PHARMACOTHERAPY OF SHOCK

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DEFINITION

- *Shock refers to conditions manifested by hemodynamic alterations (e.g.,* hypotension, tachycardia, low cardiac output [CO], and oliguria) caused by:
  - Intravascular volume deficit (hypovolemic shock)
  - Myocardial pump failure (cardiogenic shock)
  - Peripheral vasodilation (septic, anaphylactic, or neurogenic shock)
- The underlying problem in these situations is inadequate tissue perfusion resulting from circulatory failure
- *Irrespective of the cause of shock, the*

PATHOPHYSIOLOGY

- Shock results in failure of the circulatory system to deliver sufficient oxygen (O2) to body tissues despite normal or reduced O2 consumption.
- General pathophysiologic mechanisms of different forms of shock are similar except for initiating events
- Hypovolemic shock is characterized by acute intravascular volume deficiency due to external losses or internal redistribution of extracellular water
- This type of shock can be precipitated by:
  - Hemorrhage, burns, trauma, surgery, intestinal obstruction

PATHOPHYSIOLOGY

- Relative hypovolemia leading to hypovolemic shock occurs during significant vasodilation:
  - Which accompanies anaphylaxis, sepsis, and neurogenic shock.
- Regardless of the etiology, fall in blood pressure (BP) is compensated by:
  - An increase in sympathetic outflow
  - Activation of the renin-angiotensin system
  - Other humoral factors that stimulate peripheral vasoconstriction

PATHOPHYSIOLOGY

- Compensatory vasoconstriction redistributes blood away from the:
  - Skin, skeletal muscles and GI tract toward vital organs (e.g., heart, brain) in an attempt to maintain oxygenation, nutrition, and organ function.
- Severe metabolic lactic acidosis often develops secondary to tissue ischemia and causes localized vasodilation,
  - Which further exacerbates the impaired cardiovascular state

CLINICAL PRESENTATION

- Shock presents with a diversity of signs and symptoms
- Patients with hypovolemic shock may present with:
  - Thirst, anxiousness, weakness, lightheadedness, and dizziness
  - Scanty urine output and dark-yellow-colored urine
  - Hypotension, tachycardia, tachypnea, confusion, and oliguria are common symptoms
  - Myocardial and cerebral ischemia, pulmonary edema (cardiogenic shock), and multisystem organ failure often follow

CLINICAL PRESENTATION

- Significant hypotension:
  - SBP less than 90 mm Hg) with reflex sinus tachycardia (greater than 120 beats/min) and increased
- RR more than 30 breaths/min are often observed in hypovolemic patients.
- Extremities cool to the touch and a “thready/weak” pulse
- May be cyanotic due to hypoxemia.
- Sweating results in a moist, clammy feel
- Digits will have severely slowed capillary refill

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CLINICAL PRESENTATION

- Mental status changes associated may range from subtle fluctuations in mood to agitation to unconsciousness.
- Respiratory alkalosis secondary to hyperventilation is usually observed secondary to:
  - CNS stimulation of ventilatory centers as a result of trauma, sepsis, or shock
- Lung auscultation may reveal:
  - Crackles (pulmonary edema) or absence of breath sounds (pneumothorax, hemothorax).
- Chest roentgenogram can confirm:
  - Early suspicions or disclose an undetected abnormality such as pneumonia (pulmonary infiltrates)

CLINICAL PRESENTATION

- Kidneys are exquisitely sensitive to changes in perfusion pressures
- Moderate alterations can lead to significant changes in glomerular filtration rate.
- Oliguria, progressing to anuria, occurs because of vasoconstriction of afferent arterioles.
- Redistribution of blood flow away from the GI tract may cause stress gastritis, gut ischemia, and, in some cases, infarction, resulting in GI bleeding.
- Progressive liver damage (shock liver) manifests as elevated serum hepatic transaminases and unconjugated bilirubin
- Impaired synthesis of clotting factors may increase prothrombin time (PT), international

DIAGNOSIS AND MONITORING

- Regardless of the etiology, consistent findings include:
  - SBP less than 90 mm Hg
  - Depressed cardiac index (CI less than 2.2 L/min/m2)
  - Tachycardia (HR greater than 100 beats/min)
  - Low urine output (less than 20 mL/hour).

DIAGNOSIS AND MONITORING

- Noninvasive assessment of BP using the sphygmomanometer and stethoscope may be inaccurate in the shock state
- A pulmonary artery (Swan-Ganz) catheter can be used to determine:
  - Central venous pressure (CVP)
  - Pulmonary artery pressure
  - CO
  - Pulmonary artery occlusive pressure (PAOP)
  - Approximate measure of the left ventricular end-diastolic volume and a major determinant of left ventricular preload

DIAGNOSIS AND MONITORING

- CO (2.5 to 3 L/min) and mixed venous oxygen saturation (70% to 75%) may be very low in a patient with extensive myocardial damage.
- Respiratory alkalosis is associated with low partial pressure of O2 (25 to 35 mm Hg) and alkaline pH, but normal bicarbonate
- The first two values are measured by arterial blood gas(ABG), which also yields partial pressure of carbon dioxide and arterial oxygen saturation
- Circulating arterial oxygen saturation can also be measured by an oximeter, which is a noninvasive method that is fairly accurate and useful at the patient's bedside

DIAGNOSIS AND MONITORING

- Renal function can be grossly assessed by hourly measurements of urine output:
  - But estimation of creatinine clearance based on isolated serum creatinine values in critically ill patients may yield erroneous/incorrect results.
- Decreased renal perfusion and aldosterone release result in sodium retention:
  - Thus, low urinary sodium (<30 mEq/24hr). (40-220/24hr

TABLE 12-1 Hemodynamic and Oxygen-Transport Monitoring Par

Parameter	Normal Value[a]
Blood pressure (systolic/diastolic)	100–130/70–85 mm Hg
Mean arterial pressure	80–100 mm Hg
Pulmonary artery pressure	25/10 mm Hg
Mean pulmonary artery pressure	12–15 mm Hg
Central venous pressure	8–12 mm Hg
Pulmonary artery occlusive pressure	12–15 mm Hg
Heart rate	60–80 beats/min
Cardiac output	4–7 L/min
Cardiac index	2.8–3.6 L/min/m^2
Stroke volume index	30–50 mL/m^2
Systemic vascular resistance index	1,300–2,100 dyne • sec/m^2 • cm^5
Pulmonary vascular resistance index	45–225 dyne • sec/m^2 • cm^5
Arterial oxygen saturation	97% (range 95–100%)
Mixed venous oxygen saturation	70–75%
Arterial oxygen content	20.1 vol% (range 19–21%)
Venous oxygen content	15.5 vol% (range 11.5–16.5%)
Oxygen content difference	5 vol% (range, 4–6%)
Oxygen consumption index	131 mL/min/m^2 (range, 100–180)
Oxygen delivery index	578 mL/min/m^2 (range, 370–730)
Oxygen extraction ratio	25% (range, 22–30%)
Intramucosal pH	7.40 (range, 7.35–7.45)
Index	Parameter indexed to body surface area

[a]Normal values may not be the same as values needed to optimize management of a critically ill patient.

DESIRED OUTCOME

- The initial goal is:
  - To support O2 delivery through the circulatory system by:
    - Assuring effective intravascular plasma volume
    - Optimal O2-carrying capacity
    - Adequate BP while definitive diagnostic and therapeutic strategies are being determined
- The ultimate goals are:
  - To prevent further progression of the disease with subsequent organ damage

GENERAL PRINCIPLES

- Supplemental O2 should be initiated at the earliest signs of shock, beginning with 4 to 6 L/min via nasal cannula or 6 to 10 L/min by face mask.
- Adequate fluid resuscitation to maintain circulating blood volume is essential in managing all forms of shock
- If fluid challenge does not achieve desired end points:
  - Pharmacologic support is necessary with inotropic and vasoactive drugs

FLUID RESUSCITATION FOR HYPOVOLEMIC SHOCK

- Initial fluid resuscitation consists of isotonic crystalloid (**0.9% sodium chloride or lactated Ringer's solution), colloid (5% Plasmanate or albumin, 6% hetastarch), or whole blood.**
- **Choice of solution is based on:**
  - **O2-** carrying capacity (e.g., hemoglobin, hematocrit)
  - Cause of hypovolemic shock
  - Accompanying disease states
  - Degree of fluid loss
  - Required speed of fluid delivery

FLUID RESUSCITATION FOR HYPOVOLEMIC SHOCK

- Most clinicians agree that crystalloids should be the initial therapy of circulatory insufficiency
- Crystalloids are preferred over colloids as initial therapy for burn patients
  - Because they are less likely to cause interstitial fluid accumulation
- If volume resuscitation is suboptimal following several liters of crystalloid:
  - Colloids should be considered

FLUID RESUSCITATION FOR HYPOVOLEMIC SHOCK

- Some patients may require blood products:
  - To assure maintenance of O2-carrying capacity
  - As well as clotting factors and platelets for blood hemostasis

Crystalloids

- Crystalloids consist of electrolytes (e.g., Na+, Cl–, K+) in water solutions, with or without dextrose
- **Lactated Ringer's solution may be preferred:**
  - Because it is unlikely to cause the hyperchloremic metabolic acidosis seen with infusion of large amounts of normal saline

CRYSTALLOID

- Advantages of crystalloids include:
  - Rapidity and ease of administration, compatibility with most drugs, absence of serum sickness/adverse reaction to serum, and low cost.
- The primary disadvantage is:
  - The large volume necessary to replace or augment intravascular volume
  - Approximately 4 L of normal saline must be infused to replace 1L of blood loss
  - Dilution of colloid oncotic pressure leading to pulmonary edema is more likely to follow crystalloid than colloid resuscitation.

COLLOIDS

- Colloids are larger molecular weight solutions (more than 30,000 daltons) that have been recommended for use in conjunction with or as replacements for crystalloid solutions
- **Albumin is a monodisperse colloid:**
  - Because all of its molecules are of the same molecular weight
- Whereas hetastarch and dextran solutions are polydisperse compounds
  - With molecules of varying molecular weights.

COLLOIDS

- The theoretical advantage of colloids is:
  - Their prolonged intravascular retention time compared to crystalloid solutions
- Isotonic crystalloid solutions have substantial interstitial distribution within minutes of IV administration
  - But colloids remain in the intravascular space for hours or days, depending on factors such as capillary permeability
- However, even with intact capillary permeability, the colloid molecules eventually leak through capillary membranes

COLLOIDS

- **Albumin 5% and 25% concentrations are available**
- It takes approximately three to four times as much lactated Ringer's or normal saline solution to yield the same volume expansion as 5% albumin solution
- However, albumin is much more costly than crystalloid solutions
- The 5% albumin solution is relatively iso-oncotic
- Whereas 25% albumin is hyperoncotic
  - Tends to pull fluid into the compartment containing the albumin molecules

- In general, 5% albumin is used for hypovolemic states.
- The 25% solution should not be used for acute circulatory insufficiency:
  - Unless diluted with other fluids or
  - Unless it is being used in patients with excess total body water
  - But intravascular depletion, as a means of pulling fluid into the intravascular space

COLLOIDS

- **Hetastarch 6%** has comparable plasma expansion to 5% albumin solution
- But is usually less expensive, which accounts for much of its use.
- Hetastarch should be avoided in situations in which short-term impairments in hemostasis could have adverse consequences
  - e.g., cardiopulmonary bypass surgery, intracranial hemorrhage
  - Because it may aggravate bleeding due to mechanisms such as decreased factor VIII activity
- Hetastarch may cause elevations in serum

- **Dextran-40, dextran-70, and dextran-75** are available for use as plasma expanders (the number indicates the average molecular weight × 1,000).
- These solutions are not used as often as albumin or hetastarch for plasma expansion
  - Possibly due to concerns related to aggravation of bleeding (i.e., anticoagulant actions related to inhibiting stasis of microcirculation) and anaphylaxis
  - Which is more likely to occur with the higher molecular weight solutions.

COLLOIDS

- Colloids (especially albumin) are expensive solutions, and a large study involving almost 7,000 critically ill patients found no significant difference in 28-day mortality between patients resuscitated with either normal saline or 4% albumin
- For these reasons, crystalloids should be considered first line therapy in patients with hypovolemic shock.
- Adverse effects of colloids are generally extensions of their pharmacologic activity (e.g., fluid overload, dilutional coagulopathy)
- **Albumin and dextran** **M**ay be associated with anaphylactoid reactions or

BLOOD PRODUCTS

- Whole blood could be used for large volume blood loss, but most institutions use component therapy, with crystalloids or colloids used for plasma expansion.
- **Packed red blood cells contain hemoglobin that increases the O2-carrying** capacity of blood, thereby increasing O2 delivery to tissues
  - This is a function not performed by crystalloids or colloids
- Packed red cells are usually indicated in patients with continued deterioration after volume replacement
- The product needs to be warmed before

BLOOD PRODUCTS

- **Fresh frozen plasma replaces clotting factors**
- **Although it is often overused,** the product is indicated if there is ongoing hemorrhage in patients with a PT or aPTT greater than 1.5 times normal, severe hepatic disease, or other bleeding disorders.
  - aPTT (20-35 second, PT (13-15 second)
- **Platelets are used for bleeding due to severe thrombocytopenia:**
  - **Platelet** counts less than 10,000/mm3 or
  - In patients with rapidly dropping platelet counts,

BLOOD PRODUCTS

- **Cryoprecipitate and factor VIII** are generally not indicated in acute hemorrhage but may be used once specific deficiencies have been identified.
- Risks associated with infusion of blood products include:
  - Transfusion related reactions
  - Virus transmission (rare),
  - Hypocalcemia resulting from added citrate
  - Elevations in serum potassium and phosphorus concentrations from use of stored blood that has hemolyzed
  - Increased blood viscosity from supranormal hematocrit elevations
  - Hypothermia from failure to appropriately warm solutions before administration

PHARMACOLOGIC THERAPY FOR SHOCK

- Inotropic agents and vasopressors are generally not indicated in the initial treatment of hypovolemic shock (assuming that fluid therapy is adequate)
  - As the body's normal response is to increase CO and constrict blood vessels to maintain BP
- However, once the cause of circulatory insufficiency has been stopped or treated and fluids have been optimized,
  - Medications may be needed in patients who

TABLE 12-2 Receptor Pharmacology of Selected Inotropic and Vasopressor Agents Used in Septic Shock[a]

Agent	α_1	α_2	β_1	β_2	D
Dobutamine (0.5–4 mg/mL D_5W or NS)					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	++++	+++	0
Dopamine (0.8–3.2 mg/mL D_5W or NS)					
1–3 mcg/kg/min	0	0	+	0	++++
3–10 mcg/kg/min	0/+	0	++++	++	++++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine (0.008–0.016 mg/mL D_5W or NS)					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0
>0.05–3 mcg/kg/min	++++	++++	+++	+	0
Norepinephrine (0.016–0.064 mg/mL D_5W)					
0.02–3 mcg/kg/min	+++	+++	+++	+/++	0
Phenylephrine (0.1–0.4 mg/mL D_5W or NS)					
0.5–9 mcg/kg/min	+++	+	+	0	0

[a]Activity ranges from no activity (0) to maximal (++++) activity.
D, dopamine; D_5W, dextrose 5% in water; NS, normal saline.

PHARMACOLOGIC THERAPY FOR SHOCK

- Pressor agents such as **norepinephrine and high-dose dopamine** should be avoided if possible:
  - Because they may increase BP at the expense of peripheral tissue ischemia
- In patients with unstable BP despite massive fluid replacement and increasing interstitial fluid accumulation:
  - Inotropic agents such as **dobutamine** are preferred if BP is adequate (SBP 90 mm Hg

PHARMACOLOGIC THERAPY FOR SHOCK

- When pressure cannot be maintained:
  - With inotropes, or
  - When inotropes with vasodilatory properties cannot be used due to concerns about inadequate BP
    - Pressors may be required as a last resort
- The choice of vasopressor or inotropic agent in septic shock should be made

PHARMACOLOGIC THERAPY FOR SHOCK

- The traditional approach is to start with:
  - **Dopamine, then norepinephrine; dobutamine** is added for low CO states, and occasionally **epinephrine and phenylephrine** are used when necessary
- **However,** recent observations of:
  - Improved outcomes with norepinephrine and
  - Decreased regional perfusion with dopamine:

PHARMACOLOGIC THERAPY FOR SHOCK

- Potent vasoconstrictors such as norepinephrine and phenylephrine should be:
  - Given through central veins due to the possibility of extravasation and tissue damage with peripheral administration.
- Careful monitoring and calculation of infusion rates are advised:
  - Because dosing adjustments are made frequently and varying admixture

DOPAMINE

- Is often the initial vasopressor used in septic shock
  - Because it increases BP by increasing myocardial contractility and vasoconstriction.
- Although dopamine has been reported to have dose-related receptor activity at D1, β1, and α1 receptors
  - This dose–response relationship has not been confirmed in critically ill patients.
- In patients with septic shock, there is overlap of hemodynamic effects with doses as low as 3 mcg/kg/min

DOPAMINE

- Doses of 5 to 10 mcg/kg/min are initiated to improve MAP
- In septic shock, these doses increase CI by:
  - Improving ventricular contractility
  - Heart rate
  - MAP
  - Systemic vascular resistance (SVR).
- The clinical utility of dopamine in septic shock is limited because:
  - Large doses are frequently necessary to maintain CO and MAP

DOPAMINE

- At doses above 20 mcg/kg/min, there is limited further improvement in cardiac performance and regional hemodynamics
- The use of dopamine is also hampered frequently by tachycardia and tachydysrhythmias.
- Other adverse effects limiting its use in septic shock include:
  - Increases in PAOP
  - Pulmonary shunting

DOPAMINE

- Dopamine should be used with caution in patients with elevated preload, as it may worsen pulmonary edema
- Low doses of dopamine (1 to 3 mcg/kg/min) once were advocated for use in patients with septic shock receiving vasopressors with or without oliguria
- The goal of therapy is:
  - To minimize or reverse renal vasoconstriction caused by other pressors

DOPAMINE

- Based on recent clinical trial results:
  - Low-dose dopamine for treatment or
  - Prevention of acute renal failure
  - Cannot be justified and should be eliminated from routine clinical use

NOREPINEPHRIN

- Is a combined α- and β-agonist, but:
  - It primarily produces vasoconstriction, thereby increasing SVR
- It generally produces either no change or a slight decrease in CO
- Norepinephrine is initiated after:
  - Vasopressor doses of dopamine (4 to 20 mcg/kg/min), alone or
  - In combination with dobutamine (5 mcg/kg/min), fail to achieve the desired goals
- Doses of dopamine and dobutamine are kept constant or stopped;
  - In some instances, dopamine is kept at low doses for purported renal protection

NOREPINEPHRIN

- Norepinephrine, 0.01 to 2 mcg/kg/min:
  - Reliably and predictably improves hemodynamic parameters to normal or supranormal values in most patients with septic shock
- Recent data suggest that norepinephrine should potentially be repositioned as the vasopressor of choice in septic shock

DOBUTAMINE

- is primarily a selective β1-agonist with mild β2 and vascular α1 activity:
  - Resulting in strong positive inotropic activity without concomitant vasoconstriction
- Dobutamine produces a larger increase in CO and is less arrhythmogenic than dopamine
- β2-induced vasodilation and the increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to a decrease in SVR
- Even though dobutamine is optimally used for low CO states with high filling pressures or in cardiogenic shock,
  - Vasopressors may be needed to counteract arterial vasodilation.

DOBUTAMINE

- The addition of dobutamine (held constant at 5 mcg/kg/min) to epinephrine regimens can improve gastric mucosal perfusion
- Dobutamine should be started with doses ranging from 2.5 to 5 mcg/ kg/min
- Doses above 5 mcg/kg/min provide limited beneficial effects on O2 transport values and hemodynamics and may increase adverse cardiac effects
- Infusion rates should be guided by clinical end points and mixed venous oxygen saturation/central venous oxygen saturation
- Decreases in partial pressure of O2, as well as myocardial adverse effects such as tachycardia, ischemic changes on ECG, tachydysrhythmias and hypotension are

PHENYLEPHRINE

- is a pure α1-agonist and is thought to increase BP through vasoconstriction
- It may also increase contractility and CO
- Phenylephrine may be beneficial in septic shock:
  - Because of its selective α-agonism, vascular effects, rapid onset, and short duration
- Phenylephrine may be a useful alternative:
  - In patients who cannot tolerate the tachycardia or tachydysrhythmias with use of dopamine or norepinephrine
  - In patients with known underlying myocardial dysfunction

PHENYLEPHRINE

- It is generally initiated at dosages of 0.5 mcg/kg/min and may be titrated every 5 to 15 minutes to desired effects
- Adverse effects such as:
  - Tachydysrhythmias are infrequent when it is used as a single agent or with higher doses.

EPINEPHRINE

- Has combined α- and β-agonist effects and has traditionally been reserved as the vasopressor of last resort
  - Because of reports of peripheral vasoconstriction, particularly in the splanchnic and renal beds
- At the high infusion rates used in septic shock, α-adrenergic effects are predominantly seen
  - SVR and MAP are increased
- It is an acceptable single agent in septic shock due to its combined vasoconstrictor and inotropic effects
- Epinephrine may be particularly useful when used earlier in the course of septic shock in:
  - Young patients and those without known cardiac abnormalities

EPINEPHRINE

- Infusion rates of 0.04 to 1 mcg/kg/min alone increase hemodynamic and O2 transport variables to supranormal levels without adverse effects in patients without coronary heart disease
- Smaller doses (0.1 to 0.5 mcg/kg/ min) are effective if dobutamine and dopamine infusions are kept constant
- Caution must be used before considering epinephrine for managing hypoperfusion in:
  - Hypodynamic patients with coronary artery disease to avoid:
    - Ischemia
    - Chest pain

VASOPRESSIN

- Causes vasoconstrictive effects that, unlike adrenergic receptor agonists, are preserved during hypoxia and severe acidosis
- It also causes vasodilation in the pulmonary, coronary, and selected renal vascular beds that may reduce pulmonary artery pressure and preserve cardiac and renal function
- However, based on available evidence, vasopressin is not recommended as a replacement for norepinephrine or dopamine in patients with septic shock but may be considered in patients who are refractory to catecholamine vasopressors

CORTICOSTEROIDS

- Were shown in a metaanalysis to improve hemodynamics and survival and reduce the duration of vasopressor support in septic shock
- Corticosteroids can be initiated in septic shock when adrenal insufficiency is present or when weaning of vasopressor therapy proves futile/useful result
- A daily dose equivalent to 200 to 300 mg hydrocortisone should be continued for 7 days.
- Adverse events are few because of the short duration of therapy

JOIN AND BONE DISORDERS

GOUT AND HYPERURICEMIA

INTRODUCTION

- **Uric acid** is a waste product of the breakdown of purines contained in the DNA of degraded body cells and dietary protein.
- Uric acid is water soluble and excreted primarily by the kidneys, although some is broken down by colonic bacteria and excreted via the GIT
- Gout results from an **increased body pool of urate with hyperuricemia.**

- It typically is characterized by:
  - Episodic acute and chronic arthritis
  - Caused by deposition of monosodium urate crystals (MSU) in:
    - Joints
    - Connective tissue tophi (**acid deposit in body:** a hard deposit of crystalline uric acid and its salts in cartilage, joints, or skin
    - The risk for deposition in kidney interstitium or uric acid nephrolithiasis

INTRODUCTION

- Gout is a disease that most commonly manifests as recurrent episodes of ***acute joint pain and inflammation secondary to the deposition of monosodium urate (MSU) crystals in the synovial fluid and lining***.
- MSU deposition in the urinary tract can cause ***urolithiasis*** and ***urinary obstruction***.
- Although gout is often associated with hyperuricemia
  - Elevated serum uric acid (SUA) is not a prerequisite for this painful condition.
- Hence, ***gout should be considered as a clinical diagnosis and hyperuricemia***

11/11/2025

EPIDEMEOLOGY

- Gout is the most common inflammatory arthritis in the United States and western Europe.
- Recent epidemiologic data indicate that the prevalence of gout is also increasing in less-industrialized Eastern countries.
- The ***incidence increases with age*** and appears to be rising probably because of a ***larger number of patients with risk factor***s for gout.

- ***Gout is a metabolic disease that most often affects middle-aged to elderly men and postmenopausal women***.

Conditions Associated with Hyperuricemia

- Primary gout
- Diabetic ketoacidosis
- Myeloproliferative disorders
- Lactic acidosis
- Lymphoproliferative disorders
- Starvation
- Chronic hemolytic anemia
- Toxemia of pregnancy
- Pernicious anemia
- Glycogen storage disease type 1
- Psoriasis
- Hypoxanthine-guanine phosphoribosyltransferase deficiency
- Polycythemia vera
- Renal transplantation
- Obesity
- Sarcoidosis
- Congestive heart failure
- Renal dysfunction
- Down syndrome
- Lead toxicity
- Hyperparathyroidism
- Acute alcoholism
- Hypoparathyroidism
- Acromegaly
- Hypothyroidism
- Phosphoribosylpyrophosphate synthetase overactivity
- Berylliosis

PATHOPHYSIOLOGY

- Gout is caused by an abnormality in uric acid metabolism.
- Free urate crystals can activate several ***proinflammatory mediators***, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-8.
- Activation of these mediators signals chemotactic movement of ***neutrophils*** into the joint space that "ingest" monosodium urate crystals via ***phagocytosis***.
- These neutrophils then are lysed and release proteolytic enzymes that trigger the clinical manifestations of an acute gout attack such as pain and swelling.
- These inflammatory mechanisms in gout, especially in untreated disease, ***can lead to cartilage and joint destruction.***

Pathophysiology…..

- *Increased free ureate cystal*
- *Activation of proinflammatory mediators*
- *chemotactic movement of neutrophils into the joint space that "ingest" MSU via phagocytosis*
- *neutrophils then are lysed and release proteolytic enzymes*
- *Joint pain and swelling*

PATHOPHYSIOLOGY

- The increased serum uric acid involves either;
  - ***the underexcretion of uric acid (90% of patients) or***
  - ***its overproduction/10%/***
- The cause of overproduction or underexcretion of uric acid in most gout patients is ***unknown***; this is referred to as **primary gout**
- Uric acid excretion is reduced in patients with ***chronic kidney disease***, putting them at risk for hyperuricemia.
- In patients with persistently acidic urine and hyperuricemia, uric acid **nephrolithiasis can occur in up to 25% of patients; in** severe cases, uric acid stones can cause ***nephropathy and renal failure***

Drug associated hyperuricemia

Drug	Mechanism	Comments
Certain antiretrovirals[121–125]	Catabolic effect; NRTIs may increase urate through mitochondrial toxicity	NRTIs: Uric acid blood increases of 0.5–5 mg/dL have occurred in patients receiving >9.6 mg/kg/day of didanosine. Stavudine also was associated with increased uric acid. PIs: Have been associated with elevated uric acid. Ritonavir and ritonavir boosting have been associated with gout.
Cyclosporine[126,127]	Decreased urate renal clearance, either via a tubular mechanism or decrease in GFR	Cyclosporine-induced hyperuricemia may cause gout in patients with risk factors (renal dysfunction, concurrent diuretics, and male gender).
Cytotoxic chemotherapy[85]	Rapid cell lysis	Occurs primarily with lymphomas and leukemias. Uric acid nephropathy, acute renal failure, and nephrolithiasis can result.
Diuretics[128–132]	Secondary to volume contraction and increased uric acid reabsorption in the proximal tubules for all diuretics; thiazides may also competitively inhibit proximal tubular secretion	Dose- and duration-dependent elevations in uric acid
Ethambutol[133]	Decreased urate renal clearance	Hyperuricemia and gout have been demonstrated. A majority of patients were receiving 20 mg/kg/day orally.
Ethanol[65,134]	Increased uric acid production due to adenine nucleotide turnover, lead-tainted moonshine and/or high purine content in some alcoholic beverages, such as beer	Associated with increased uric acid and acute gout. Even a light-to-moderate amount triggers recurrent gout attacks within 24 hours.
Filgrastim[135]	Increased WBC production	Transient effect, seen more often with higher doses (30–60 mg/kg/day).
Isotretinoin[136]	Hypervitaminosis A	Hyperuricemia and rare gout cases have been reported.

Drug associated hyperuricemia..

Drug	Mechanism	Comments
Levodopa[137]	Inhibition of urate excretion	Patients taking therapeutic doses have experienced hyperuricemia and gout. Secondarily, interference with colorimetric assay of uric acid may contribute a false-positive increment.
Niacin[138,139]	Decreases excretion of urate	Hyperuricemia and gout have occurred.
Pancreatic enzymes: pancreatin and pancrelipase[140]	Ingestion of pancreatic enzyme products having high purine content.	Hyperuricemia, hyperuricosuria, and uric acid crystalluria have occurred with high dosages.
Pyrazinamide[141,142]	Inhibition of renal tubular urate secretion	Hyperuricemia is more common with daily than with intermittent administration. Gouty attacks have occurred in those with a history of gout. Asymptomatic hyperuricemia was the only manifestation seen in one trial of pediatric patients.
Ribavirin and interferon[143]	Mechanism unclear; commonly associated with hemolysis	Nephrolithiasis developed in a patient with diabetes and hypertension. Hyperuricemia noted in 24% of those receiving ribavirin with interferon.
Aspirin (low dose)[87]	Inhibition of proximal tubular secretion of urate	Doses <1 g/day cause hyperuricemia.
Tacrolimus[144,145]	Reduced urate excretion	Associated with hyperuricemia and cases of gout; however, two prior case reports demonstrated resolution of polyarticular gout after switching cyclosporine to tacrolimus.
Teriparatide[146]	Mechanism unknown	Elevated uric acid levels, mainly with higher doses and with moderate renal impairment, but no association with increased gout, arthralgia or nephrolithiasis.
Theophylline[147,148]	Interference with uric acid assay	False-positive elevation with automated Bittner adapted method. Interference does not appear to occur with phosphotungstate assay method.

COMPLICATIONS

- *Long-term consequences of gout and hyperuricemia include;*
  - *joint destruction*
  - *tophi*
  - *nephrolithiasis.*
  - *Renal failure*
- Tophi are hard nodules of MSU crystals that have deposited in soft tissues and are most commonly found in the toes, fingers, and elbows.

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 monarticular, 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.

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.

PRESENTATION OF ACUTE GOUTY ARTHRITIS

Laboratory Tests

- The white blood cell (WBC) count in peripheral blood may be only mildly elevated.
- The serum uric acid level often is elevated but may be normal during an acute attack.
- Other laboratory markers of inflammation [e.g., increased erythrocyte sedimentation rate (ESR)] are often present.

PRESENTATION OF ACUTE GOUTY ARTHRITIS

- Acute arthritis is the most common early clinical manifestation of gout.
- The ***first episode of acute gouty arthritis frequently begins at night*** with dramatic joint pain and swelling.
- Joints rapidly become ***warm, red, and tender, with a clinical appearance that often mimics that of cellulitis***
- Large and gritty deposits- **tophi**

clin./ presentation…



Tophaceous gout



Acute gout attack of the first metatarsophalangeal joint

DIAGNOSIS

- Aspiration of affected joint fluid
  - Joint fluid has an elevated WBC count with neutrophils predominating.
- a 24-hour urine collection/rare/
  - to determine if the patient is an overproducer or an under excretor of uric acid
- Radiographs of affected joints

Criteria for Diagnosis of Gout (at least six criteria are needed for diagnosis unless MSU crystals are present in joint fluid aspirate)

1. More than one acute attack of arthritis
2. Attack of monoarticular arthritis
3. Joint inflammation maximal within 1 day
4. Negative synovial joint fluid culture
5. Erythema over involved joint(s)
6. Podagra (first metatarsophalangeal joint)
7. Unilateral podagra
8. Unilateral attack involving tarsal joint
9. Tophi
10. Hyperuricemia
11. Asymmetric swelling within a joint on radiograph
12. Subcortical cysts without erosions on radiograph

TREATMENT

- Treatment of gout involves ;
- (1) acute relief of a gouty arthritis attack and
- (2) long-term maintenance treatment to prevent future attacks
  - ANTIHYPERURICEMIC GOUT PROPHYLAXIS
    - Increasing uric acid excretion/uricosurics
    - Decreasing synthesis

TREATMENT

- **Desired Outcomes**
- ***The goals of therapy of an acute attack are***;
- (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

NONPHARMACOLOGIC THERAPY

- Control of body weight
- Low-purine diet
- Increase in liquid intake
- ***Limitation of alcohol consumption***
- Decreased use of fructose-containing foods and beverages
- Avoidance of diuretics

PHARMACOLOGIC THERAPY

- **For acute attacks/gouty arithrits;**
  - **Antiinflammatory agents**
    - **NSAIDs**
    - **Colchicine,**
    - **Corticosteroids are used**
- Selection depends on several patient factors, **especially renal function.**
- Generally, the earlier in the course of the arthritic attack these agents are employed, the better the outcome.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- These agents are ***most effective when given within the first 24 hours of the onset of pain***.
- Most studies have shown similar results among agents, and all NSAIDs are considered to be effective.
- Doses at the higher end of the therapeutic range are often needed.
- Indomethacin was used traditionally, but its relative cyclooxygenase-1 (COX-1) selectivity theoretically increases its gastropathy risk.
- Thus other generic NSAIDs may be preferred

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- **Commonly used drugs and dosages are as follows**:
  - **Indomethacin [Indocin]—50 mg 4 times daily for 3 to 6 days**
  - **Naproxen [Naprosyn]—500 mg 2 or 3 times daily for 3 to 6 days**
  - **Diclofenac sodium [Voltaren]—50 mg 3 times daily for 3 to 6 days**
- There is no good evidence that any NSAID is superior to the others for treatment of gout.
- NSAIDs generally **should be avoided** in patients;
  - At risk for peptic ulcers,
  - Taking warfarin, and
  - With renal insufficiency or
  - With uncontrolled hypertension
  - With heart failure

COLCHICINE

- Colchicine is thought to exert its ***anti-inflammatory effects*** by ***interfering with the function of mitotic spindles in neutrophils by binding of tubulin dimers***;
  - This inhibits phagocytic activity…. ***no subsequent release of lysosomal enzymes***
  - Whose effects are ***specific for gout***.
- It is ***used infrequently today because of its low therapeutic index.***
- Oral colchicine is absorbed rapidly from the GIT and metabolized extensively in the liver.

COLCHICINE

- Colchicine is toxic to any tissue that has a large percentage of proliferating cells.
- Disruption of cell division underlies the GI toxicity of the drug.
- **Precautions**
  - Elderly and debilitated patients,
  - In patients with cardiac, renal, and GI diseases.
  - Classified in FDA Pregnancy Risk Category C (for oral use) and Category D (for IV use).

COLCHICINE

- For an acute gouty attack, the dosage is 1.2 mg initially followed by 1.2 mg every 1 to 2 hours.
- The usual dosage for prophylaxis is 0.6 mg/day
- ***The most characteristic side effects;***
  - ***nausea, vomiting, diarrhea, abdominal pain***
  - bone marrow suppression,
  - renal failure,
  - hepatic necrosis,
  - seizures, and death

CORTICOSTEROIDS

- Systemic corticosteroids are a useful option in:
  - Patients with C/I to NSAIDs or colchicine (primarily renal impairment) or
  - Polyarticular attacks, especially in elderly patients.
  - Patients with severe gout that is unresponsive to NSAIDs.
- A single IM. injection of a long acting corticosteroid such as triamcinolone hexacetonide may be used.
- Oral agents may be needed, especially for severe attacks.
- ***Prednisone 40 to 60 mg*** (or an equivalent dose of another agent) is given daily, with a

CORTICOSTEROIDS

- Short-term adverse effects from corticosteroids include
  - fluid retention,
  - hyperglycemia,
  - central nervous system stimulation,
  - weight gain, and
  - increased risk of infection.
- *Patients with diabetes should have blood glucose levels monitored carefully during the corticosteroid course.*
- Too rapid tapering of corticosteroids can cause a ***rebound gouty flare;***
  - ***Low dose*** colchicine (0.6 mg PO daily) used

Dosage regimen for acute treatment

Drug	Dose
Drugs for Treatment of Acute Gout	
NSAIDs[a]	
Fenoprofen	800 mg PO q 6 hour
Flurbiprofen	100 mg PO qid for 1 day, then 50 mg PO qid
Ibuprofen	600 to 800 mg PO qid
Indomethacin*	150–200 mg PO daily (in 3 divided doses) for three days, then 100 mg PO daily (in 2 divided doses) for 4 to 7 days
Indomethacin*	50 mg PO tid
Ketoprofen	50 mg PO qid or 75 mg PO tid
Meclofenamate	100 mg PO tid to qid
Naproxen*	1000 mg daily × 3 days, then 500 mg daily × 7 days *or* 750 mg PO initially, then 250 mg PO q8h
Piroxicam	40 mg PO once daily
Sulindac*	200 mg bid × 7 to 10 days
Tolmetin	400 mg PO tid to qid
Celecoxib	200 mg PO bid
Meloxicam	7.5–15 mg PO once daily
Colchicine	0.6 mg PO every hour for up to 3 doses, then 0.6 mg 1–2 times daily if desired before antihyperuricemic therapy is started; may occasionally use in low doses for prophylaxis; avoid the intravenous formulation
Local corticosteroids	
Methylprednisolone	10–40 mg × 1 dose by intraarticular injection
Systemic corticosteroids	
Prednisone (example)	40–60 mg PO once daily × 3 days, then decrease by 10 mg every 3 days
Triamcinolone acetonide	60 mg × 1 dose by intramuscular injection

2. ANTIHYPERURICEMIC GOUT PROPHYLAXIS

- **Hyperuricemia—defined** as blood uric acid above 7 mg/dL in men, or 6 mg/dL in women.
- The decision to initiate hypouricemic therapy usually is made taking into ***considerations***;
  - The **number of acute attacks** /after two attacks),
  - Serum ***uric acid levels*** [progression is more rapid in patients with serum uric acid ***>535 mol/L*** (>9.0 mg/dL)],
  - The patient's ***willingness*** to commit to lifelong therapy, or
  - The presence of ***uric acid stones***

2. ANTIHYPERURICEMIC GOUT PROPHYLAXIS

- **XANTHINE OXIDASE INHIBITORS/*decreasing uric acid production /***
  - **allopurinol**
- ***URICOSURICS / increasing its excretion/***
  - **Probenecid**
  - **febuxostat**
  - **Benzbromarone**

ALLOPURINOL/XANTHINE OXIDASE INHIBITOR

- Used ***empirically***, because;
  - ***effective in both overproducers and underexcretors***
  - generally well tolerated
  - ***patients with renal disease***
- The drug and its primary active metabolite, oxypurinol, reduce serum uric acid concentrations by ***inhibiting the enzyme xanthine oxidase***, thereby blocking the

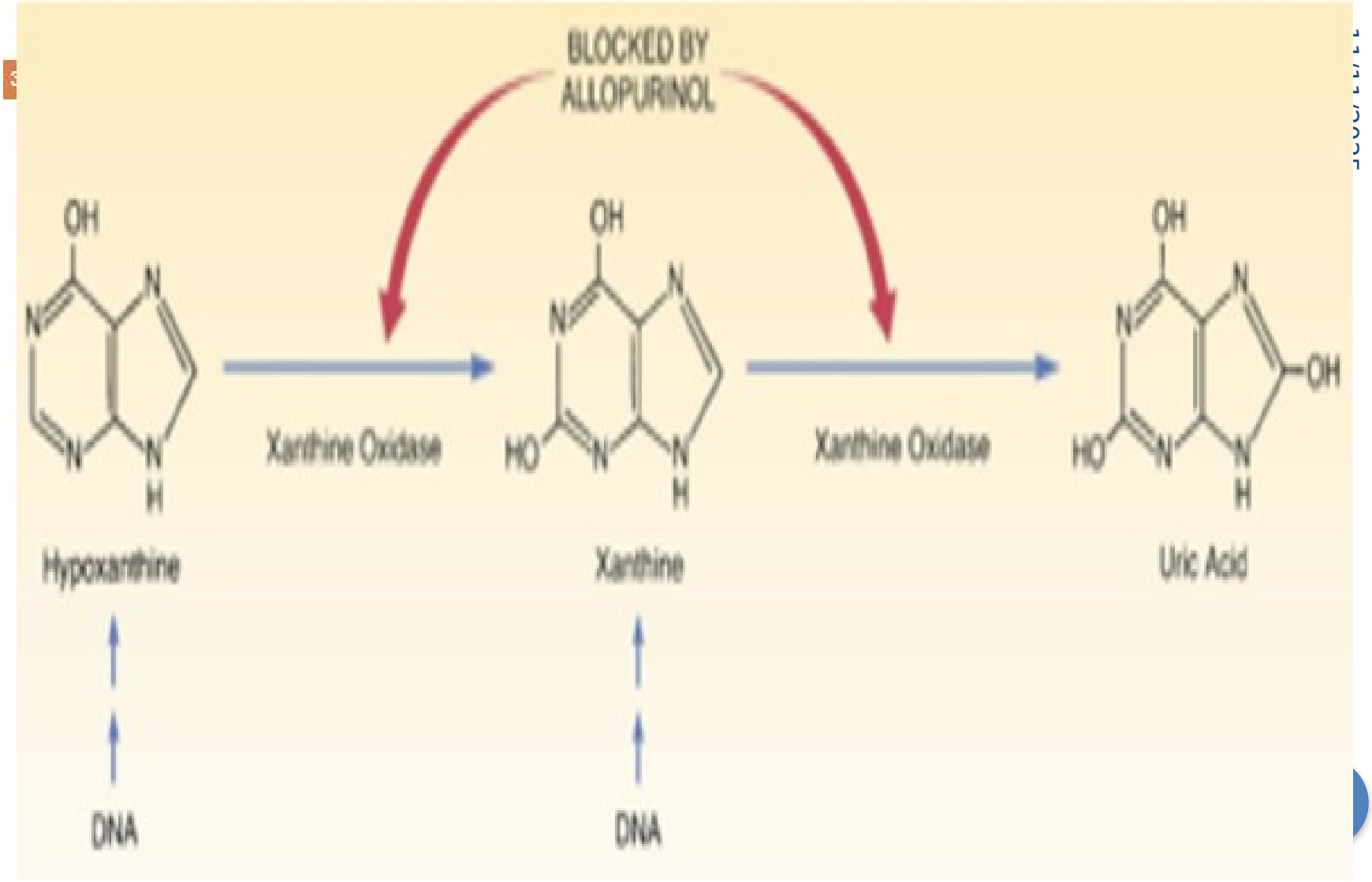
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ALLOPURINOL

- Current drug of choice for **chronic tophaceous gout.**
- Can also be used for hyperuricemia that develops secondary to cancer chemotherapy and to certain blood dyscrasias/blood disorders, such as polycythemia vera, myeloid metaplasia, and leukemia.
- To minimize ***chemotherapy induced hyperuricemia***, allopurinol should be administered before chemotherapy starts
- Why does hyperuricemia develop during chemotherapy?
  - Because, when cells die, breakdown of DNA releases uric acid.

11/11/2025

Reduction of uric acid formation by allopurinol



ALLOPURINOL

- 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.
- Allopurinol ***should not be started during an acute gout attack*** because sudden shifts in serum uric acid levels may precipitate or exacerbate gouty arthritis.
- Rapid shifts in serum uric acid can change the concentration of ***monosodium urate crystals in synovial fluid***, causing more crystals to precipitate.
- Thus some clinicians advocate a ***prophylactic dose of colchicine (0.6 mg/day) during initiation of antihyperuricemic therapy.***
- Acute episodes should be treated appropriately before maintenance treatment is started

ALLOPURINOL DOSING

- The **initial dose of allopurinol is based on the patient's renal function.**
- Patients with CrCl of ≤50 mL/minute
  - a starting dose of ***<300 mg/day*** to minimize AKI.
- It is reasonable to reduce the dose temporarily in patients who develop reversible acute renal failure.
- Serum uric acid levels must be monitored periodically, with the first follow-up level obtained 6 months (or sooner) after starting therapy
- The ***target serum uric acid level is less than 6 mg/dL*** (less than 357 µmol/L).
- The dose should be titrated upward (to a maximum of 800 mg/day) or downward as these levels dictate.

ADVERSE EFFECTS OF ALLOPURINOL

- Allopurinol generally is well tolerated;
  - ***nausea and diarrhea occur in a small percentage of patients.***
  - ***A generalized, maculopapular rash occurs in about 2% of patients.***
  - ***Stevens-Johnson syndrome.***
  - **allopurinol hypersensitivity syndrome*/ most feared side effect.***
    - ***severe desquamating skin lesions, high fever (usually greater than 39°C or 102.2°F), hepatic dysfunction, leukocytosis with predominant eosinophilia, and renal failure.***
- Although rare, this severe reaction has a 20% mortality rate.
- Patients with a history of the syndrome should never again receive allopurinol

DRUG INTERACTIONS OF ALLOPURINOL

- Potentiates the effects of/inhibiting metabolism.
  - ***warfarin***
  - ***Azathioprine (immunosupressant)***
  - ***6-mercaptopurine***
  - ***theophylline***
- ***the dose of these drugs must be reduced by 75% with allopurinol cotherapy.***
- ***ampicillin - rash***

URICOSURICS/PROBENECID

- Probenecid is a uricosuric agent that ***blocks the tubular reabsorption of uric acid, increasing its excretion.***
- ***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 creatinine clearance is 50 mL/minute or less***.
- Its uricosuric effect is ***counteracted by low aspirin doses***, which many patients receive for prophylaxis of coronary heart disease.

URICOSURICS/PROBENECID

- Urine volume must be maintained by ingestion of 1500 mL of water every day.
- Probenecid can be started at a dose of ***250mg twice daily*** and increased gradually as needed up to 3g per day to maintain a serum uric acid level <360 mol/L (6 mg/dL).

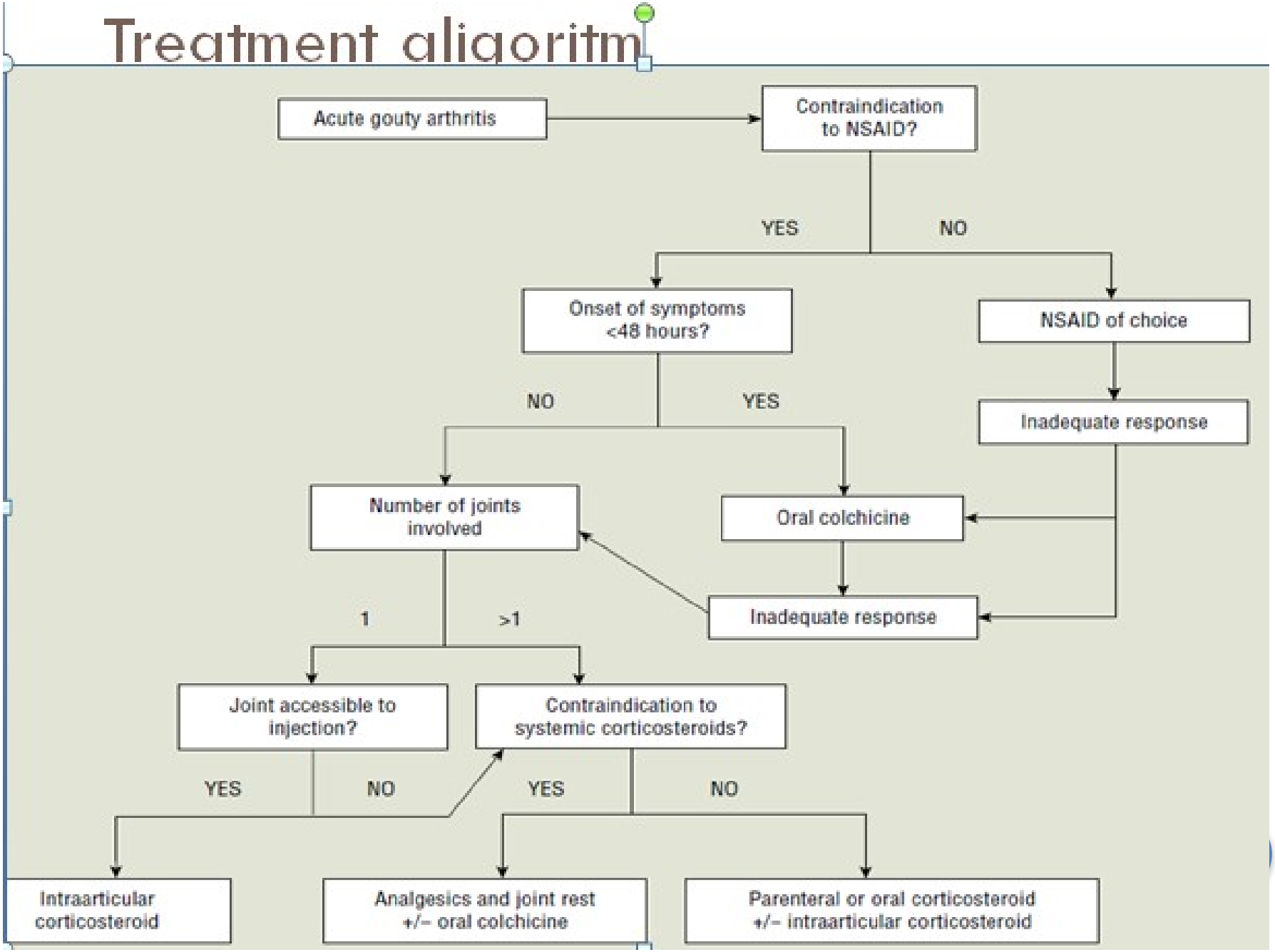
ADVERSE EFFECTS OF PROBENECID

- GIT effects: nausea
- Fever
- Rash
- Rarely, hepatic toxicity.
- Patients should be instructed to maintain an ***adequate fluid intake and urine output to decrease the risk of uric acid stone formation.***
- Some experts advocate ***alkalinizing the urine to decrease this risk.***

OTHER URICOSURICS

- ***Losartan*** increases both uric acid excretion and urine pH and may be an option in hypertensive patients with gout.
- ***Fenofibrate*** is also a uricosuric and may be appropriate in selected dyslipidemic patients with gout.
- New agents undergoing investigation for hyperuricemia include ***febuxostat and polyethylene glycol–bonded uricase***.
- ***Sulfinpyrazone*** was used in the past but is no longer available in the United States

Treatment aligoritm



OUTCOME EVALUATION

- **Acute Gout**
  - Monitor the patient for ***pain relief and decreased swelling of the affected joints.***
  - Both parameters should be improved significantly within 48 hours of starting acute gout therapy.
  - Assess the patient's subjective ***complaints*** and objective information for adverse effects.
  - Assess patients receiving systemic ***corticosteroids*** for mental status changes, fluid retention, increased blood glucose, muscle weakness, or development of new infections.
  - Counsel the patient to inform you of any new medications started or stopped while taking colchicine.

OUTCOME EVALUATION

- **Antihyperuricemic Therapy**
- Assess for new gouty arthritis attacks or the development of tophi.
- If neither one develops, continue antihyperuricemic therapy as prescribed.
- Obtain the first follow-up serum uric acid level within 6 months of starting therapy.
- Then monitor levels at least every 6 to 12 months, and adjust the dose to achieve a target serum uric acid level of ***less than 6 mg/dL*** (less than 357 µmol/L).
- Evaluate patients taking allopurinol for development of rash, nausea, or new fever.
- These symptoms usually appear within the first 3 months of therapy but can occur anytime.
- Assess patients receiving probenecid for fever, nausea, or skin rash.
- Reevaluate therapy if a significant decrease in urine output occurs (greater than 50% in a 24-hour period).

OSTEOPOROSIS

DEFINITION

- Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing individuals to an increased fracture risk.
- Categories of osteoporosis include:
  - (1) Postmenopausal osteoporosis
  - (2) Age related osteoporosis
  - (3) Secondary osteoporosis

PATHOPHYSIOLOGY

- Bone loss occurs when bone resorption exceeds bone formation:
  - Usually from high bone turnover when the number and/or depth of bone resorption sites greatly exceed the rate and ability of osteoblasts /bone forming cell to form new bone
- In addition to reduced bone mineral density (BMD), bone quality and structural integrity are impaired:
  - Because of the increased quantity of immature bone that is not yet adequately mineralized
- Men and women begin to lose a small amount of bone mass starting in the third or fourth decade as a consequence of reduced bone formation

- Estrogen deficiency during menopause increases proliferation, differentiation, and activation of new osteoclasts and prolongs survival of mature osteoclasts
  - This increases bone resorption more than formation
- Men do not undergo a period of accelerated bone resorption similar to menopause.
- The etiology of male osteoporosis is

PATHOPHYSIOLOGY

- Age-related osteoporosis occurs mainly because of hormone, calcium, and vitamin D deficiencies leading to accelerated bone turnover and reduced osteoblast formation.
- Drug-induced osteoporosis may result from systemic corticosteroids (prednisone doses greater than 7.5 mg/day), thyroid hormone replacement, some antiepileptic drugs (e.g., phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other

CLINICAL PRESENTATION

- Many patients are unaware that they have osteoporosis and only present after fracture
- Fractures can occur after bending, lifting, or falling, or independent of any activity.
- The most common osteoporosis-related fractures involve the vertebrae, proximal femur/main bone in thigh, and distal radius (wrist or Colles' fracture)
- Two-thirds of patients with vertebral fractures are asymptomatic; the remainder present with moderate to severe back pain that radiates down a leg after a new vertebral fracture

CLINICAL PRESENTATION

- The pain usually subsides significantly after 2 to 4 weeks, but residual, chronic, low-back pain may persist
- Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis) with or without significant back pain
- Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site

DIAGNOSIS

- A patient history should be obtained to identify history of adult fractures, comorbidities, surgeries, falls, and the presence of risk factors for osteoporosis.
- Major risk factors include current smoker, low body weight (<127 lb in postmenopausal women), history of osteoporotic fracture in a first-degree relative, and personal history of low-trauma fracture as an adult
- Other independent risk factors include age, high bone turnover, low body mass index (<19 kg/m2), rheumatoid arthritis, and glucocorticoid use

DIAGNOSIS

- A complete physical examination and laboratory analysis are needed to rule out secondary causes and to assess kyphosis and back pain
- Laboratory testing may include complete blood count, liver function tests, creatinine, urea nitrogen, calcium, phosphorus, alkaline phosphatase, albumin, thyroid- stimulating hormone, free testosterone, 25-hydroxyvitamin D, and 24-hour urine concentrations of calcium and phosphorus

DIAGNOSIS

- Measurement of central (hip and spine) BMD with dual-energy x-ray absorptiometry (DXA) is the gold standard for osteoporosis diagnosis.
- Measurement at peripheral sites (forearm, heel, and phalanges/bones of the foot) with ultrasound or DXA is used only for screening purposes and to determine the need for further testing.

DESIRED OUTCOME

- The primary goal of osteoporosis management is prevention
- Optimizing skeletal development and peak bone mass accrual in childhood, adolescence, and early adulthood will reduce the future incidence of osteoporosis.
- Once osteopenia or osteoporosis develops:
  - The objective is to stabilize or improve bone mass and strength and prevent fractures.

DESIRED OUTCOME

- Goals in patients who have already suffered osteoporotic fractures include:
  - Reducing future falls and fractures
  - Improving functional capacity
  - Reducing pain and deformity
  - Improving quality of life

PREVENTION AND TREATMENT

- Management algorithms that incorporate both:
- Nonpharmacologic
- Pharmacologic

NONPHARMACOLOGIC THERAPY

- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D**
- If adequate dietary intake cannot be achieved:
  - Calcium supplements are necessary.
- Because excessive caffeine consumption increases calcium excretion
  - Caffeine intake should ideally be limited to two servings per day
- Moderate caffeine intake (2 to 4 servings per day) should not be a concern:
  - If adequate calcium intake is achieved.

NONPHARMACOLOGIC THERAPY

- Smoking cessation can help:
  - To optimize peak bone mass
  - To minimize bone loss
  - Ultimately reduce fracture risk.
- Weight-bearing aerobic and strengthening exercises can decrease:
  - The risk of falls and fractures by:
    - Improving muscle strength, coordination, balance, and mobility.

TABLE 3-1 Daily Calcium and Vitamin D Recommendations

	Institute of Medicine Adequate Intake	
Group and Ages	***Elemental Calcium (mg)*[a]**	***Vitamin D (units)*[a,b]**
Infants		
Birth to 6 months	210	200
6–12 months	270	200
Children		
1–3 years	500	200
4–8 years	800	200
9–13 years	1,300	200
Adolescents		
14–18 years	1,300	200
Adults		
19–50 years	1,000	200
51–70 years	1,200	400
>70 years	1,200	600

[a]U.S. Institute of Medicine of the National Academy of Sciences recommends no more than 2,500 mg/day elemental calcium and 2,000 units/day vitamin D.

[b]Most experts believe the recommended adequate intakes for vitamin D are too low.

TABLE 3–2 Dietary Sources of Calcium and Vitamin D[a]

Food	Serving Size	Calcium Content (mg)	Vitamin D Content (units)
Milk	1 cup	300	100
Powdered nonfat milk	1 teaspoon	50	—
Ice cream	1 cup	200	—
Yogurt, fortified	1 cup	240–415	60
American cheese	1 oz	150	—
Cheddar cheese	1 oz	211	—
Cottage cheese	1/2 cup	100	—
Swiss cheese	1 oz	250	—
Parmesan cheese	1 tablespoonful	70	—
Cheese pizza	1 slice	150	—
Macaroni and cheese	1 cup	360	—
Slim Fast	11 oz	400	140
Orange juice, fortified	1 cup	350	100
Soymilk, fortified	1 cup	80–300	100
Bread, fortified	1 slice	100	—
Cereals, fortified	1 cup	100–250	60
Sardines with bones	3 oz	370	230
Salmon with bones	3 oz	170–210	310
Catfish	3 oz	—	570
Halibut	3 oz	—	680
Tuna	4 oz	—	260
Almonds	1 oz	80	—
Bok choy	1/2 cup	125	—
Broccoli	1 cup	130–160	—
Collards	1/2 cup	180	—
Corn bread	1 slice	85	—
Egg, medium	1	55	25
Figs, dried	5 medium	125	—
Kale	1/2 cup	95	—
Orange	1	52	—
Soybeans	1 cup	130	—
Spinach	1/2 cup	110	—
Tofu	4 oz	140	—
Turnip greens	1/2 cup	125	—

[a]To calculate calcium content, multiply percentage on package by 1,000. To calculate vitamin D content, multiply percentage on package by 400.

PHARMACOLOGIC THERAPY

- ANTIRESORPTIVE THERAPY

Calcium

- **Calcium** should be ingested in adequate amounts to prevent secondary hyperparathyroidism and bone destruction
- Although calcium increases BMD, fracture prevention is minimal
- It should be combined with vitamin D and osteoporosis medications when needed.
- **Calcium carbonate** is the salt of choice because it contains the highest concentration of elemental calcium (40%) and is the least expensive
- It should be ingested with meals to enhance absorption from increased acid secretion.

CALCIUM

- **Calcium citrate** absorption is acid independent and need not be taken with meals
- Because the fraction of calcium absorbed decreases with increasing dose:
  - Maximum single doses of 600 mg or less of elemental calcium are recommended.
- Constipation is the most common adverse reaction:
  - It can be treated with increased water intake, dietary fiber (given separately from calcium), and exercise
- Calcium carbonate can create gas, sometimes causing flatulence or upset stomach.

VITAMIN D SUPPLEMENTATION

- **Vitamin D deficiency** results from insufficient intake, decreased sun exposure, decreased skin production, decreased liver and renal metabolism, and winter residence in northern climates.
- Supplemental vitamin D maximizes intestinal calcium absorption and has been shown to increase BMD; it may also reduce fractures
- Although the vitamin D intakes included in Table 3-1 are usually recommended,
  - Many experts feel that adult intake should be 800 to 1,000 units daily

TABLE 3-3 Calcium and Vitamin D Product Selection

Product (% calcium)[a]	Elemental Calcium (mg)	Vitamin D (units)
Calcium carbonate (40%)[b]	—	—
Trade and generic products	200–600	100–200
Mylanta Supreme liquid (5 mL)	160	—
Tums Chewable	200	—
Tums E-X	300	—
Tums Ultra	400	—
Rolaids chewable	471	—
Os-Cal sugar-free chewable	500	400
Viactiv chews[c]	500	200
CalMax powder (10 mL)	400	—
Bayer's Women[d]	300	—
Ensure high calcium[e] (8 oz)	400	140
Calcium citrate (24%)	—	—
Generic	315	200
Citracal + Vit D	200–315	200
Citracal chew	500	200
Tricalcium phosphate (39%)	—	—
Posture-D	600	125
Vitamin D_3 (cholecalciferol)	0	400, 700, 800, or 1,000
Ergocalciferol (D_2)[e]	—	—
Liquid (1 mL)	—	8,000
Tablets/capsules	—	25,000 or 50,000
Intramuscular	—	500,000

[a]Many products are adding magnesium, boron, zinc, copper, vitamin K, and/or manganese; sometimes adding "Plus" or "Ultra" to their name. These products are not listed here.
[b]There are many trade-name products for calcium carbonate (e.g., Calel-D, Caltrate, Os-Cal). Only calcium carbonate alternative dosage forms (i.e., chewable, liquid, power) are specifically listed.
[c]Contains vitamin K.
[d]Contains aspirin 81 mg.
[e]Prescription products.

BISPHOSPHONATES

- Bisphosphonates 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.
- Of the antiresorptive agents available, bisphosphonates provide the greatest BMD increases and fracture risk reductions
- Fracture reductions are demonstrated as early as

BISPHOSPHONATES

- BMD increases are dose dependent and greatest in the first 6 to 12 months of therapy
- Small increases continue over time at the lumbar spine but plateau after 2 to 5 years at the hip
- After discontinuation, the increased BMD is sustained for a prolonged period that varies depending on the bisphosphonate used.
- **Alendronate, risedronate**, and **oral ibandronate** are FDA approved for prevention and treatment of postmenopausal osteoporosis.
- **IV ibandronate** and **zoledronic acid** are indicated only for treatment of postmenopausal women
- Risedronate and alendronate are also approved for male and glucocorticoid-induced osteoporosis

BISPHOSPHONATES

- Bisphosphonates must be administered carefully to optimize the clinical benefit and minimize the risk of adverse GI effects
- All bisphosphonates are poorly absorbed (bioavailability 1% to 5%) even under optimal conditions.
- Each oral tablet should be taken in the morning with at least 6 oz of plain tap water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for oral ibandronate) before consuming any food, supplement, or medication
- The patient should remain upright (sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration to prevent

BISPHOSPHONATES

- Most patients prefer once-weekly or once-monthly bisphosphonate administration over daily therapy
- If a patient misses a weekly dose, it can be taken the next day
- If more than 1 day has elapsed, that dose is skipped until the next scheduled ingestion
- If a patient misses a monthly dose, it can be taken up to 7 days before the next scheduled dose

BISPHOSPHONATES

- The most common bisphosphonate adverse effects are nausea, abdominal pain, and dyspepsia
- Esophageal, gastric, or duodenal irritation, perforation, ulceration, or bleeding may occur when administration directions are not followed or when bisphosphonates are prescribed for patients with contraindications.
- The most common adverse effects of IV bisphosphonates include fever, flu-like symptoms, and local injection-site reactions
- Osteonecrosis of the jaw occurs rarely; if it develops, oral chlorhexidine washes, systemic antibiotics, and systemic analgesics are used based on severity

MIXED ESTROGEN AGONISTS/ANTAGONISTS

- **Raloxifene** is an estrogen agonist on bone but an antagonist on the breast and uterus
- It is approved for prevention and treatment of postmenopausal osteoporosis
- Other estrogen agonists/antagonists may be approved soon (e.g., bazedoxifene, lasofoxifene).
- Raloxifene decreases vertebral fractures and increases spine and hip BMD, but to a lesser extent than bisphosphonates
- After discontinuation, the beneficial effect is lost and bone loss returns to age- or disease-related rates

MIXED ESTROGEN AGONISTS/ANTAGONISTS

- Raloxifene (like tamoxifen) is associated with decreased breast cancer risk.
- Raloxifene is associated with:
  - Decreases in total and LDL cholesterol
  - Neutral effects on high-density lipoprotein cholesterol
  - But slight increases in triglycerides
  - No beneficial cardiovascular effects have yet been demonstrated.

MIXED ESTROGEN AGONISTS/ANTAGONISTS

- Raloxifene is well tolerated overall
- Hot flushes occur more frequently:
  - In women recently finishing menopause or
    - Discontinuing estrogen therapy (ET).
- Endometrial bleeding occurs rarely
- Raloxifene is contraindicated in women with:
- An active or past history of venous thromboembolism
- Therapy should be stopped if a patient anticipates extended immobility

CALCITONIN

- **Calcitonin** is released from the thyroid gland when serum calcium is elevated.
- Salmon calcitonin is used clinically because it is more potent and longer lasting than the mammalian form
- Calcitonin is reserved as a third-line agent because efficacy is less robust than with the other antiresorptive therapies.
- Calcitonin is indicated for osteoporosis treatment for women at least 5 years past menopause
- Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy
- Calcitonin does not consistently affect hip BMD and does not decrease hip fracture risk

CALCITONIN

- Calcitonin may provide pain relief to some patients with acute vertebral fractures
- If used:
  - It should be prescribed for short-term treatment (4 weeks)
  - Should not be used in place of other more effective and less expensive analgesics
  - Nor should it preclude the use of more appropriate osteoporosis therapy.
- The intranasal dose is 200 units daily, alternating every other day.
- Subcutaneous administration of 100 units daily is available but rarely used because of adverse effects and cost

ESTROGEN THERAPY

- Estrogens are FDA approved for prevention of osteoporosis, but they should only be used short-term in women who need ET for the management of menopausal symptoms such as hot flushes
- The risks of long-term ET outweigh the potential bone benefits.
- The enhanced BMD effects from ET and combined estrogen-progestin hormonal therapy (HT):
  - Significantly reduce fracture risk
  - But are less than those from bisphosphonates
  - But greater than those from raloxifene or calcitonin.
- Oral and transdermal estrogens at

ESTROGEN THERAPY

- Effect on BMD is dose dependent with some benefit seen with lower estrogen doses
- When ET or HT is discontinued, bone loss accelerates and fracture protection is lost.
- The lowest effective dose of ET and HT should still be used for preventing and controlling menopausal symptoms with use discontinued with symptom abatement
- Many contraindications to ET and HT exist and must be identified before starting therapy

TESTOSTERONE

- Testosterone replacement is not FDA approved for the prevention or treatment of osteoporosis.
- It should not be used solely for these indications but might be beneficial to reduce bone loss in patients needing therapy for hypogonadal symptoms
- In a few studies, women receiving oral **methyltestosterone** 1.25 or 2.5mg daily or **testosterone implants 50mg every 3** months had increased BMD

TESTOSTERONE

- Various salt forms of testosterone were associated with increased BMD in some studies of hypogonadal men or senior men with normal hormone levels or mild hormonal deficiency
- Transdermal gel, oral, intramuscular, and pellet testosterone products are available.
- Patients using them should be evaluated within 1 to 2 months of initiation and then every 3 to 6 months thereafter

THIAZIDE DIURETICS

- Thiazide diuretics increase urinary calcium reabsorption
- Two controlled trials demonstrated small increases in bone mass over placebo.
- Prescribing thiazide diuretics solely for osteoporosis is not recommended:
- But is a reasonable choice for patients with osteoporosis who require a diuretic and
- For patients on glucocorticoids with a 24-hour urinary calcium excretion >300 mg

TABLE 3-4 Medications Used to Prevent and Treat Osteoporosis

Drug	Adult Dosage	Pharmacokinetics	Adverse Effects	Drug Interactions
Calcium	Adequate intake (Table 3-1) in divided doses	Absorption–predominantly active transport with some passive diffusion, fractional absorption 10–60%, fecal elimination for the unabsorbed and renal elimination for the absorbed calcium	Constipation, gas, upset stomach, rare kidney stones	Carbonate salts–decreased absorption with proton pump inhibitors Decrease absorption of iron, tetracycline, quinolones, bisphosphonates, phenytoin, and fluoride when given concomitantly Might antagonize verapamil Might induce hypercalcemia with thiazide diuretics Fiber laxatives (variable), oxalates, phytates, and sulfates can decrease calcium absorption if given concomitantly
D_3 (cholecalciferol)	Adequate intake (Table 3-1); if malabsorption or multiple anticonvulsants might require higher doses (~≥4,000 or more units daily)	Hepatic metabolism to 25(OH) vitamin D and then renal metabolism to active compound $1,25(OH)_2$ vitamin D, other active and inactive metabolites	Hypercalcemia, (weakness, headache, somnolence, nausea, cardiac rhythm disturbance), hypercalciuria	Phenytoin, barbiturates, carbamazepine, rifampin increase vitamin D metabolism
D_2 (ergocalciferol)	For vitamin D deficiency, 50,000 units once weekly or once monthly; dosed dependent on serum calcium			Cholestyramine, colestipol, orlistat, or mineral oil decrease vitamin D absorption
$1,25(OH)_2$ vitamin D (calcitriol, Rocaltrol po, Calcijex IV)	0.25–0.5 mcg orally or 1–2 mcg/mL intravenously daily for renal osteodystrophy, hypoparathyroidism, and refractory rickets			Might induce hypercalcemia with thiazide diuretics in hypoparathyroid patients
Oral bisphosphonates		Poorly absorbed–<1% decreasing to zero with food or beverage intake–long $T_{1/2}$ (<10 years); renal elimination (of absorbed) and fecal elimination (unabsorbed)	Nausea; heartburn; GI pain, irritation, perforation, ulceration, and/or bleeding; transient flu-like illness; muscle pains; black box warning for rare osteonecrosis of the jaw	Do not coadminister with any other medication or supplements (including calcium and vitamin D)
Alendronate (Fosamax, Fosamax plus D)	5 mg daily, 35 mg weekly (prevention) 10 mg daily, 70 mg tablet, 70 mg tablet with vitamin D 2,800 or 5,600 units, or 75 mL liquid weekly (treatment)			
Risedronate (Actonel)	5 mg daily, 35 mg weekly, 75 mg on 2 consecutive days once monthly, 150 mg monthly			
Ibandronate (Boniva)	2.5 mg daily, 150 mg once monthly			

Intravenous bisphosphonates				
Ibandronate (Boniva)	5 mg IV infusion yearly		Muscle pains, transient flu-like illness, redness or swelling at injection site, black-box warning for rare osteonecrosis of the jaw	
Zoledronic acid[a] (Reclast)				
Mixed estrogen agonist/antagonist		Hepatic metabolism	Hot flushes, leg cramps, venous thromboembolism, peripheral edema, rare cataracts and gallbladder disease; black box warning for fatal stroke	None
Raloxifene (Evista)	60 mg daily			
Calcitonin (Miacalcin)	200 units intranasal daily, alternating nares every other day	Renal elimination 3% nasal availability	Rhinitis, epistaxis	None
Teriparatide (1–34 units, Forteo)	20 mcg subcutaneously daily for up to 2 years	95% bioavailability T_{max} ~30 minutes $T_{1/2}$ ~60 minutes Hepatic metabolism	Pain at injection site, nausea, dizziness, leg cramps, rare increase in uric acid, slightly increased calcium	None
Testosterone products		10% gel absorption (5 mg absorbed from 50 mg testosterone in 5 g of gel)	Weight gain, acne, hirsutism, dyslipidemia, hepatic consequences, gynecomastia, priapism, prostate disorders, testicular atrophy, sleep apnea, and skin reactions with patches	
Transdermal patch				
(Testoderm TTS, Androderm, Testim)	5 mg patch applied to arm, back, or thigh every evening (patches 2.5, 4, 5, & 6 mg)[a]			
Testoderm (R) with or without adhesive)	6 mg applied to scrotal skin every evening			
Gel (AndroGel 1%, Testim 1%)	5 g gel applied to shoulder, upper arm, or abdomen every morning			
Buccal system (Striant 30 mg)	Place one system in gum area twice a day. Alternate sides of mouth. Do not crush or swallow			
Injection				
Cypionate (100 or 200 mg/mL) or enanthate (200 mg/mL) salt	200–300 mg IM every 2–3 weeks			
Methyltestosterone (for women)	1.25–2.5 mg with esterified estrogen			

GI, gastrointestinal; IM, intramuscular; T_{max}, time to maximum concentration; $T_{1/2}$, half life

RHEUMATOID ARTHRITIS

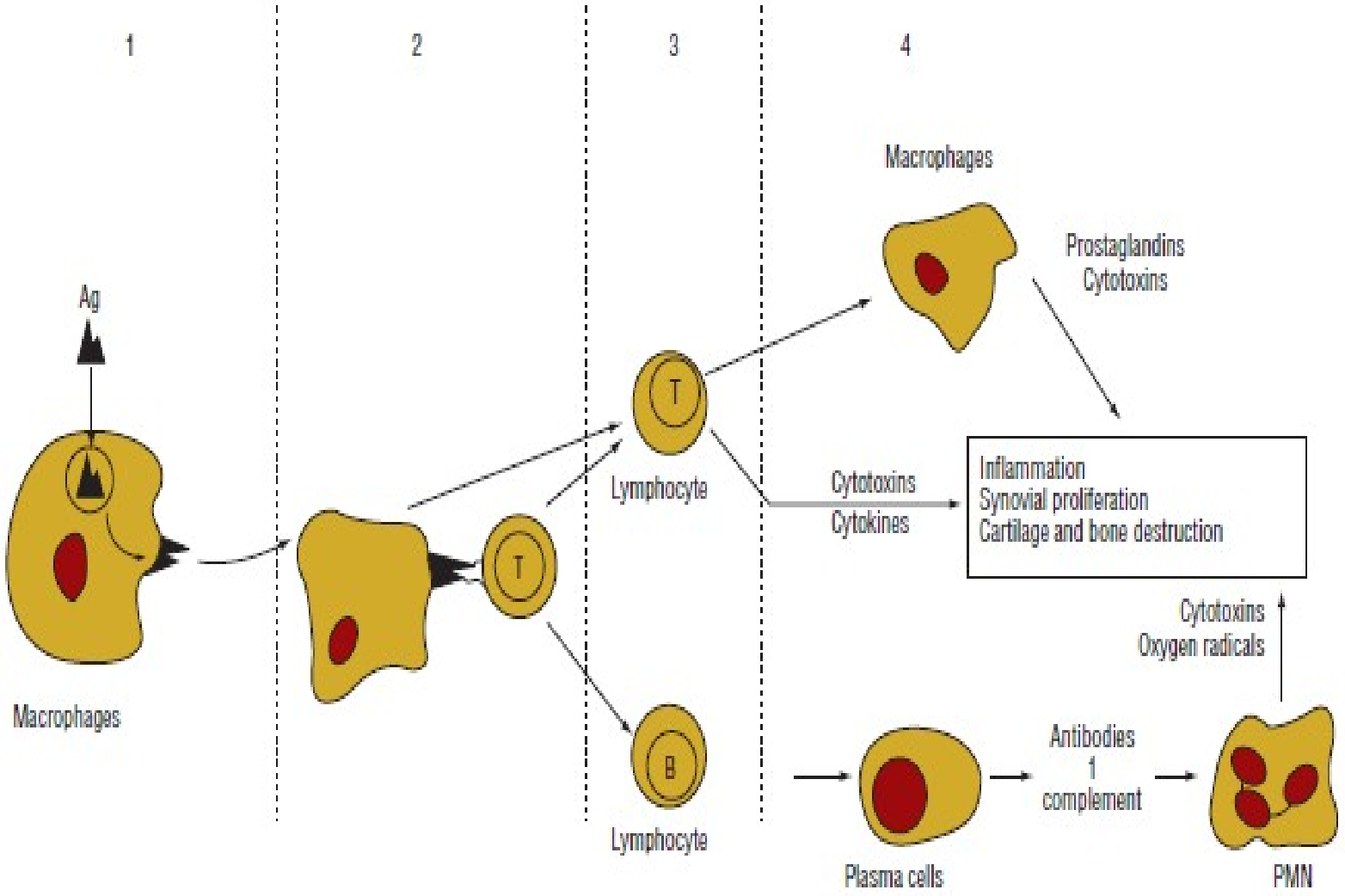
RHEUMATOID ARTHRITIS

- Chronic, progressive, inflammatory, systemic disease that primarily affects synovial joints
- Unknown- etiology
- Characterized by
  - Symmetric synovitis
  - Joint erosions
  - Multisystem extra-articular manifestations

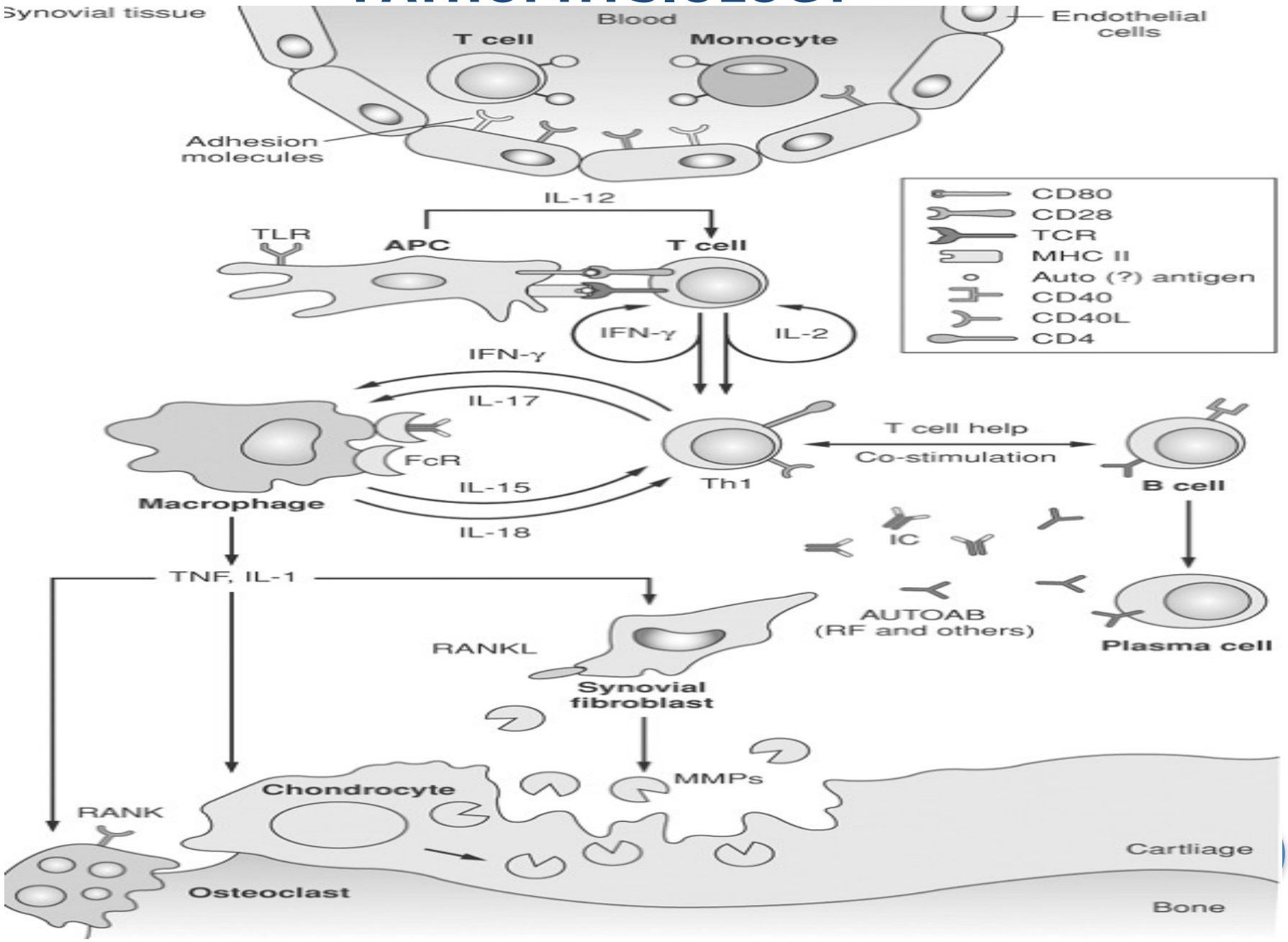
EPIDEMIOLOGY

- RA affects approximately 0.5–1% of the adult population worldwide
- 2-3 times more common in women
- In people ages 15 to 45 years, women predominate by a ratio of 6:1
- Epidemiologic data suggest that a genetic predisposition and exposure to unknown environmental factors may be necessary for expression of the disease

PATHOPHYSIOLOGY



PATHOPHYSIOLOGY



dysregulation of the humoral and cell mediated components of the immune system

↓

Chronic inflammation of the synovial tissue

↓

Pannus formation

↓

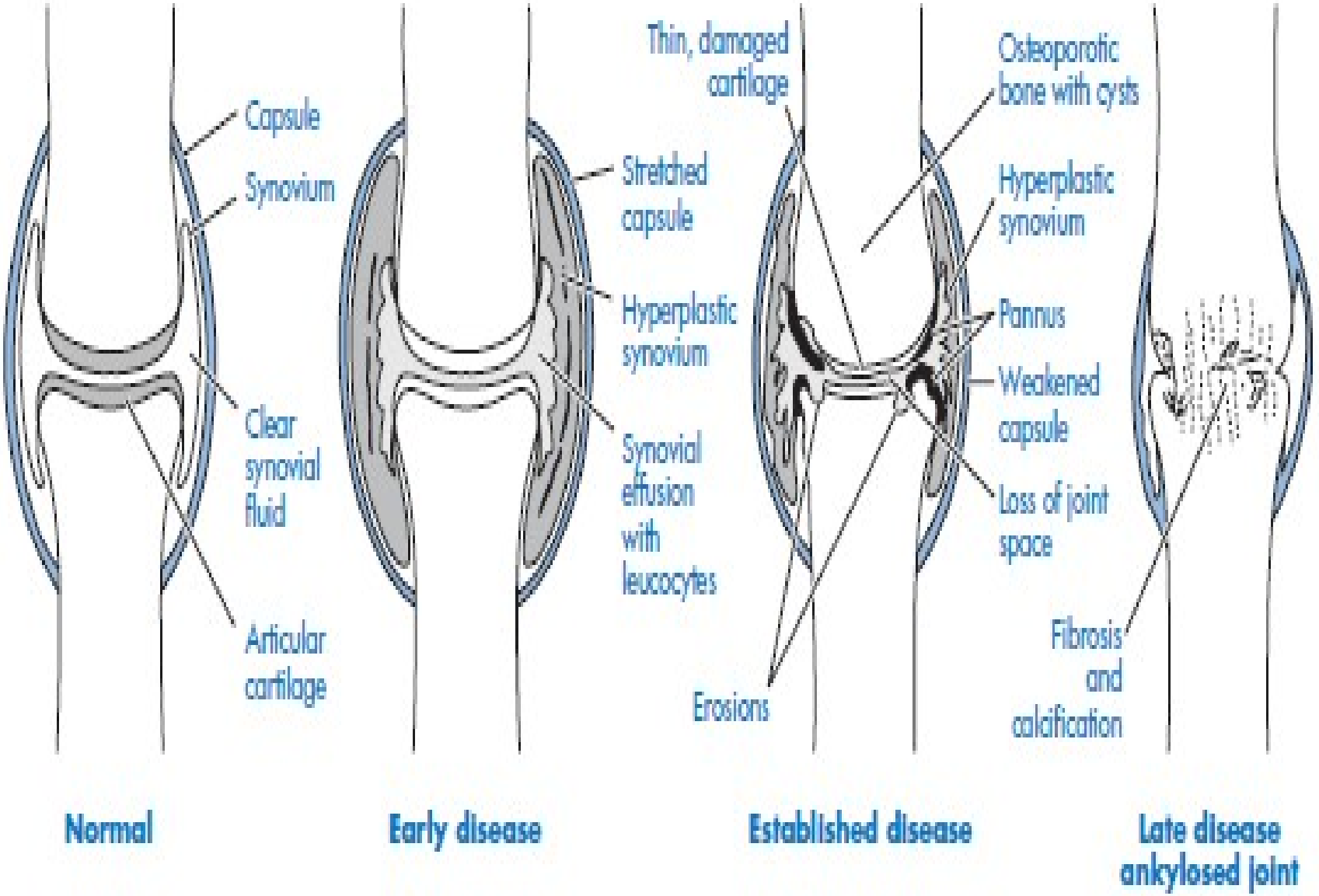
Invades the cartilage and bone surface

↓

Erosion of bone and cartilage

↓

Destruction of the joint


Capsule
Synovium
Clear synovial fluid
Articular cartilage
Stretched capsule
Hyperplastic synovium
Synovial effusion with leucocytes
Thin, damaged cartilage
Osteoporotic bone with cysts
Hyperplastic synovium
Pannus
Weakened capsule
Loss of joint space
Erosions
Fibrosis and calcification
Normal
Early disease
Established disease
Late disease ankylosed joint

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms

- Joint pain and stiffness of more than 6 weeks' duration. May also experience fatigue, weakness, low-grade fever, loss of appetite. Muscle pain and afternoon fatigue may also be present. Joint deformity is generally seen late in the disease.

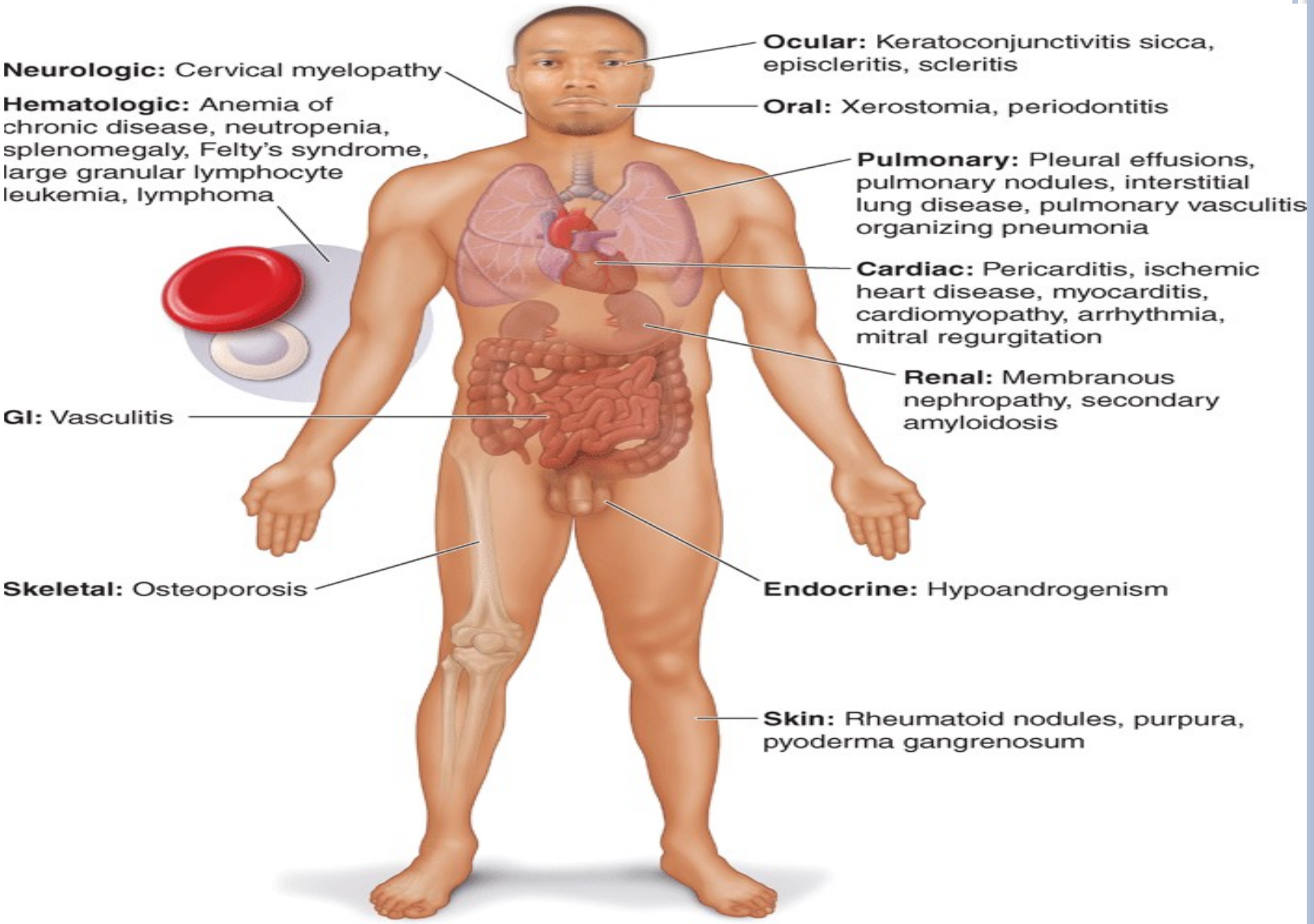
Signs

- Tenderness with warmth and swelling over affected joints usually involving hands and feet. Distribution of joint involvement is frequently symmetrical. Rheumatoid nodules may also be present.

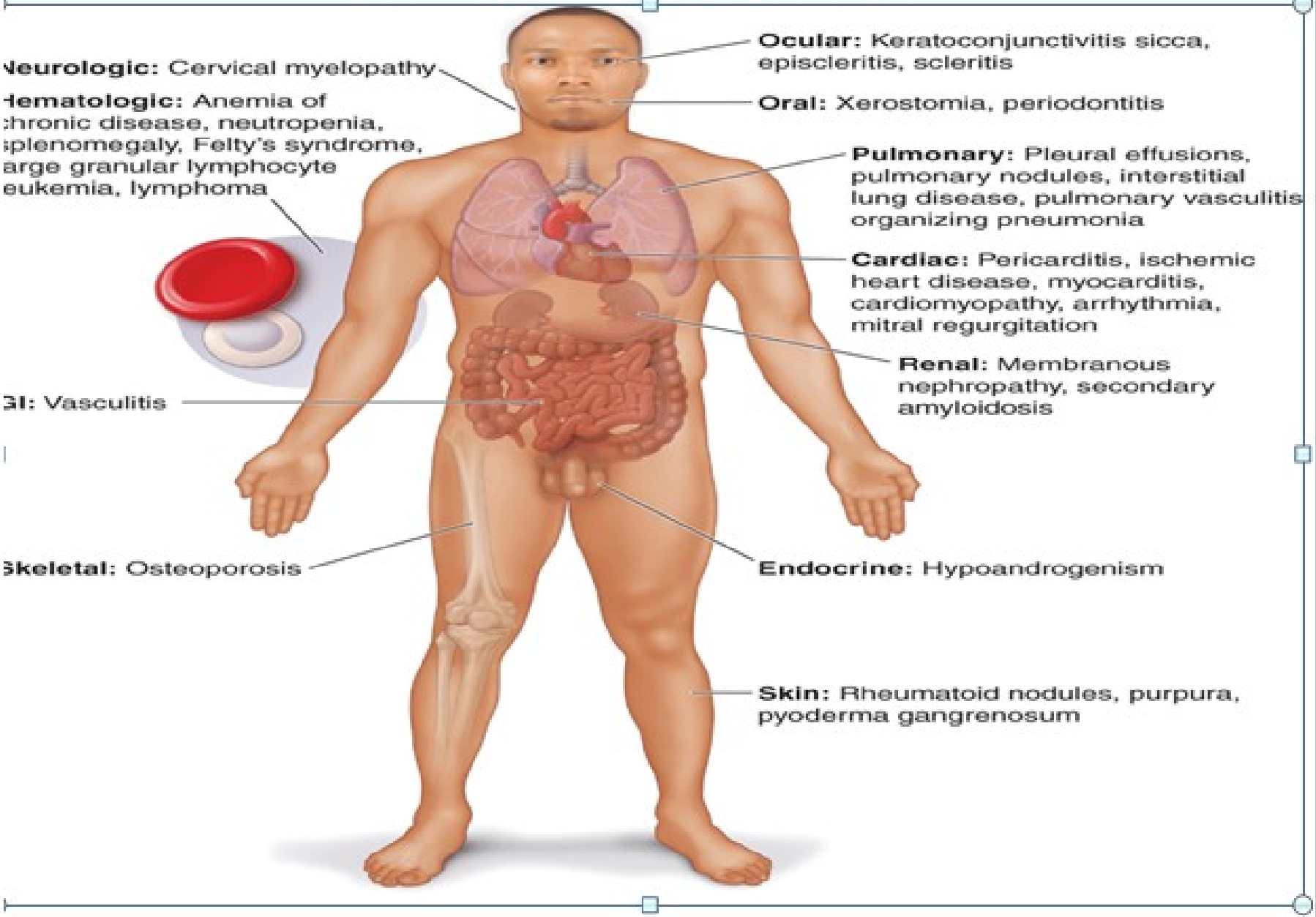
Laboratory Tests

- Rheumatoid factor (RF) detectable in 60% to 70%.
- Anticyclic citrullinated peptide (anti-CCP) antibodies have similar sensitivity to RF (50% to 85%) but are more specific (90% to 95%) and are present earlier in the disease.
- Elevated erythrocyte sedimentation rate and C-reactive protein are markers for inflammation.
- Normocytic normochromic anemia is common as is thrombocytosis.

EXTRA-ARTICULAR INVOLVEMENT



Extra-articular involvement



CLINICAL PRESENTATION AND DIAGNOSIS

- Other diagnostic tests
  - Joint fluid aspiration may show increased white blood cell counts without infection, crystals.
  - Joint radiographs may show
    - Periarticular osteoporosis,
    - Joint space narrowing, or
    - Erosions

a) Normal: note the clearly defined joint ‘spaces’ in both the hand and the wrist. (b) Severe rheumatoid arthritis: note the loss of joint space

Normal



Severe rheumatoid



CLASSIFICATION CRITERIA FOR RA

Synovitis plus score of ≥6/10 needed for the classification of definite RA

Joint involvement	One large joint	0
	2-10 large joints	1
	1-3 small joints*	2
	4-10 small joints*	3
	>10 joints (at least one small joint)	5
Serology#	RF- and ACPA-	0
	Low RF+ or low ACPA+	2
	High RF+ or high ACPA+	3
Acute-phase reactants#	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1

*With or without involvement of large joints. # at least one test result needed for classification. ACPA: Anti-citrullinated protein/peptide antibodies; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

Aletaha et al. Ann Rheum Dis 2010;69:1580-1588

SEVERITY OF RA

- Mild disease
  - less than six inflamed joints,
  - no extraarticular disease, and
  - no evidence of erosions or cartilage loss
- **Moderate disease**
  - 6 and 20 inflamed joints and
  - have some combination of the following clinical features:
    - Absence of extraarticular disease
    - Elevation in ESR and/or CRP
    - Positive RF and/or anti-CCP antibodies
    - Evidence of inflammation

SEVERITY OF RA

- Severe disease
  - more than 20 inflamed joints,
  - an elevation in the ESR and/or serum CRP, and
  - one or more of the following:
    - Anemia of chronic disease and/or hypoalbuminemia
    - Rheumatoid factor positivity (often in high titer) and/or anti-CCP antibodies
    - Rapid appearance of bony erosions and loss of cartilage
    - Extraarticular disease

DESIRED OUTCOME

- The primary objectives:
  - To reduce joint swelling, stiffness, and pain;
  - Preserve range of motion and joint function
  - Improve quality of life;
  - Prevent systemic complications; and slow destructive joint changes

TREATMENT

- Nonpharmacologic and preventive therapies
  - Patient education and counseling
  - Rest, exercise
  - Physical therapy, occupational therapy
  - Nutrition and dietary therapy
  - Bone protection
  - Atherosclerosis risk factor modification
  - Vaccinations

PHARMACOLOGIC THERAPY

- Drug therapy is the mainstay of treatment for all patients except for those in clinical remission
- Drug classes
  - Analgesics: topical (eg, capsaicin), paracetamol, tramadol
  - NSAIDs
    - do not alter disease outcomes
  - Glucocorticoids: predinsolone
    - Higher doses are more effective in relieving joint pain and tenderness

PHARMACOLOGIC THERAPY

- DMARDs (A disease-modifying antirheumatic drug)
  - Nonbiologic: sulfasalazine, **leflunomide, methotrexate**
  - Biologic:
    - IL-1, IL-6 receptor antagonists
    - TNF- inhibitors (infliximab)
- Have the potential to reduce or prevent joint damage, preserve joint integrity and function.

CURRENT APPROACH

- Specific therapy of RA varies with
  - disease severity
  - the response to previous regimens
- Early, mildly active RA =
  - full therapeutic dose NSAIDS
- Does not remit after 6 wks to 3 mths
  - Add sulfasalazine or hydroxychloroquine

CURRENT APPROACH

- Early, moderately active RA
  - Use of NSAIDS, and single agents or combinations of nonbiologic DMARDs
  - Methotrexate as the initial DMARD
  - Alternatives:
    - Combination of hydroxychloroquine and sulfasalazine, or
    - A tumor necrosis factor (TNF) inhibitor
      - Screen for latent tuberculosis infection

CURRENT APPROACH

- Both intraarticular and oral glucocorticoids can be useful as adjuncts to NSAIDS and DMARDS

Early, severely active RA

- Methotrexate as the initial DMARDs
- Add NSAIDS or systemic and/or intraarticular glucocorticoids when needed
- High levels of disease activity on MTX alone
  - DMARDs Triple therapy: MTX, SSZ and HCQ
  - MTX + TNF inhibitor

FDA-Approved DMARDs and BRMs for Treatment of Rheumatoid Arthritis

Drug	Dose	Route	Time to Effect	ADRs	Monitoring	Counseling Points
Methotrexate	7.5–20 mg once weekly	Oral or IM	4–8 weeks	N, D, hepatotoxicity, alopecia, new-onset cough or SOB, MYL	CBC, creatinine, LFTs q 4–8 weeks Monitor for signs of infection	Concomitant use of folic acid Avoid alcohol Use contraception if childbearing potential
Hydroxychloroquine	200 mg bid	Oral	8–24 weeks	N, D, HA, vision changes, skin pigmentation	Eye exam every 12 mo.	
Sulfasalazine	1000 mg bid–tid	Oral	8–12 weeks	N, D, rash, yellow-orange discoloration, photosensitivity, MYL	CBC q 2–4 weeks for 3 mo. then q 3 mo.	Sunscreen use
Leflunomide (Arava)	100 mg daily for 3 days; then 20 mg daily	Oral	4–12 weeks	Hepatotoxicity, D, N, HTN, rash, HA, abdominal pain	CBC, creatinine, LFTs q mo. for 6 mo.; then q 4–8 weeks Monitor for signs of infection	Avoid alcohol Use contraception if childbearing potential
Etanercept (Enbrel)	25 mg twice weekly or 50 mg once weekly	SC injection	1–4 weeks	ISR	Monitor for infection	ISR—topical corticosteroids, antipruritics, analgesics, rotate injection sites Screen for tuberculosis
Infliximab (Remicade)	3–10 mg/kg at 0, 2, and 6 weeks; then q 8 weeks	IV infusion	1–4 weeks	IR (rash, urticaria, flushing, HA, fever, chills, nausea, tachycardia, dyspnea)	Monitor for infection	Screen for tuberculosis
Adalimumab (Humira)	40 mg every other week	SC injection	1–4 weeks	ISR	Monitor for infection	Screen for tuberculosis
Anakinra (Kineret)	100–150 mg daily	SC injection	2–4 weeks	HA, N, V, D, ISR	Monitor for infection	
Rituximab (Rituxan)	Two 1000-mg infusions separated by 2 weeks	IV infusion	4 weeks	IR	Monitor for infection	

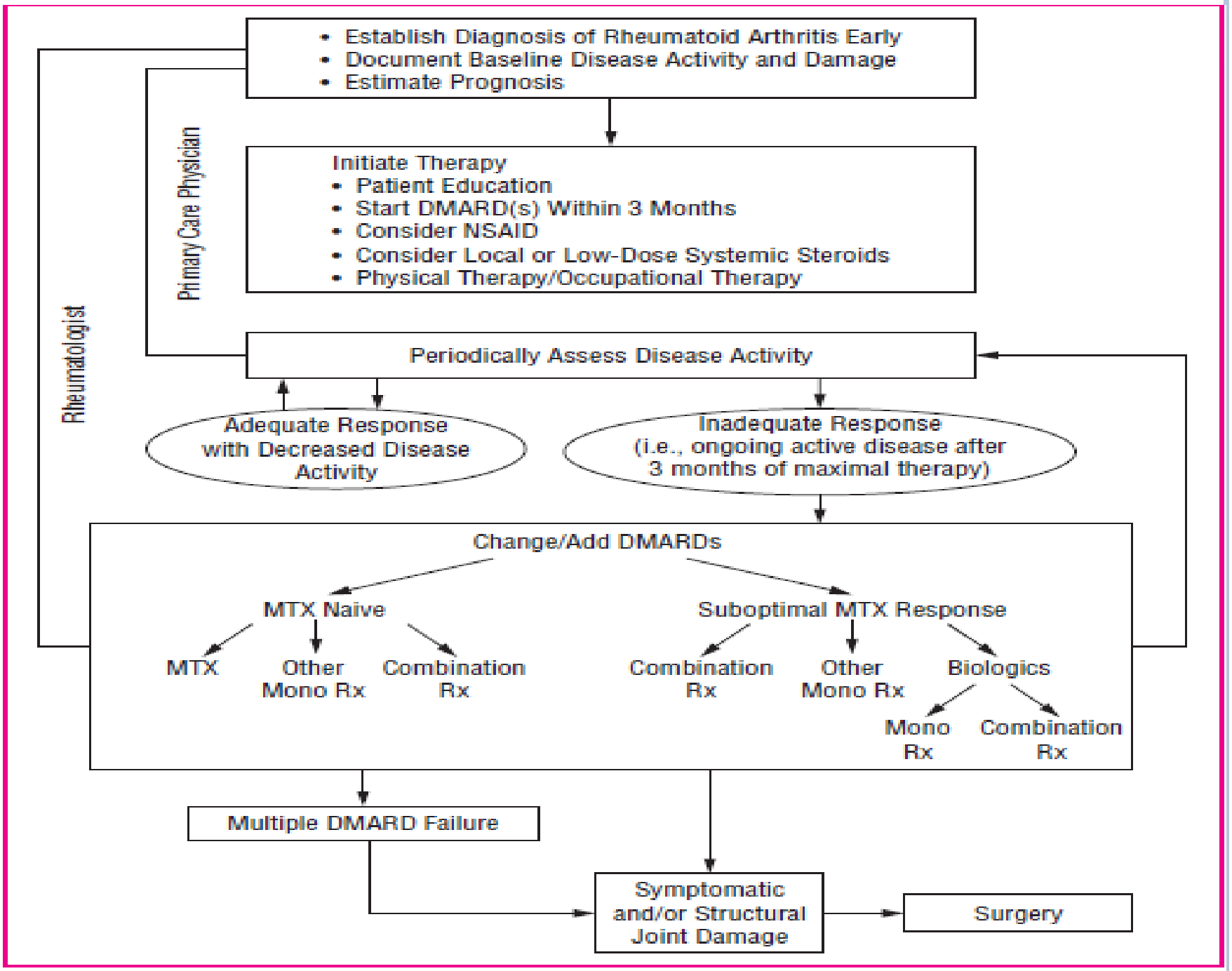
N, nausea; D, diarrhea; HA, headache; SOB, shortness of breath; HTN, hypertension; LFTs, liver function tests; CBC, complete blood count; ISR, injection-site reactions; IR, infusion reactions; IV, intravenous; MYL, myelosuppression (watch for fever, symptoms of infection, easy bruisability, and bleeding); SC, subcutaneous.

PARAMETERS USED TO ASSESS DISEASE ACTIVITY AND DRUG RESPONSE IN RA

- Duration and intensity of morning stiffness
- Number of painful or tender joints
- Number of swollen joints; severity of joint swelling
- Range of joint motion
- Time to onset of fatigue
- ESR or CRP
- Anti-CCP
- Radiographic changes: osteopenia, joint space narrowing, bony erosions
- Hgb / Hct
- Subcutaneous nodules, pleuritis, pneumonitis, myocarditis, vasculitis

EVALUATION OF RESPONSE TO THERAPY

- Periodic reevaluation at approximately four- to six-week intervals
  - at least every 2 to 3 months
- Frequent reevaluation allows
  - assessment of disease activity,
  - identification of any adverse effects of treatment
  - Identification of any intervention to supplement or modify therapy


• Establish Diagnosis of Rheumatoid Arthritis Early
• Document Baseline Disease Activity and Damage
• Estimate Prognosis
Primary Care Physician
Initiate Therapy
• Patient Education
• Start DMARD(s) Within 3 Months
• Consider NSAID
• Consider Local or Low-Dose Systemic Steroids
• Physical Therapy/Occupational Therapy
Rheumatologist
Periodically Assess Disease Activity
Adequate Response with Decreased Disease Activity
Inadequate Response (i.e., ongoing active disease after 3 months of maximal therapy)
Change/Add DMARDs
MTX Naive
Suboptimal MTX Response
MTX
Other Mono Rx
Combination Rx
Combination Rx
Other Mono Rx
Biologics
Mono Rx
Combination Rx
Multiple DMARD Failure
Symptomatic and/or Structural Joint Damage
Surgery