	Asthma
Cells	Neutrophils Macrophages CD8+ T lymphocytes	Eosinophils Macrophages CD4+ TH2 lymphocytes Activation of mast cells
Mediators	LTB4 IL-8 TNF-α	LTD4 IL-4, IL-5 (Plus many others)
Consequences	Squamous metaplasia of epithelium Parenchymal destruction Mucus metaplasia Glandular	Fragile epithelium Thickening of basement membrane Mucus metaplasia Glandular enlargement


ASTHMA
Allergens
Ep cells
Mast cell
CD4+ cell
(Th2)
Eosinophil
Bronchoconstriction
AHR
COPD
Cigarette smoke
Alv macrophage
Ep cells
CD8+ cell
(Tc1+Tc2)
Neutrophil
Small airway narrowing
Alveolar destruction
Airflow Obstruction
Fully Reversible
NOT Fully Reversible

Pathophysiology

- **Parenchymal changes**: affect the gas-exchanging units of the lungs (***alveoli and pulmonary capillaries)***
- Smoking-related **centrilobular emphysema**
  - Primarily affects respiratory bronchioles.
- AAT deficiency –relate **panlobular emphysema** extends to the alveolar ducts and sacs.

Pathophysiology

- **Vascular changes** include:
  - Thickening of pulmonary vessels that may lead to endothelial dysfunction of the pulmonary arteries
  - Later, structural changes ***increase pulmonary pressures***, especially during exercise
- In severe COPD, secondary pulmonary HTN leads to ***right-sided heart failure*** (***cor pulmonale***)

Clinical Presentation

History

- Risk factors
- Cough, sputum production, and exertional dyspnea
- Symptoms for months or years before seeking medical attention

Clinical Presentation

- Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for patients with COPD
- Activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated
- Worsening dyspnea on exertion is the principal feature of advanced COPD

Differences between COPD and asthma

	COPD	Asthma
Age	> 35 years	Any age
Cough	Persistent and productive	Intermittent and non-productive
Smoking	Almost invariable	Possible
Breathlessness	Progressive and persistent	Intermittent and variable
Nocturnal symptoms	Uncommon unless in severe disease	Common
Family history	Uncommon unless family members also smoke	Common
Concomitant eczema or allergic rhinitis	Possible	Common

Clinical Presentation

Physical Findings

- ***Early stages of COPD***
  - Normal physical examination
  - Current smokers - signs of active smoking (an odor of smoke or ***nicotine staining of fingernails***)



Patients with advanced COPD can develop an increased anteroposterior chest diameter—a barrel shaped chest

Clinical Presentation

- ***Advanced disease***
  - Systemic wasting - significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue
  - Paradoxical inward movement of the rib cage with inspiration (Hoover's sign)
  - Signs of overt right heart failure

Laboratory Findings

- Arterial blood gases and oximetry
- Hematocrit: ***Secondary polycythemia***
- Pulmonary function testing
  - ✓ Reduction in FEV_1 and FEV_1/FVC
  - ✓ Lung volumes may increase, resulting in an **increase in total lung capacity, functional residual capacity, and residual volume**

Staging of COPD

GOLD Disease Stratification Guidelines for Severity of COPD[1,17]

GOLD Stage	Severity	Postbronchodilator FEV_1/FVC	FEV_1, % predicted	Clinical symptoms
0	At risk	> 0.7	≥ 80	Asymptomatic smoker, ex-smoker, or chronic cough/sputum
1	Mild COPD	≤ 0.7	≥80	Breathlessness when hurrying or walking up slight hill
2	Moderate COPD	≤ 0.7	50-80	Breathlessness causing patient to stop after walking about 100 m or after a few minutes on level ground
3	Severe COPD	≤ 0.7	30-50	Breathlessness resulting in patient too breathless to leave the house, breathlessness after undressing, presence of chronic COPD respiratory failure, or clinical signs of right heart failure
4	Very Severe COPD	≤ 0.7	< 30	

Management

Desired Outcome

- The goals of therapy are
  - To prevent disease progression
  - To relieve symptoms,
  - To improve exercise tolerance and overall health status
  - To prevent and treat exacerbations
  - To prevent and treat complications and
  - To reduce morbidity and mortality

Management

- **Nonpharmacologic Therapy**
  - Smoking cessation
  - Pulmonary Rehabilitation
  - Lung Volume Reduction Surgery (LVRS)
  - Lung Transplantation
  - Vaccination: influenza and pneumococcal

0: At risk	I Mild	II Moderate	III Severe	IV: Very severe
Avoidance of risk factor(s); influenza vaccination, pneumococcal vaccine				
	Add short-acting bronchodilator when needed			
		Add regular treatment with one or more long-acting bronchodilators; Add rehabilitation		
			Add inhaled glucocorticosteroids if repeated exacerbations	
				Add long-term O_2 if chronic respiratory failure Consider surgical

Corticosteroids

- Used due to the mucosal inflammation, however its use is controversial in COPD management due to poor risk vs. benefit ratio. Appropriate situations include:
- ✓ Short-term systemic use for acute exacerbations
- ✓ Inhalation therapy for chronic stable COPD – associated with decrease in exacerbation frequency, therefore decrease in hospitalizations
- Bring reduction in capillary permeability to decrease mucus, inhibition of release of proteolytic enzymes from leukocytes, and inhibition of prostaglandins

Corticosteroids

- Fluticasone propionate (Flovent diskus)
  - 500mcg INH BID
- Combination with salmeterol
  - 250/50mcg INH BID
- SE (systemic): osteoporosis, adrenal suppression and insufficiency, development of cataracts
- SE (inhaled): oral candidiasis, hoarseness, sore throat

Exacerbations of COPD

- Goals of therapy
  - Prevention of hospitalization
  - Prevention of acute respiratory failure and death
  - Resolution of exacerbation symptoms

Exacerbations of COPD

Treatment

- Antimicrobial therapy if symptoms suggest (1) increased dyspnea; (2) increased sputum volume; and (3) increased sputum purulence – macrolides , 3rd generation cephalosporin, doxycycline
  - Levofloxacin (Levaquin): 500mg PO/IV q24hr X 5 days
  - Moxifloxacin (Avelox): 400mg PO/IV q24hr X 5 days
  - Clarithromycin (Biaxin): 500mg PO q12hr X 7 days
- Bronchodilators: short acting β_2 agonists are preferred
- Corticosteroids: use is well established in COPD exacerbation
  - Prednisone 30 – 40mg PO QD X 14 days

NEONATAL RESPIRATORY DISTRESS SYNDROME

Introduction

- This disorder is caused primarily by deficiency of pulmonary surfactant in an immature lung.
- RDS is a major cause of morbidity and mortality in preterm infants.
- The fetal lung is filled with fluid and provides no respiratory function until birth.
- In preparation for air breathing, surfactant is expressed in the lung during the third trimester of pregnancy.
- Surfactant reduces the alveolar surface tension, thereby facilitating alveolar expansion and reducing the likelihood of alveolar collapse (atelectasis)

Introduction

- Because of the developmental regulation of surfactant production, the most common cause of surfactant deficiency is preterm delivery.
- In addition, mutations in the genes encoding surfactant proteins SP-B and SP-C and the ATP-binding cassette (ABC) transporter A3 (ABCA3) may cause surfactant deficiency and/or dysfunction, and ***hereditary*** respiratory failure in infants born at term.

Pathophysiology

- The primary abnormality in RDS is surfactant deficiency.
- In inadequate surfactant activity, the resultant ***higher surface tension*** leads to instability of the lung at end-expiration, ***low lung volume***, and decreased compliance.
- These changes in lung function cause hypoxemia primarily due to a mismatch between ventilation and perfusion due to collapse of large portions of the lung (atelectasis)
- Surfactant deficiency also leads to ***lung inflammation*** and respiratory **epithelial injury**, which may result in pulmonary edema and increased airway resistance.

Prematurity

- In the preterm infants, both a decrease in the quantity and quality of surfactant contributes to decreased surfactant activity resulting in RDS
- Surfactant from immature lungs compared to surfactant from mature lungs contains:
  - Larger amounts of phosphatidylinositol (10 vs 2%) and
  - Smaller amounts of phosphatidylglycerol (less than 1 vs 10%)
- The protein content of surfactant from preterm lung is low relative to the amount of surfactant lipid.

Clinical Manifestations

- The clinical manifestations of RDS result primarily from abnormal pulmonary function and **hypoxemia**
- Because RDS is primarily a developmental disorder of deficient surfactant production, it presents within the first minutes or hours after birth.
- If untreated, RDS progressively worsens over the first 48 hours of life

Clinical Manifestations

- The affected infant is almost always premature and exhibits signs of respiratory distress that include:
  - **Tachypnea**
  - **Nasal flaring**: the use of accessory respiratory muscles and lowers total respiratory resistance.
  - Expiratory **grunting**, which results from exhalation through a partially closed glottis .
  - Intercostal, subxiphoid, and subcostal retractions, .
  - **Cyanosis** due to right-to-left intra- and extra-pulmonary shunting

Diagnosis

- Based on
  - Clinical picture of a premature infant with the onset of progressive respiratory failure shortly after birth (manifested by an increase in the work of breathing and an increase in the oxygen requirement),
  - Characteristic chest radiograph
  - Arterial blood gas measurement

Prevention and treatment of RDS

- As RDS is generally due to lung immaturity, the best intervention would be to prevent premature birth.
- However, if premature birth cannot be avoided, RDS may be prevented or its severity decreased with:
  - The use of antenatal **steroid** therapy,
  - Early neonatal administration of exogenous surfactant, and
  - Continuous positive airway pressure (CPAP)

Antenatal corticosteroid therapy

- Antenatal corticosteroid (ACS) therapy is given to pregnant women at risk for preterm labor to prevent or decrease the severity of neonatal RDS.
- ACS enhances maturational changes in fetal lung architecture and biochemistry with increased synthesis and release of surfactant, resulting in improved neonatal lung function.
- As a result, all pregnant mothers at risk for preterm delivery at or below 34 weeks gestation should receive ACS

Antenatal corticosteroid therapy

- The reduction in the severity and incidence of RDS has resulted in:
  - Decreased requirements for surfactant therapy,
  - Lower concentrations of supplemental oxygen, and
  - Decreased need for prolonged mechanical ventilation in the neonatal period
- Antenatal corticosteroid therapy leads to improvement in neonatal lung function via two mechanisms:
  - Enhancing **maturational** changes in lung architecture, and
  - Inducing lung enzymes that play a role in biochemical maturation

Antenatal corticosteroid therapy

- Drug and dose:
  - Betamethasone (two doses of 12 mg given IM 24 hours apart)
  - Dexamethasone (four doses of 6 mg given IM 12 hours apart).
  - Hydrocortisone: if both betamethasone and dexamethasone are unavailable,
    - Hydrocortisone 500 mg IV Q12 hrs for four doses
- Gestational age at administration: 26 to 34 weeks of gestation

Surfactant therapy

- Exogenous surfactant replacement therapy is effective in reducing RDS mortality and morbidity in preterm infants
- When surfactant therapy is used, the following issues must be addressed:
  - Selection of surfactant preparation
  - Indications for surfactant therapy
  - Timing of administration
  - Technical aspects of administration

Surfactant therapy

Types of surfactant

- Obtained from animal lung by lipid extraction

- Poractant alfa
  - Initial dose: 2.5 mL/kg (200 mg/kg PL)
  - Repeat dose: 100 mg/kg PL Q12 h PRN up to 2 total doses
- Calfactant
  - Initial dose: 3 mL/kg (105 mg/kg PL)
  - Repeat dose: 105 mg/kg PL Q12 h PRN up to 3 total doses
- Beractant
  - Initial dose: 4 mL/kg (100 mg/kg PL)
  - Repeat dose: same dose Q6 h PRN for total of 4 doses

DRUG-INDUCED RESPIRATORY DISORDERS

Drug-Induced Respiratory Disorders

- Adverse pulmonary reactions are **uncommon** in the general population
  - But are among the most serious reactions, often requiring intervention
- Of the reactions considered to be life-threatening, 12.3% were respiratory

1) Drug-Induced Apnea

- Apnea may be induced by CNS depression or respiratory neuromuscular blockade.
- Patients with the following conditions have an exaggerated respiratory depressant response
  - Chronic obstructive airway disease,
  - Alveolar hypoventilation, and
  - Chronic carbon dioxide retention

Drugs that Induce Apnea

CNS depression	Respiratory muscle dysfunction	Myopathy
Narcotic analgesics	Aminoglycosides	Aminocaproic acid
Barbiturates	Polymyxin	Clofibrate
Benzodiazepines	NM blockers	Corticosteroids
TCAs	Quinine	Diuretics
Phenothiazines	Digitalis	
Ketamine		
Antihistamines		
Anesthetics		

Drug-induced Apnea

- Respiratory failure has been known to occur following **local spinal anesthesia**.
- Apnea from respiratory paralysis and rapid respiratory muscle fatigue has followed the administration of **polymyxin** and **aminoglycoside** antibiotics.
- The mechanism appears to be related to the complexation of calcium and its **depletion** at the myoneural junction.
- **Intravenous calcium chloride** has been variably effective in reversing the paralysis

Drug-Induced Apnea

- The **aminoglycosides** competitively block NM junctions.
- This has resulted in life-threatening apnea when neomycin, gentamicin, streptomycin, or bacitracin has been administered into the peritoneal and pleural cavities.
- The aminoglycosides will produce an additive blockade and ventilatory paralysis with **succinylcholine** and in patients with **myasthenia gravis**
- Treatment consists of **ventilatory support** and administration of an **antiChE** agent (neostigmine or edrophonium)

2) Drug-Induced Bronchospasm

- Bronchoconstriction is the most common drug-induced respiratory problem.
- Drug-induced bronchospasm is a problem of patients with preexisting bronchial hyperreactivity (e.g., asthma, chronic obstructive lung disease)
- Mechanisms include:
  - Cholinergic or anticholinesterase agents
  - β2-receptor blockade
  - Immunoglobulin (Ig) E-mediated reactions
  - Histamine release from mast cells and basophils

Drugs that Induce Bronchospasm

Anaphylaxis (IgE-mediated)	Direct airway irritation	COX inhibition	Mast-cell degranulation
Penicillins	Acetate	Aspirin/NSAIDs	Narcotic analgesic
Sulfonamides	Smoke	Phenylbutazone	Local anesthetics
Cephalosporins	N-acetylcysteine	Paracetamol	Iron–dextran
Cimetidine	Inhaled steroids		Pancuronium
Tetracycline			Benzalkonium

Drugs that Induce Bronchospasm

Pharmacologic effects	Unknown mechanisms
α-Adrenergic receptor blockers	ACE inhibitors
Cholinergic stimulants	Losartan
Anticholinesterases	Tartrazine
β-Adrenergic antagonists	

Aspirin-Induced Bronchospasm

- Aspirin sensitivity or intolerance occurs in 4% to 20% of all asthmatics.
- The frequency of aspirin-induced bronchospasm increases with **age**.
- Patients older than age 40 years have a frequency **four times** that of patients younger than 20 years.
- The frequency increases to 14% to 23% in patients with **nasal polyps**.
- **Women** predominate over men, and there is no evidence for a genetic or familial predisposition

Aspirin-Induced Bronchospasm

- The classic description of the aspirin-intolerant asthmatic includes the triad of severe asthma, nasal polyps, and aspirin intolerance.
- The definitive diagnosis is made by aspirin provocation tests

Aspirin-Induced Bronchospasm

- The currently accepted hypothesis of aspirin-induced asthma is that aspirin intolerance is integrally related to inhibition of COX.
- This is supported by the following evidence:

(a) All NSAIDs that inhibit COX produce reactions,

(b) The degree of cross-reactivity is proportional to the potency of COX inhibition, and

(c) Each patient with aspirin sensitivity has a threshold dose for precipitating bronchospasm that is specific for the degree of COX inhibition produced

Aspirin-Induced Bronchospasm

- Arachidonic acid metabolism through the 5-lipoxygenase pathway may lead to the excess production of leukotrienes C_4 and D_4
- Leukotrienes C_4, D_4, and E_4 produce bronchospasm and promote histamine release from mast cells.

Tolerance of Anti-inflammatory and Analgesic Drugs in Aspirin-Induced Asthma

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Cross-Reactive Drugs	Drugs with No Cross-Reactivity
Diclofenac	Corticosteroids
Fenoprofen	Salicylamide
Ibuprofen	Sodium salicylate
Indomethacin	Chloroquine
Ketoprofen	Benzydamine
Naproxen	
Phenylbutazone	
Piroxicam	
Sulindac	
Mefenamic acid	

Treatment

- In theory, 5-lipoxygenase inhibitors such as zileuton or leukotriene antagonists should provide specific therapy
- Therapy of aspirin-sensitive asthmatics takes one of two general approaches: desensitization or avoidance

β-Blockers

- β-Adrenergic receptor blockers can be hazardous to a person with asthma.
- Even the more cardioselective agents such as acebutolol, atenolol, and metoprolol have been reported to cause asthma attacks
- If a patient with bronchial hyperreactivity requires β-blocker therapy, one of the selective β1-blockers (acebutolol, atenolol, metoprolol, or pindolol) should be used at the lowest possible dose.
- Celiprolol and betaxolol appear to possess greater cardioselectivity than currently marketed drugs.

β-Blockers

- Fatal status asthmaticus has occurred with the topical administration of the nonselective timolol maleate ophthalmic solution for the treatment of open-angle glaucoma.
- Early investigations with ophthalmic betaxolol suggest that it is well tolerated even in timolol-sensitive asthmatics

3) ACEi–Induced Cough

- Cough has become a well-recognized side effect of ACE inhibitor therapy.
- In a retrospective analysis, 14.6% of women had cough compared with 6.0% of the men on ACE inhibitors
- Studies specifically evaluating cough caused by ACE inhibitors report a prevalence of 19% to 25%

ACEI–Induced Cough

- Patients receiving ACE inhibitors had a 2.3 times greater likelihood of developing cough than a similar group of patients receiving diuretics
- **African Americans** and **Chinese** have a higher incidence of cough.
- 26% of patients with **heart failure** had ACE inhibitor induced cough compared with 14% of those with **hypertension**.
- Cough can occur with all ACE inhibitors.

ACEI–Induced Cough

- The cough typically is **dry** and **nonproductive**, **persistent**, and not paroxysmal.
- The severity of cough varies from a “tickle” to a debilitating cough with insomnia and vomiting.
- The cough can begin within **3 days** or have a delayed onset of up to 12 months following initiation of ACE inhibitor therapy.
- The cough remits within **1 - 4 days** of discontinuing therapy but (rarely) can last up to **4 weeks** and recur with rechallenge

ACEI–Induced Cough

- Patients should be given a 4-day withdrawal to determine if the cough is induced by ACE inhibitors.
- The chest radiograph is normal, as are pulmonary function tests (spirometry and diffusing capacity).
- Bronchial hyperreactivity, as measured by methacholine provocation, may be worsened in patients with underlying bronchial hyperreactivity such as asthma and chronic bronchitis.

ACEI–Induced Cough

- The mechanism of ACE inhibitor–induced cough is still unknown
- Possible mechanisms:
  - ACE catalyzes bradykinin and substance P that produce or facilitate inflammation and stimulate lung irritant receptors
  - ACE inhibitors also may **induce COX** to cause the production of prostaglandins.

ACEI–Induced Cough

- The cough generally is unresponsive to cough suppressants or bronchodilator therapy.
- The preferred therapy is withdrawal of the ACE inhibitor and replacement with an alternative antihypertensive agent
  - Angiotensin II receptor antagonists

Quiz 2 (10%)

1. The risk of asthma related death is reduced by: (1.5 pt).

   A) SABA B) ICS C) OCS D) LABA

2. Among b-blockers, which drug has the lowest risk of bronchospasm? (1.5 pt)

   A) Metoprolol B) Atenolol C) Propranolol D.) Betaxolol

3. What are the advantages of ICS over OCS? (3 pts).
4. What do you counsel asthmatic patients to reduce oropharmangeal candidiasis associated with ICS? (2 pts)
5. Describe the mechanism of Aspirin induced bronchospasm (2 pts)

BONE AND JOINT DISORDERS

CHAPTER FOUR

GOUT AND HYPERURICEMIA

Introduction

- The term **gout** describes a heterogeneous clinical spectrum of diseases including:
  - ✓ Elevated serum urate (**hyperuricemia**),
  - ✓ Recurrent attacks of **acute arthritis** associated with monosodium urate crystals in synovial fluid leukocytes,
  - ✓ Deposits of monosodium urate crystals (**tophi**) in tissues in and around joints, and
  - ✓ Uric acid **nephrolithiasis**

Introduction

- All patients with gout have hyperuricemia (super-saturation of serum for urate) at some point in their disease
- However, most ***hyperuricemic*** individuals never experience a clinical event resulting from urate crystal deposition.
- Therefore, hyperuricemia is viewed as a **necessary** but **not sufficient** precondition for the development of urate crystal deposition disease, and is to be distinguished from **gout**, the **clinical syndrome**.

Introduction

- At 37°C (98.6°F), serum urate concentrations above **7mg/dL** begin to exceed the limit of solubility for monosodium urate.
- Gout affects **men** about **seven to nine times** more often than women.
- The incidence of gout increases with **age**
- Serum uric acid levels in women approach those of men once **menopause** has occurred

Pathophysiology

- Excess accumulation may result from either ***overproduction*** or ***underexcretion of uric acid***.
- ***Uric acid*** is a waste product of the breakdown of purines contained in the DNA of degraded body cells and dietary protein.
- It is **water soluble** and excreted primarily by the kidneys
- The solubility of uric acid depends on concentration and temperature.
- At high serum concentrations, lower body temperature causes the precipitation of monosodium urate crystals.
- Collections of these crystals (called **microtophi**) can form in joint spaces in the distal extremities.

Pathophysiology

- Free urate crystals activate several pro-inflammatory mediators, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-8
  - → Movement of neutrophils into the joint space that “ingest” monosodium urate crystals via phagocytosis
  - → Neutrophils are lysed and release proteolytic enzymes
  - → Trigger the clinical manifestations of an acute gout attack such as pain and swelling.
- These inflammatory mechanisms in gout can lead to **cartilage and joint destruction**

Pathophysiology

- The increased serum uric acid involves either the **underexcretion** of uric acid (80% of patients) or its **overproduction**.
- The cause of overproduction or underexcretion of uric acid in most gout patients is unknown;
  - This is referred to as **primary gout**.

Risk Factors

1. **Hyperuricemia**:

- The risk of gout increases as the serum uric acid concentration increases, and approximately 30% of patients with levels greater than **10 mg/dL** develop symptoms of gout within 5 years
- However, most patients with hyperuricemia are asymptomatic

Risk Factors

2. **Chronic Kidney Disease**
- Uric acid excretion is reduced in patients with chronic kidney disease, putting them at risk for hyperuricemia
3. **Drugs:**
- **Chemotherapy**: extreme hyperuricemia can occur because of rapid tumor cell destruction in patients
- *Thiazide diuretics, niacin, pyrazinamide, cyclosporine, and aspirin*: **block uric acid secretion in the kidney**
4. **Other Risk Factors**: obesity, ethanol use, and dyslipidemia

Presentation of Acute Gouty Arthritis

- **General**
  - Patients are usually in acute distress.
- **Symptoms**
  - Severe pain, swelling, and warmth in the affected joint(s)
  - The attack is usually **mono-articular**, and the most common sites are the **metatarsophalangeal** and **knee joints**.
  - In elderly patients, gouty attacks may be atypical with insidious onset and polyarticular, often involving hand or wrist joints.

Presentation of Acute Gouty Arthritis

- **Signs**
  - Affected joint(s) are warm, erythematous, and swollen.
  - Mild fever may be present.
  - Tophi (usually on hands, wrists, elbows, or knees) may be present in chronic, severe disease.
- **Laboratory Tests**
  - ↑ in WBC, serum uric acid level and erythrocyte sedimentation rate (ESR)

Tophous of the Knee



Swelling of MTP





Inflamed tophaceous gout

Diagnosis

- **Aspiration of joint fluid**: monosodium urate crystals, ↑WBC count with neutrophils predominating
- **24-hour urine collection**: to determine if the patient is an overproducer or an underexcretor of uric acid.
  - ✓>800 mg/day of uric acid: ***overproducers.***
  - ✓< 600 mg/day: ***underexcretors***
- **X-ray**

Treatment

- Treatment of gout involves:

(1) Acute relief of a gouty arthritis attack and

(2) Long-term maintenance treatment to prevent future attacks.

Treatment

- **Desired Outcomes**
  - (1) Achieving rapid and effective **pain relief**
  - (2) Maintaining **joint function**
  - (3) Preventing disease **complications**
  - (4) Avoiding treatment-related **adverse effects**
  - (5) Providing **cost-effective** therapy, and
  - (6) Improving **quality of life**

Treatment

- Nonpharmacologic Therapy:
  - Immobilization of the affected extremity speeds resolution of the attack.
  - Applying ice packs to the joint also decreases pain and swelling

Pharmacologic Therapy

Acute Gouty Arthritis

- The mainstay of treatment during an acute attack is the administration of **anti-inflammatory drugs** such as
  - *NSAIDs*
  - *Colchicine, or*
  - *Glucocorticoids*.
- NSAIDs: **Indomethacin, Naproxen, Sulindac**
- Adverse effects of NSAIDs include gastropathy (primarily peptic ulcers), renal dysfunction, and fluid retention.
- CI: peptic ulcers, those taking warfarin, renal insufficiency, uncontrolled hypertension or heart failure

Acute Gouty Arthritis

- **Colchicine**: exert its anti-inflammatory effects by interfering with the function of mitotic spindles in neutrophils by binding of tubulin dimers; this inhibits phagocytic activity
- Adverse effects: Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, and abdominal pain), myopathy and bone marrow suppression (usually neutropenia).
- Flare treatment: Initial: 1.2 mg at the first sign of flare, followed in 1 hour with a single dose of 0.6 mg (maximum: 1.8 mg within 1 hour)

Acute Gouty Arthritis

- ***Corticosteroids***: when only ***one or* two joints** are affected, **intraarticular** corticosteroid injection can provide rapid relief
- Joint fluid obtained by **arthrocentesis** should be examined for evidence of joint-space infection and crystal identification.
- If no infection is present, intraarticular injection can proceed.

Acute Gouty Arthritis

- Systemic corticosteroids are a useful option in patients with ***contraindications to NSAIDs or colchicine*** (primarily renal impairment) or ***polyarticular attacks***, especially in elderly patients

- Adverse effects: fluid retention, hyperglycemia, central nervous system stimulation, weight gain, and increased risk of infection

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

- Asymptomatic hyperuricemia usually does not require treatment
- Nonpharmacologic Therapy:
  - Lose weight if obese
  - Discontinue ethanol consumption.
  - Low-purine diets
  - Drugs that may cause or aggravate hyperuricemia should be discontinued

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

Pharmacologic Therapy

- Patients with recurrent attacks, evidence of tophi or joint destruction, or uric acid nephrolithiasis are candidates for maintenance therapy with **allopurinol** or **probenecid** to lower serum uric acid levels
- Prophylactic therapy involves either decreasing uric acid production or increasing its excretion

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

1. Allopurinol

- The drug and its primary active metabolite, **oxypurinol**, reduce serum uric acid concentrations by inhibiting the enzyme **xanthine oxidase**, thereby blocking the oxidation of ***hypoxanthine*** and ***xanthine*** to ***uric acid***.
- ***Allopurinol*** is well absorbed with a short half-life of 2 to 3 hours.
- The half-life of ***oxypurinol*** approaches 24 hours, allowing allopurinol to be dosed once daily.
- Dose:
  - Initial: 100 mg/day, increasing the dose gradually every 4 weeks, while monitoring plasma uric acid levels
  - Max: 900mg/day (rarely)

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

- Adverse effects:
  - Allopurinol generally is well tolerated;
  - Precipitate acute gouty arthritis
  - Nausea and diarrhea, maculopapular rash, allopurinol hypersensitivity syndrome
  - Leukopenia or thrombocytopenia,
- DI:
  - Effects of both theophylline and warfarin may be potentiated by allopurinol
  - Azathioprine and 6-mercaptopurine are purines whose metabolism is inhibited by allopurinol

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

2. Probenecid

- Is a **uricosuric agent** that blocks the tubular reabsorption of uric acid, increasing its excretion
- It is contraindicated in patients with a history of uric acid stones or nephropathy.
- Probenecid loses its effectiveness as renal function declines and should be avoided when the **CrCl is ≤ 50 mL/minute.**
- Its uricosuric effect is counteracted by aspirin
- Patients should be instructed to maintain an adequate fluid intake and urine output to decrease the risk of uric acid stone formation

Probenecid

- Dose:
  - Initial: 250 mg twice daily
  - Maintenance: 500 – 1000 mg two or three times daily
  - Max: 3000 mg/day.
- Side effects
  - Rash
  - Precipitation of acute gouty arthritis
  - Gastrointestinal intolerance
  - Uric acid stone formation

RHEUMATOID ARTHRITIS

Introduction

- Rheumatoid arthritis (RA) is a complex systemic inflammatory condition manifesting initially as **symmetric** swollen and tender joints of the hands and/or feet.

- It results from a complex interaction between genes and environment, leading to a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern.

Epidemiology

- RA is estimated to have a prevalence of 1%
- It can occur at any age, with increasing prevalence up to the seventh decade of life.
- The disease is three times more common in **women**.
  - In people ages 15 to 45 years, women predominate by a ratio of 6:1;
  - The sex ratio is approximately equal among patients in the 1st decade of life and in those older than age 60 years.

Risk Factors

- Female gender (3:1 females to males)
- Increasing age (peak onset 35 – 50 years of age)
- Current tobacco smoking
- Family history of RA
  - HLA-DR1 and HLA-DR4

Etiology and Pathogenesis

- The cause of RA remains unknown.
  - Variations between ethnic groups in susceptibility to RA,
  - Heterogeneity of disease course and
  - Variations in clinical, radiological and laboratory findings within groups

↳ Strongly suggest that multiple factors, both environmental and genetic, influence onset and progression of RA.

Etiology and Pathogenesis

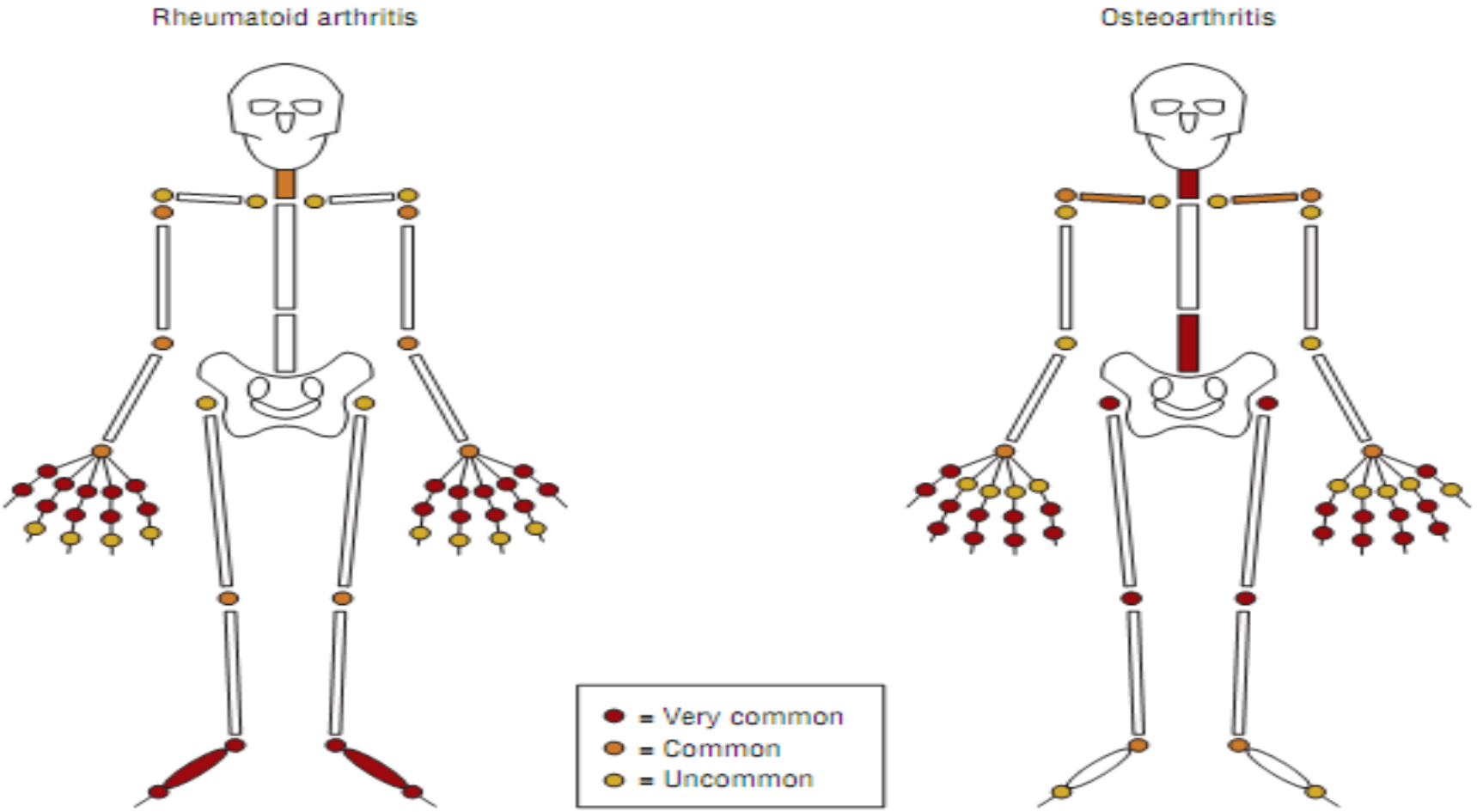
- From an immunological point of view, RA is considered an **autoimmune disease**
- Factors contributing to RA development
  - Genetic variations,
  - Autoantibodies,
  - Cellular immune responses,
  - Hormones and
  - Gene-environment interactions

Clinical Presentation

- **Symptoms**
  - Nonspecific systemic symptoms: fatigue, weakness, anorexia, and diffuse musculoskeletal pain
  - Pain in involved joints and prolonged morning joint stiffness.
- **Signs**
  - The metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP), and wrist joints are involved frequently.
  - Joint involvement is usually **symmetric**.
  - Limited joint function.
  - Signs of joint inflammation (tenderness, warmth, swelling, and erythema).
  - Low-grade fever

Clinical Presentation

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Clinical Presentation

- **Extraarticular** manifestations:
  - **Skin***:* Subcutaneous nodules
  - **Ocular***:* Keratoconjunctivitis sicca, scleritis
  - **Pulmonary***:* Interstitial fibrosis, pulmonary nodules, pleuritis, pleural effusions
  - **Vasculitis***:* Ischemic ulcers, skin lesions, leukocytoclastic vasculitis
  - **Neurologic***:* Peripheral neuropathy
  - **Hematologic***:* Anemia, thrombocytosis

Laboratory Tests

- Positive rheumatoid factor (the test is negative in up to 30% of patients
- Elevated ESR (ESR: >20 mm/hour in men; >30 mm/hour in women)
- Elevated C-reactive protein (CRP) (>0.7mg/dL)
- CBC: slight elevation in WBC count with a normal differential; slight anemia; thrombocytosis
- Positive anticitrullinated protein antibodies (ACPA)

Laboratory Tests

- **Other Diagnostic Tests**
  - **Synovial fluid analysis***:* Straw colored, slightly cloudy, WBC 5 – 25 × $10^3/mm^3$, no bacterial growth if cultured
  - **Joint x-rays:** To establish baseline and evaluate joint damage
  - **MRI***:* May detect erosions earlier in the course of disease than x-rays but is not required for diagnosis

ACR/EULAR Classification Criteria for RA

Criteria		Score
Joint involvement	1 large joint (hips, knees, ankles, elbows, shoulders)	0
	2–10 large joints	1
	1–3 small joints (MCPs, PIPs, MTPs, wrists)	2
	4–10 small joints	3
	More than 10 joints (at least one small joint)	5
Serology	Negative RF and negative ACPA	0
	Low positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	Less than 6 weeks	0

Treatment

- Goals of treatment
  - (a) Reduce or eliminate pain,
  - (b) Protect articular structures,
  - (c) Control systemic complications,
  - (d) Prevent loss of joint function, and
  - (e) Improve or maintain quality of life.

Non-Pharmacologic Treatment

- Rest
  - Reduces pain and stress on joints
- Occupational therapy,
- Physical therapy,
- Use of assistive devices,
- Weight reduction, and
- Surgery
  - Tenosynovectomy,
  - Tendon repair, and
  - Joint replacements

Pharmacologic therapy

- Non-steroidal anti-inflammatory drugs (NSAIDs),
- Glucocorticoids,
- DMARDs,
  - DMARDs should be started within the first 3 months of symptom onset for better outcome
- Biologic response modifiers (BRM)

Pharmacologic Therapy

- **Bridge Therapy/Symptomatic Relief**
  - The current standard of care for RA treatment is to initiate disease-modifying therapy immediately.
  - While this step is critical to control the underlying disease activity, it may take weeks to months for the patient to experience relief.
  - It is acceptable to initiate “bridge therapy” or short-term use of certain medications to provide symptomatic relief until the disease modifying drug reaches its therapeutic effect.
  - The most common classes used for bridge therapy are NSAIDs and glucocorticoids

NSAIDs

- Provide analgesic and anti-inflammatory benefits for joint pain and swelling.
- Do not prevent joint damage or change the underlying disease.
- Associated with an increased risk of:
  - GI ulcers or hemorrhage
  - Fluid retention
  - Exacerbation of existing hypertension
  - Renal function impairment

Glucocorticoids

- Used in RA for anti-inflammatory and immunosuppressive effects
- Mechanisms
  - Interfere with antigen presentation to T lymphocytes
  - Inhibit prostaglandin and leukotriene synthesis
  - Inhibit neutrophil and monocyte superoxide radical generation.

Glucocorticoids

- Low-dose glucocorticoid treatment (prednisone ≤10 mg/day or equivalent) effectively reduces inflammation through inhibition of cytokines and inflammatory mediators and prevents disease progression.
- Oral corticosteroids can be used in several ways.
  - Bridging therapy,
  - Continuous low-dose therapy, and
  - Short-term high-dose bursts to control flares

Corticosteroids

- **Major side effects of systemic glucocorticoids**
  - Cushingoid appearance and weight gain
  - Skin thinning
  - Cataracts and glaucoma
  - Ischemic heart disease and heart failure
  - Increased risk of gastritis, ulcer formation, and GI bleeding, if used with NSAIDs
  - Menstrual irregularities, lower fertility
  - Osteoporosis
  - Hyperglycemia
  - Increase risk of infection

DMARDs

- DMARDs are the mainstay of RA treatment because they modify the disease process and prevent or reduce joint damage
- Methotrexate alone or in combination therapy is the initial treatment of choice for patients with aggressive disease.
- **Methotrexate** 7.5mg once-weekly doses should be initiated within 3 months of diagnosis and increased steadily until the patient has symptomatic improvement or a maximum dose of 20 mg/wk is reached
- Concomitant **folic acid** is given routinely to reduce the risk of folate-depleting reactions induced by methotrexate therapy (eg, stomatitis, diarrhea, nausea, alopecia, myelosuppression, and elevations in liver function tests)

Pharmacologic Therapy

- Other DMARDs
  - Hydroxychloroquine
  - Sulfasalazine
  - Leflunomide
  - Etanercept
  - Infliximab

Summary Questions

1. Allopurinol is contraindicated for acute gout arthritis (1 pt)

   A. True B. False

2. Which NSAIDs is not indicated in the management of acute gout arthritis? (1 pts)

   A. Diclofenac B. Indomethacin C. Aspirin D. Ibuprofen

3. List three risk factors of gouty arthritis. (3 pts)

4. Which joints are commonly affected by gout? (2.5pts)

OSTEOPOROSIS

Osteoporosis

- A bone disorder
  - Low bone density
  - Impaired bone architecture, increased fracture risk
  - Compromised bone strength
- In US 8 million women and 2 million men
- Affect all ethnic groups
- Prevalence increases with age

Osteoporosis

Fracture incidence

- Wrist and vertebral fractures: common adulthood
- Hip fractures: common in seniors
  - In a woman's lifetime, hip fracture,17%; vertebral fracture,15.6%; and forearm fracture, 16%
  - Man's lifetime:13 – 30%

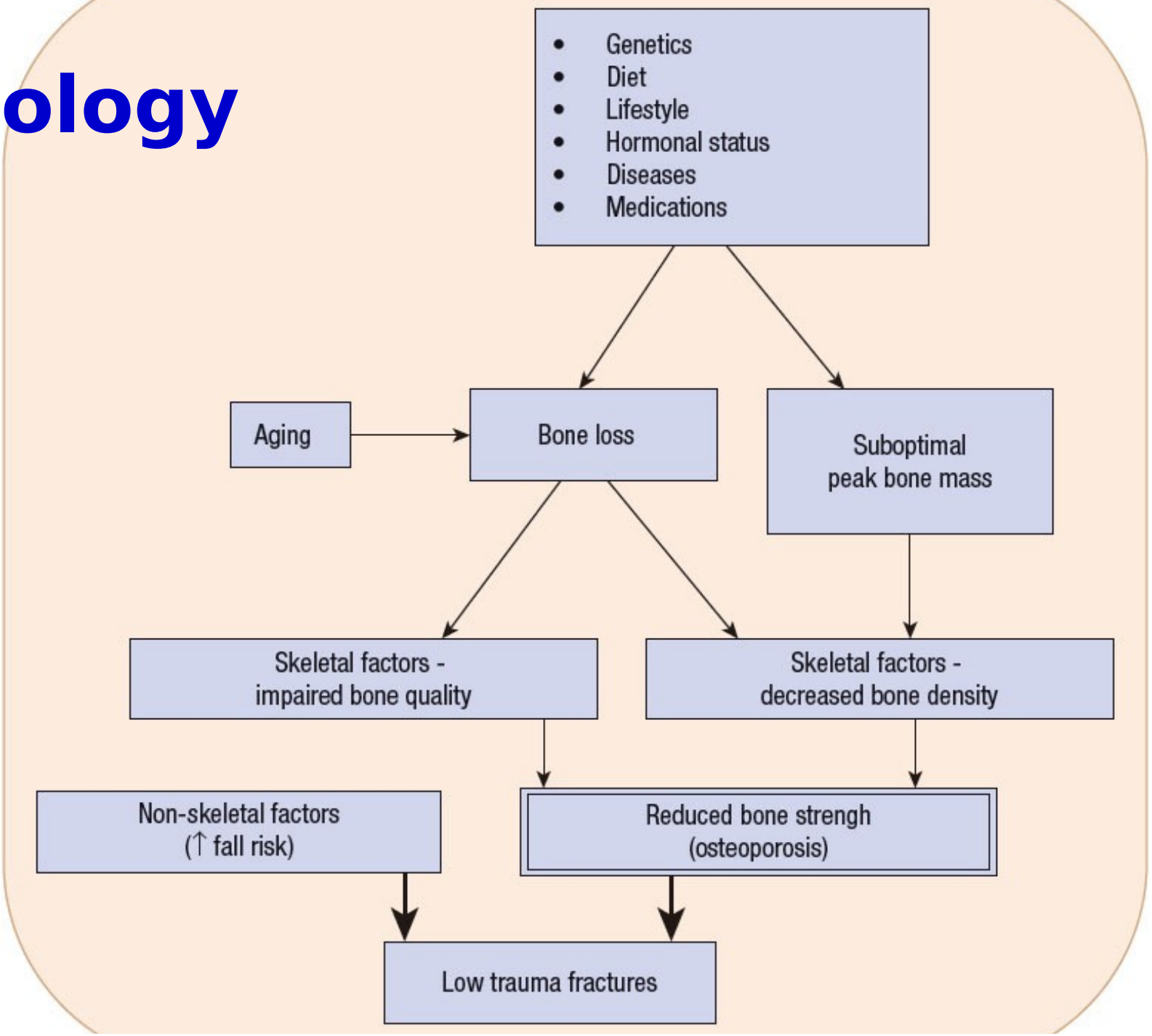
Bone Physiology

- The skeleton has two types of bone
  - Cortical bone (80%)
    - Forearm
    - Femoral neck of the hip
    - Wrist
  - Trabecular bone (20%)
    - Spine (66 – 75%)
    - 5 to 10 times higher metabolic turnover

Bone Physiology

- Bone is made of:
  - Collagen
    - Flexibility and energy absorbing capacity
  - Mineral components
    - Strength and stiffness
- Bone strength: integration of bone quality and bone mineral density (bone mass)
- Peak bone mass is dependent on:
  - Genetic factors (60 – 80%)
  - Modifiable factors (20 – 40 %): nutritional intake (calcium, vitamin D, and protein), exercise, adverse lifestyle practices (smoking), hormonal status, and certain diseases and medications

Etiology


Genetics
Diet
Lifestyle
Hormonal status
Diseases
Medications
Aging
Bone loss
Suboptimal peak bone mass
Skeletal factors - impaired bone quality
Skeletal factors - decreased bone density
Non-skeletal factors (↑ fall risk)
Reduced bone strengh (osteoporosis)
Low trauma fractures

Risk Factors for Osteoporosis

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- Low bone mineral density
- Female sex
- Advanced age
- History of previous low trauma (fragility) fracture as an adult
- FH of osteoporotic fracture (especially parental hip fracture)
- Low body weight or BMI
- Premature menopause (before 45 years old)b
- Secondary osteoporosis (especially rheumatoid arthritis)
- Past or present systemic oral glucocorticoid therapy
- Current cigarette smoking
- Alcohol intake of three or more drinks per day
- Low calcium intake
- Low physical activity
- Minimal sun exposure

Drugs Associated with Osteoporosis

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- Anticoagulants (heparin, warfarin)
- Anticonvulsants (phenytoin, phenobarbital)
- Aromatase inhibitors (anastrozole, exemestane, letrozole)
- Cytotoxic drugs (methotrexate, cisplatin)
- Glucocorticoids (5 mg or more of prednisone daily or equivalent for at least 3 months)
- Gonadotropin-releasing hormone analogs (leuprolide acetate, nafarelin, goserelin)
- Immunosuppressants (tacrolimus)
- Lithium
- Medroxyprogesterone acetate
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors
- Thiazolidinediones
- Thyroid supplements (due to over-replacement)
- Total parenteral nutrition

Clinical Presentations

- **Symptoms**
  - Frequently asymptomatic
  - Pain
  - Immobility
  - Depression, fear, and low self-esteem from physical limitations and deformities
- **Signs**
  - Shortened stature (>3.81cm loss), kyphosis, or lordosis
  - Atraumatic vertebral, hip, wrist, or forearm fracture

Laboratory tests

- CBC, ALP, Cr, Ca^{2+}, PO_4^{3-}, TSH, total testosterone, 25(OH) vitamin D, and 24-hour urine concentrations of $Ca^{2+}$and PO_4^{3-} are frequently assessed
- Other diagnostic tests
  - Spine and hip bone density measurement using dual-energy x-ray absorptiometry (DXA) scan
  - Vertebral fracture assessment (VFA)

Prevention and Treatment

- Osteoporosis prevention and treatment begins with a bone-healthy lifestyle and uses nonprescription and prescription medications as needed
- Desired outcomes
  - Primary goal: prevention
  - Once developed: stabilize or improve bone mass and strength and prevent fractures
  - If there is fracture: reducing future falls and fractures, improving functional capacity, reducing pain and deformity, and improving quality of life

General Approach

- Bone healthy life style should begin at birth and continue
- First line drug choice
  - Vitamin D with Calcium or alendronate

Non pharmacologic therapy

- Diet
  - Vitamin D and calcium
  - Optimize caffeine intake
  - Excessive Alcohol intake
- Smoking cessation
- Exercise
  - Weight bearing aerobic exercises
- Fall prevention
  - Programmed exercise
  - Hip Protectors

Recommended Ca and Vitamin D

Group and Ages	Elemental Calcium (mg)	Calcium Upper Limit (mg)	Vitamin D (units)[a]	Vitamin D Upper Limit (units)
Infants				
Birth to 6 months	200	1,000	400	1,000
6–12 months	260	1,500	400	1,500
Children				
1–3 years	700	2,500	600	2,500
4–8 years	1,000	2,500	600	3,000
9–18 years	1,300	3,000	600	4,000
Adults				
19–50 years	1,000	2,500	600[b]	4,000
51–70 years (men)	1,000	2,000	600[b]	4,000
51–70 years (women)	1,200	2,000	600[b]	4,000
>70 years	1,200	2,000	800[b]	4,000

Pharmacologic Therapy

Antiresorptive Therapy

- Calcium
  - Should be ingested in adequate amounts to prevent secondary hyperparathyroidism and bone destruction
  - Combined with vitamin D and osteoporosis medications when needed
  - Calcium carbonate
    - Drug of choice
    - Need acidic medium for absorption
    - 600 mg elemental calcium is enough
  - Calcium citrate
- Vitamin D Supplementation
  - Cholicalciferol
  - Ergocalciferol

Bisphosphonates

- Mimic **pyrophosphate**, an endogenous bone resorption inhibitor
- Bind to hydroxyapatite in bone and decrease resorption by inhibiting osteoclast adherence to bone surfaces
- All bisphosphonates become incorporated into bone, giving them long biologic half-lives of up to 10 years
- Provide the greatest BMD increases and fracture risk reductions
- Oral and IV ibandronate for postmenopausal women
- Alendronate, risedronate, and intravenous zoledronic acid approved for male and glucocorticoid-induced osteoporosis.

Bisphosphonates

- Absorption:
  - Poor
  - Should be taken in empty stomach with plenty of fluid
- Administration
  - Per day, Per week, Per month
  - **Risedronate**: 5 mg daily, 35 mg weekly, 75 mg on 2 consecutive days once monthly, 150 mg monthly
  - **Alendronate**: 10mg PO daily, 70mg PO weekly
- SE
  - Nausea, abdominal pain, and dyspepsia

Mixed Estrogen Agonists/Antagonists

- **Raloxifene (60mg daily)**
  - An estrogen agonist on bone but an antagonist on the breast and uterus
  - Decreases vertebral fractures and increases spine and hip BMD, but to a lesser extent than bisphosphonates
  - Contraindicated in women with an active or past history of venous **thromboembolism**

Evaluation of therapeutic outcomes

- Bone mass examination annually
- Presence of possible fracture symptoms
- Medication adherence and side effects

DISORDERS OF EENT

Chapter Five

GLAUCOMA

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Definition

The glaucomas

- Are a group of ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disk) that is associated with loss of visual sensitivity and potentially total vision loss
- Increased intraocular pressure (IOP), a traditional diagnostic criterion for glaucoma; now no longer a diagnostic criterion
- But associated with an increased prevalence and progression of glaucoma

Introduction

- Two major types of glaucoma have been identified: **open angle** and **closed angle**.
- Open-angle glaucoma accounts for the great majority of cases.
- Either type can be a **primary** inherited disorder **(congenital)**, or **secondary** to disease, trauma, or drugs, and can lead to serious complications
- Both primary and secondary glaucomas may be caused by a combination of open-angle and closed-angle mechanisms

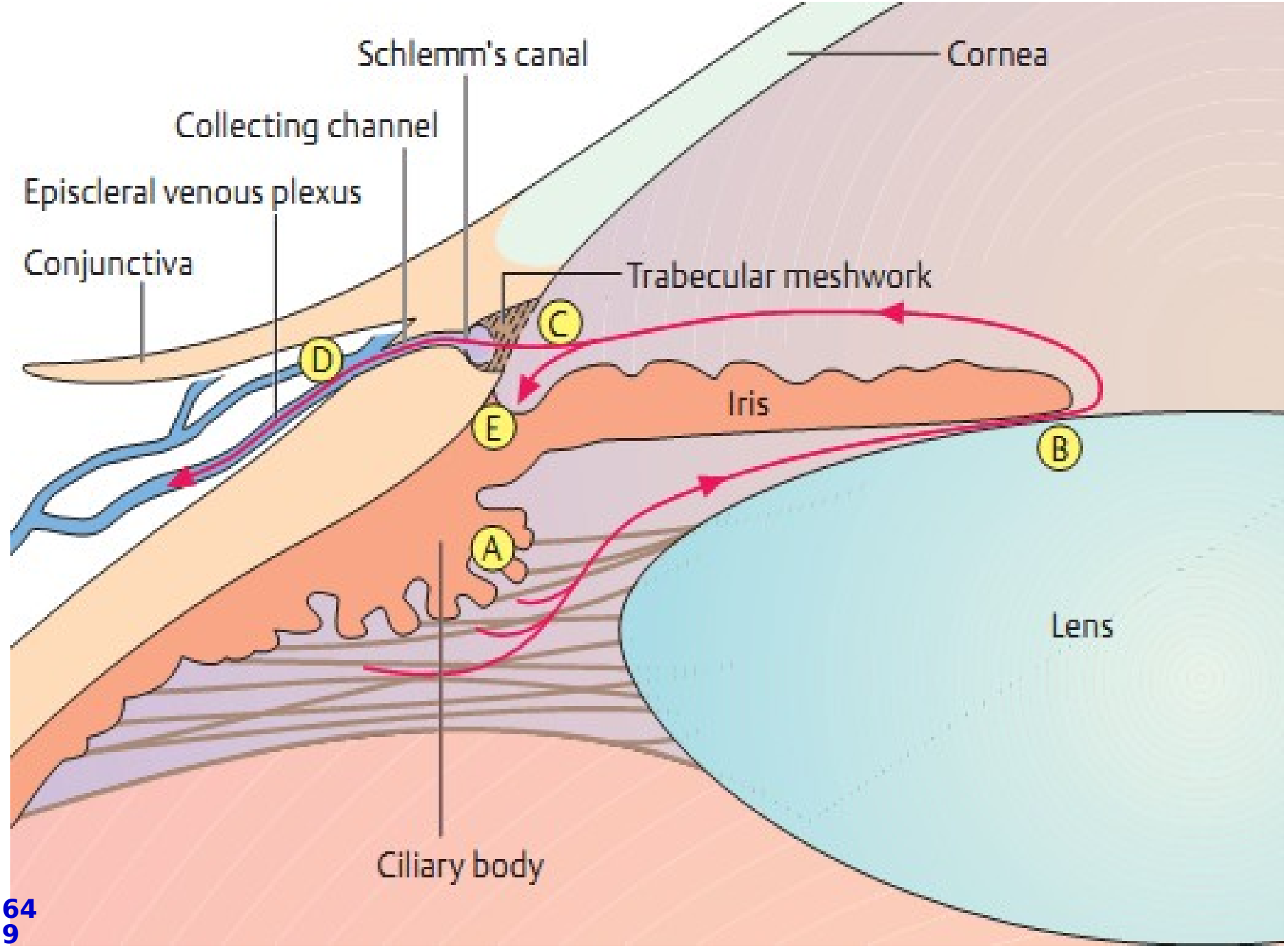
Epidemiology

- Throughout the world, there are about **70 million** people suffering from glaucoma and **7 million** have been blinded by the disease.
- Glaucoma is the 2nd most frequent cause of blindness in developing countries after diabetes mellitus
- Some 15–20% of blind persons have lost their eyesight as a result of glaucoma

Aqueous Humor Dynamics and IOP

- The aqueous humor is produced by the non-pigmented epithelial cells of the **ciliary body** through the diffusion and ultrafiltration of plasma

- Secreted in to PC → flows through the pupil into the AC b/n iris & lens → exits the anterior chamber (via angle of AC) through the trabecular meshwork and drains into Schlemm's canal → then passes to small episcleral **veins** to enter ocular venous system


Schlemm's canal
Cornea
Collecting channel
Episcleral venous plexus
Conjunctiva
Trabecular meshwork
C
D
Iris
E
B
A
Lens
Ciliary body

Aqueous Humor Dynamics and IOP

- IOP is controlled by the balance b/n production & drainage of aqueous.
- Impaired drainage high IOP glaucoma
- Aqueous humor in the AC leaves the eye by two routes:

(a) Filtration through the trabecular meshwork (conventional outflow) to the Schlemm canal (80% to 85%) and

(b) Through the ciliary body and the suprachoroidal space (uveoscleral outflow or unconventional outflow) < 20%

Aqueous Humor Dynamics and IOP

- Uveoscleral outflow pharmacologically modulated by
  - **Adrenoceptors** (β, α_2),
  - **Prostanoid receptors**, and
  - **Prostamide receptors**
- The refractive properties of the eye depend on IOP to maintain the curvature of the cornea

The Intraocular Pressure (IOP)

- The normal IOP = 10-22 mmhg.
- The higher the IOP, the more likely that the optic nerve will be damaged.
- Sensitivity to higher IOP varies among eyes of different people.
  - ✓ IOP > 30mmhg → almost certainly the patient has glaucoma.
  - ✓ IOP 20-30mmhg → may or may not have glaucoma
  - ✓ Raised IOP but no sign of glaucoma → ocular hypertension
  - ✓ IOP< 20mmhg but definite glaucomatous signs → normal tension glaucoma

Risk factors

Risk Factors for Glaucoma

POAG	PACG
Elevated IOP	Advancing age
African or Hispanic descent	Asian or Eskimo ethnicity
Family history of glaucoma	Female sex
Older age	Hyperopia
Thinner CCT	Shallow anterior chamber
Type 2 diabetes	Family history of angle-closure glaucoma
Low ocular perfusion pressures	
Myopia	

Drugs That May Induce or Potentiate Increased IOP

Open-angle glaucoma

Ophthalmic corticosteroids (high risk)

Systemic corticosteroids

Nasal/inhaled corticosteroids

Fenoldopam

Ophthalmic anticholinergics

Succinylcholine

Vasodilators (low risk)

Cimetidine (low risk)

Closed-angle glaucoma

Topical anticholinergics

Topical sympathomimetics

Systemic anticholinergics

Heterocyclic antidepressants

Low-potency phenothiazines

Antihistamines

Ipratropium

Benzodiazepines (low risk)

Theophylline (low risk)

Vasodilators (low risk)

Systemic sympathomimetics (low risk)

CNS stimulants (low risk)

Serotonin-selective reuptake inhibitors

Imipramine

Venlafaxine

Topiramate

Tetracyclines (low risk)

Carbonic anhydrase inhibitors (low risk)

Monoamine oxidase inhibitors (low risk)

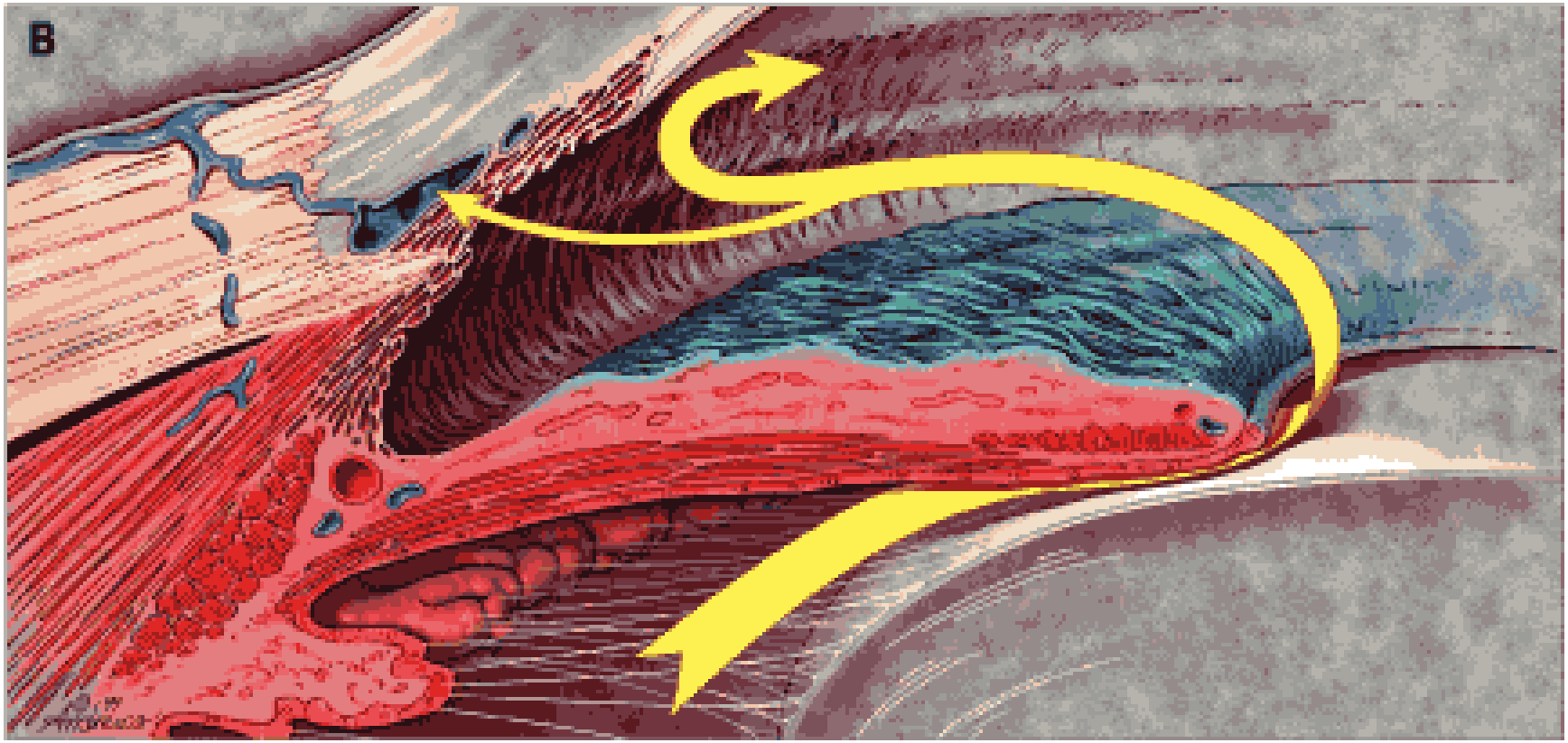
Topical cholinergics (low risk)

POAG – Primary Open Angle Glaucoma

- **POAG** –production of aqueous humor is normal while it does not drain properly
- Open-angle glaucoma is the second leading cause of blindness
- Increased susceptibility of **the optic nerve to ischemia, a reduced** or **dysregulated blood flow**, **excitotoxicity**, **autoimmune reactions**
- Result **apoptosis** of the retinal ganglion cells w/c bring axonal degeneration, and finally **permanent loss of vision**

POAG

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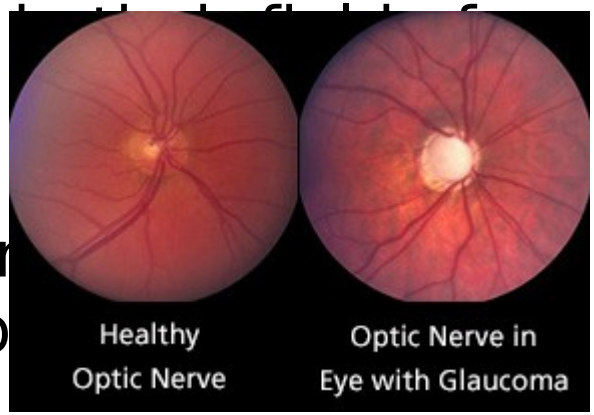
POAG

- POAG is a **bilateral**,
- Patients may be unaware they have glaucoma and may be diagnosed during routine eye evaluation

POAG

Symptoms

- Patients with severe disease progression may report loss of peripheral vision and may describe the presence of scotomata (blind spots) [illegible] vision



Signs

- Ophthalmoscopic examination may r[illegible]
  - Optic nerve head (optic disc) cupp[illegible]
  - Large cup-to-disc ratio.
  - Diffuse thinning, focal narrowing, or notching of the optic nerve head rim

Diagnostic Tests

- Gonioscopy, applanation tonometry, pachymetry
- Assessment of the visual fields, and measurement of IOP

Treatment

Desired Outcomes and Goals

- To prevent further loss of visual function
- Minimize adverse effects of therapy and its impact on the patient's vision, general health, and quality of life
- Maintain IOP at or below a pressure at which further optic nerve damage is unlikely to occur.
- Educate and involve the patient in the management of their disease

Goals

Generally 2 aims in managing POAG

1. **Early detection –** to identify and diagnose the disease before the patient has lost significant vision
2. **Effective treatment –** to prevent further loss of vision

NB: the already lost vision could not be reversed with any treatment because the atrophied optic nerve fibers could not regenerate forever!

Approach to Treatment

- A **well-tolerated** ocular antihypertensive at the **lowest concentration** should be selected as the initial medication
- If monotherapy alone lowers IOP but does not reach target pressure, then **combination** therapy or **switching** to another agent is appropriate.
- Increasing the concentration or dose frequency can also be tried when possible .
- A uniocular trial can be used to assess safety and effectiveness of a topical medication prior to initiation in both eyes
  - Except in pts with very high IOP or advanced visual field loss

Non Pharmacologic Therapy

Laser and Surgical Procedures

- Laser trabeculoplasty, Trabeculectomy

When to use:

- ✓ Advanced glaucoma
- ✓ Failed medical treatment
- ✓ Poor drug compliance
- ✓ Drug intolerance
- ✓ Difficulty of follow up

Approach to Ocular HTN Pharmacotherapy

- 20% decrease in IOP can reduce the progression from ocular hypertension to POAG over a 5-year period
- Take in consideration of to identify risk factors for treatment =>IOP > 25 mm Hg, and CCT < 555 micrometers, FH, age, female gender, black, severe myopia, only with one eye
- Patients without risk factors typically are not treated => followed up for glaucomatous changes

Pharmacotherapeutic Approach

- **β-blockers**, the **prostaglandin analogs** (latanoprost, travoprost, and bimatoprost), **brimonidine** (an α_2-agonist), and the fixed combination product of **timolol** and **dorzolamide**

  - **β-blocker**: long history of successful use, providing a combination of clinical efficacy and tolerability

  - The newer ones: **prostaglandin analogs**, **brimonidine**, and **topical CAIs**, suitable first-line therapy or alternative initial therapy for pts C/I to BB

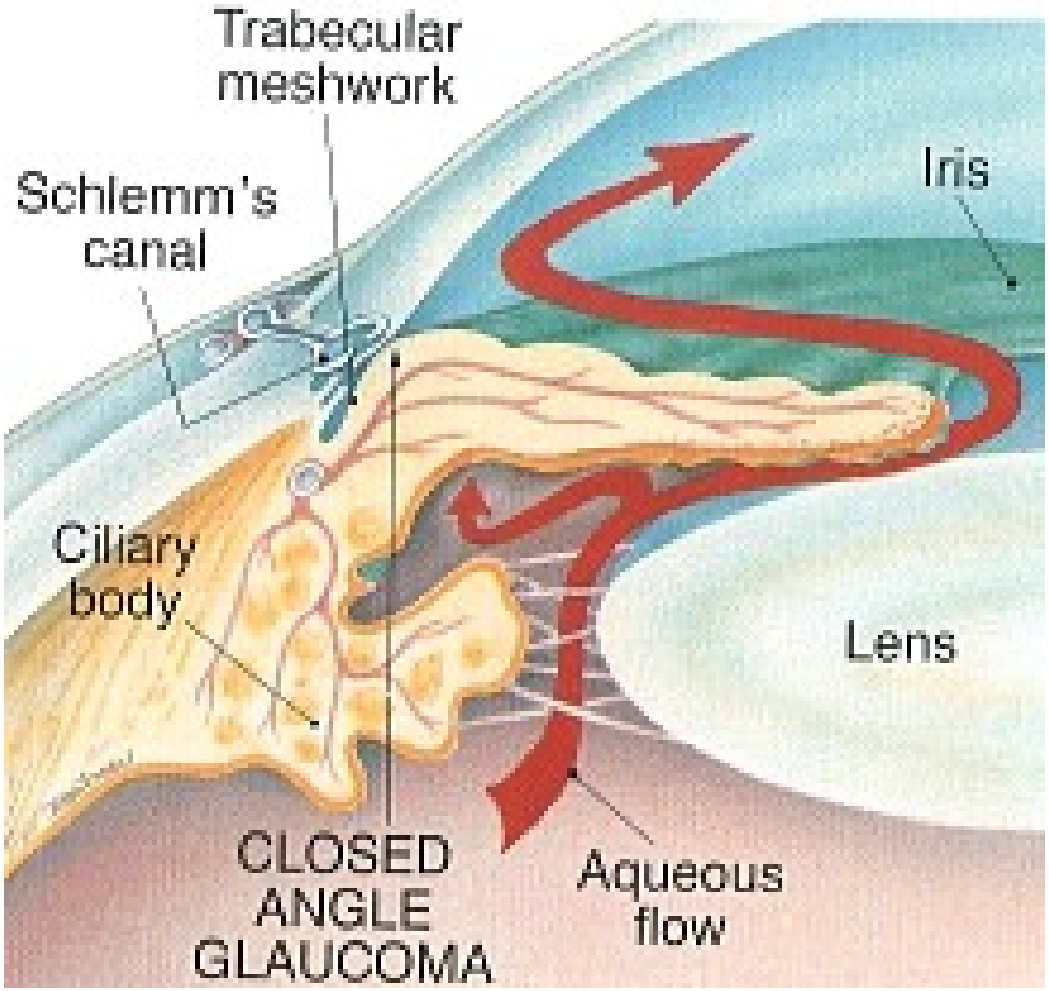
Pharmacotherapeutic Approach

- **Pilocarpine and dipivefrin** are used as third-line therapies
- **Carbachol**, topical cholinesterase inhibitors, and oral CAIs are considered last-line agents
- Controversies arise in use of BB, PG analogs and brimonidine, and laser therapy as 1st line choices

PACG – Angle Closure Glaucoma

- Mechanical obstruction of aqueous humor outflow through the trabecular meshwork by the peripheral iris
- Obstruction through **pupillary block** (peripheral iris to bow forward and obstruct the trabecular meshwork) and an abnormality of the iris called **iris plateau** (an anterior displacement of the peripheral iris)
- Impaired outflow causing IOP elevation at extreme levels that can lead to vision loss in hours to days

PACG – Angle Closure Glaucoma



PACG – Angle Closure Glaucoma

- Anatomic risk factors : smaller anterior chamber, thick, anteriorly displaced lens
- Medications: anticholinergics → mydriasis → pupilary block & iris plataeu

PACG – Angle Closure Glaucoma

Acute PACG symptoms –

- **Unilateral** in presentation, but the fellow eye is at risk
- **Sudden severe ocular pain, red eye, blurry vision**, halos around lights,
- Systemic symptoms may develop: nausea and vomiting, abdominal pain, headache, diaphoresis

PACG – Angle Closure Glaucoma

Signs

- ✓ Very high IOP, 40-60mmHg
- ✓ Decreased VA
- ✓ Marked conj. and ciliary injection
- ✓ Cornea: Cloudy, endothelial loss, correlates with duration of ↑IOP
- ✓ A/C: Shallow with fare and cells
- ✓ Pupil: Mid-dilated, sluggish and irregular

Treatment

Goals of Therapy

- To preserve visual function by controlling the elevation in IOP
- Manage an acute attack of angle closure
- Reverse or prevent angle closure using a laser and/or surgical intervention

General Approach

- **Iridectomy** (laser or surgical) is the definitive treatment of CAG
- Medical therapy is used to lower IOP, reduce pain, and reverse corneal edema prior to the iridotomy
- Drug therapy of an acute attack typically involves administration of pilocarpine, hyperosmotic agents, and a secretory inhibitor (a β-blocker, α_2-agonist, prostaglandin $F_2\alpha$ analog, or a topical or systemic CAI)
- Miotics /pilocarpine/- ineffective with high IOP/>60mmhg/, used to break the pupillary attack

General Approach

- **Oral glycerin** 1 to 2 g/kg or **intravenous mannitol** 1 to 2 g/kg – rapidly reduce IOP
  - Are among the first line drugs in acute CAG or other forms of acute very high IOP elevations
- **Topical corticosteroids /NSAIDS** often are used to reduce the ocular inflammation and reduce the development of synechiae in CAG eyes
- **Peripheral iridectomy** essentially “cures” primary CAG without significant synechiae
- Long-term drug therapy is not used unless indicated

General Approach

Surgical treatment

- ✓ **Laser irodotomy**; in few hours after the attach
- ✓ **Incisional iridectomy**; after 1 to 2 days
- ✓ **Peripheral laser iridoplasty**
- ✓ **Laser pupiloplasty**
- ✓ **Filtration surgery**: uncontrolled IOP
- ✓ **Prophylactic PI** to the fellow eye: 50 – 75% develop attack in 5 to 10 years
- ❖ Once IOP is controlled with 1st line agents, pilocarpine should be given QID until iridectomy is performed

Pharmacologic Agents Used in Glaucoma

β-BLOCKING DRUGS

- Betaxolol, Timolol, Carteolol, Levobunolol, Metipranolol
- Reduce aqueous humor production, lower IOP by 20% to 30%
- Are the agents of first choice in treating POAG if no CI
- Limitation: tachyphylaxis (20 to 50%)- need of additional agents
- Concomitant systemic B-blockers use doesn’t have additive IOP lowering effect rather more systemic SE

β-Adrenergic Blocking Agents

Drug	Strength (%)	Usual Dose	Mechanism of Action
Betaxolol	0.5	One drop twice a day	All reduce aqueous production of ciliary body
Timolol	0.25, 0.5	One drop every day—one to two times a day	

Prostaglandin Analogues

- Including **latanoprost**, travoprost, and bimatoprost,
- Reduce IOP by increasing the uveoscleral and to less extent trabecular outflow of aqueous humor
- Significant and sustainable IOP lowering effect than timolol
- The most potent of the topical glaucoma drugs
- Excellent systemic safety profile (reported symptoms are rare and mild and are flu like symptoms and joint pains)

Prostaglandin Analogues

- Very few systemic contraindications (pregnancy)
- Additive to the all the other topical medications
- First-line alternatives to topical β-blockers or 1st line by some authorities
- Limitation: **cost** – quite expensive
- S/E- iris pigmentation, **hypertrichosis**, darkening of the eyelashes, exacerbation of CME, uveitis

Prostaglandin Analogs

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Drug	Strength (%)	Usual Dose	Mechanism of Action
Latanoprost	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	0.01, 0.03	One drop every night	
Travoprost	0.004	One drop every night	
Tafluprost	0.0015	One drop every night	

α_2-Adrenergic Agonists

Selective(Alpha$_2$)

1. **Apraclonidine** (0.5%, 1%), short term use due to allergic rxn and tachycardia = no longer for POAG chronic Rx

   for post surgical IOP, tachyphylaxis!

2. **Brimonidine** (0.15%, 2%) – may have neuroprotective effect – on study
   - ✓ Reduce aqueous production
   - ✓ Increase Uveo-scleral outflow
   - ✓ Indicated for OAG and OHT – considered 1st line
   - ✓ Comparable in efficacy to timolol, lower IOP by 4 - 6mmHg
   - ✓ Contraindicated in children due to somnolence and lethargy

α_2-Adrenergic Agonists

Non selective

- Epinephrine and Dipivefrin – less commonly used, last line agents, increase both trabecular & uveoscleral out flow
- C/I – in narrow angles – aggravate CAG

α_2-Adrenergic Agonists

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Drug	Strength (%)	Usual Dose	Mechanism of Action
Apraclonidine	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine	0.15, 0.1	One drop two to three times a day	

Carbonic Anhydrase Inhibitors (CAIs)

- Decrease aqueous humor production
- Oral: **Methazolamide**, **Acetazolamide** (IV for CAG)– third-line agents
- **Topical** (tid) – **Dorzolamide** (2%), **Brinzolamide** (1%)
  - ✓ Equally effective and reduce IOP by 15% to 24% as monotherapy
  - ✓ Much less systemic SE than systemic CAIs - sulfa allergy a C/I
- No advantage of concomitant use of systemic and topical CAIs
- Side effects are usually dose related (oral)= paresthesias of the hands and feet, nausea, vomiting, and weight loss, systemic acidosis, hypokalemia, hyponatremia, unpleasant taste

Carbonic Anhydrase Inhibitors (CAIs)

Drug	Strength (%)	Usual Dose	Mechanism of Action
Topical			
Brinzolamide	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide	2	Two to three times a day	
Systemic			
Acetazolamide	125mg, 250mg, 500mg	125–250 mg two to four times a day	All reduce aqueous humor production of ciliary body
Methazolami	25 mg,	5–50 mg two	

Cholinergic Agonists

4th or 5th line use

- Additive effect with beta blockers, CAIs, alpha agonist and hyperosmotic agents
- Potential antagonistic effect with PG analogues, reduced uveoscleral outflow
- Pilocarpine and carbachol commonly used. C/I = severe myopia
- Pilocarpine in 1%, 2%, 4%, 6%, and 8% concentrations, Q6hrs
- Pilocarpine 4% gel = once daily use nocte.
- Used in all forms of chronic open angle glaucoma and some form of ACG

Hyperosmotic Agents

- Used in emergency condition like acute ACG with very high IOP
- Rarely used to reduce vitreous volume prior to surgery
- Mech: gradient b/n bld hyperosmolality and vitreous- dehydration and reduction of volume

Hyperosmotic Agents

- Oral

- **Glycerin** / Isosorbide 1.5 g/Kg (3ml/kg, 50% soln)

  Action: Onset 30 min, peak 60 min, duration 6 hrs

- Parenteral (IV)

- **Mannitol** 2 g/Kg (20%, 50% soln), 60 drops/min over 20 -30 min

  Action: peak 30 min, duration 6 hrs

- SE: Nausea and vomiting, confusion, headache, backache, intracranial hemorrhage, pulmonary edema, precipitate cardiac and renal failure and urinary retention,

ALLERGIC RHINITIS

Definition

- Rhinitis is inflammation of the lining of the nose and contiguous parts of the upper respiratory tract
- AR is an allergen-induced, immunoglobulin E (IgE)-mediated inflammatory condition of the lining of the nose and upper respiratory tract
- AR affects up to 30% of adults and 40% of children in the United States,
- The total direct and indirect costs of AR in the US were estimated to be about **11 billion USD** in 2005

Classification

- AR categorized as
  - **Seasonal allergic rhinitis (SAR):**
    - Attributed to inhaled allergens (aeroallergens) that have a seasonal variation.
    - Common allergens: grass, tree or weed pollens and substances from molds and fungi.
    - Usually encountered outdoors
  - **Perennial allergic rhinitis (PAR):**
    - Attributed to aeroallergens that are present in the patient's environment almost continuously throughout the year
    - Usually encountered indoors.
    - Common allergens: house dust mite, indoor molds and fungi, insects (especially cockroaches), and companion animals (pets)

Risk factors

- Family history of atopy (AR, asthma, eczema, or food allergies);
- Elevated serum IgE levels (especially before the age of 6 years);
- Higher socioeconomic class
- Positive skin test results
- Exposure to particulate air pollution
- Maternal smoking
- Firstborn status
- Emigration into a Western industrialized environment

Pathophysiology

- AR is an IgE-mediated disorder of people who are allergy prone.
- Initial contact is required to sensitize the patient to subsequent exposures.
- Many types of cells, mediators, and intermediate substances (including cytokines) are involved
- There is an early-phase and often a late-phase allergic response

Early phase

Trigger allergen becomes bound to IgE that is fixed to mast cells in the nasal mucosa

↓

Degranulate and release preformed mediators (histamine)

↓

Stimulates more mast cells and macrophages, eosinophils, and basophils to produce cysteine leukotrienes and prostaglandin D2

↓

Vasodilation, mucosal edema, and hypertrophy all contribute to nasal congestion, clear, watery, and often profuse rhinorrhea

Late phase

- Occurs in about 50% of AR sufferers.
- It can begin as soon as 2 hours after the early phase and usually peaks between 6 and 12 hours.
- It involves a second release of many of the mediators of the early phase.
- It is characterized by an inflammatory component caused by infiltration of several cell types into the nasal mucosa.
- The most significant manifestation during the late phase is nasal **congestion** that is often severe and long lasting

Clinical Presentation

- **Typical Symptoms**
  - **Rhinorrhea** (usually clear and bilateral; primarily anterior but may be posterior [postnasal drip])
  - **Sneezing**
  - **Itching** (mostly nasal, but also palate, throat, eyes, ears)
  - **Nasal congestion** (not in all patients, but when present, usually the most troublesome symptom)

Clinical Presentation

- **Other Symptoms**
  - Ocular manifestations (itch, redness, tearing, chemosis, periorbital edema)
  - Sleep disturbances often with fatigue, asthenia, malaise, and irritability
  - Presenteeism (impaired performance at work or school)
  - Absenteeism from work or school
  - Quality of life impairment (including social function)
  - Headache, mild facial or ear pain, or fullness
  - Cough (especially in those with concurrent asthma)
  - Children (especially): snorting, sniffling, clearing the throat, learning or attention problems, poor appetite

Treatment

- The goals of treatment of AR are
  - Minimize the frequency and severity of symptoms,
  - Prevent comorbid disorders and complications,
  - Improve the patient’s quality of life,
  - Improve work attendance and productivity and/school attendance/performance, and
  - Minimize adverse effects of therapy

Nonpharmacologic Therapy

- Avoidance of allergen triggers
  - To the extent they have been identified and to the extent such avoidance is possible

Pharmacologic Therapy

- **Routine first-line agents**
  - Intranasal corticosteroids
  - Oral (possibly intranasal) antihistamines.
- **Secondary agents**
  - Oral (rarely intranasal) decongestants,
  - Intranasal mast cell stabilizer cromone (cromolyn),
  - Oral leukotriene receptor antagonist (LTRA) (montelukast),
  - Intranasal antimuscarinic (ipratropium),
  - Intranasal saline irrigation.

Intranasal corticosteroids (INCS)

Corticosteroid	Mcg/ Dose	Usual adult dose
Beclomethasone	42 mcg	1–2 sprays twice daily
Budesonide	32 mcg	2 sprays once daily
Fluticasone	27.5 mcg	2 sprays once daily
Mometasone	50 mcg	2 sprays once daily

Administration Instructions for Intranasal Solution Medications

- Clear the nose of mucus and debris
- Do not tilt head backward. This increases drug lost down the esophagus
- Bend the head forward (flex the chin onto the chest) so that the nose is the lowest portion of the head
- Use the contralateral hand to insert the spray nozzle or dropper into one nostril (ie, the left hand for right nostril).
- Use the other hand to occlude the opposite nostril (the one not being medicated)
- Aim the spray or drops toward the outer (lateral) inside surface of each nostril and away from the nasal septum.
- Breath in slowly but deeply through the medicated nostril.
- Repeat this procedure to apply medication to the other nostril

2nd -Generation Antihistamine Products

Generic name	Usual adult dose
Cetirizine	5–10 mg once daily
Desloratadine	5 mg once daily
Loratadine	10 mg once daily



Thanks

