لجنة عمداء كليات الصيدلة

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تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتيبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء . نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

College of Pharmacy
Fourth year. Clinical Pharmacy
Cardiovascular disorders
Hypertension

Introduction

1-Hypertension is defined as **persistently elevated arterial blood pressure** (BP). (See Table -1 for the classification of BP in adults).

Table-1: Classification of Blood Pressure in Adults

Classification	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

2-**Isolated systolic hypertension** is diastolic blood pressure (DBP) <80 mm Hg and systolic blood pressure (SBP) ≥130 mm Hg.

3-**Hypertensive crisis** (BP >180/120 mm Hg) is categorized as **hypertensive emergency** (extreme BP elevation **with acute or progressing end-organ damage**) or h**ypertensive urgency** (extreme BP elevation **without acute or progressing end-organ injury**).

Pathophysiology

1-Hypertension may result from an unknown etiology (**primary or essential hypertension**) or from a specific cause (**secondary hypertension**).

2-Secondary hypertension (<**10% of cases**) is usually caused by **chronic kidney disease (CKD) or renovascular disease.**

3-**Examples of drugs that may increase BP include** corticosteroids, estrogens, NSAIDs, cyclosporine, erythropoietin, and venlafaxine.

4-Major causes of death include cerebrovascular events, cardiovascular (CV) events, and renal failure.

Clinical presentation

1-Patients with **uncomplicated primary hypertension are usually asymptomatic initially**.

2-Patients with **secondary hypertension** may have **symptoms of the underlying disorder**.

Diagnosis

1-Elevated BP may be the only sign of primary hypertension on physical examination.

2-Diagnosis should be based on the average of **two or more readings taken at each of two or more clinical encounters.**

3-**Signs of end-organ damage occur primarily in the eyes, brain, heart, kidneys, and peripheral vasculature**.

Treatment

1-Goals of Treatment: The overall goal is to reduce morbidity and mortality from CV events. The 2017 ACC/AHA **guideline recommends a goal BP of <130/80 mm Hg for most patients**.

2-For **institutionalized older patients and those with a high disease burden or limited life expectancy**, consider a relaxed SBP goal of **<150 mm Hg (or <140 mm Hg if tolerated).**

Nonpharmacologic Therapy

A-Implement lifestyle modifications in all patients with elevated BP or stage 1 or 2 hypertension.

B-Lifestyle modifications shown to lower BP include:
(1) **weight loss** if overweight or obese, (2) the Dietary Approaches to Stop Hypertension (**DASH**) eating plan, (3) **reduced salt intake**, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride), (4) **physical activity** (90–150 min/week of aerobic or dynamic resistance training), and (5) **moderation of alcohol intake**. Although **smoking** cessation does not control BP, it reduces CV disease risk and **should be encouraged**.

Pharmacologic Therapy

General Approach to Treatment

1-Initial drug selection depends on the **degree of BP elevation** and presence of **compelling indications** for certain drugs.

2-Use a **single first-line drug** as initial therapy in most patients with newly diagnosed **stage 1 hypertension.**

3-Start **combination drug therapy** (preferably with two first-line drugs) as the initial regimen in patients with newly diagnosed **stage 2 hypertension**.

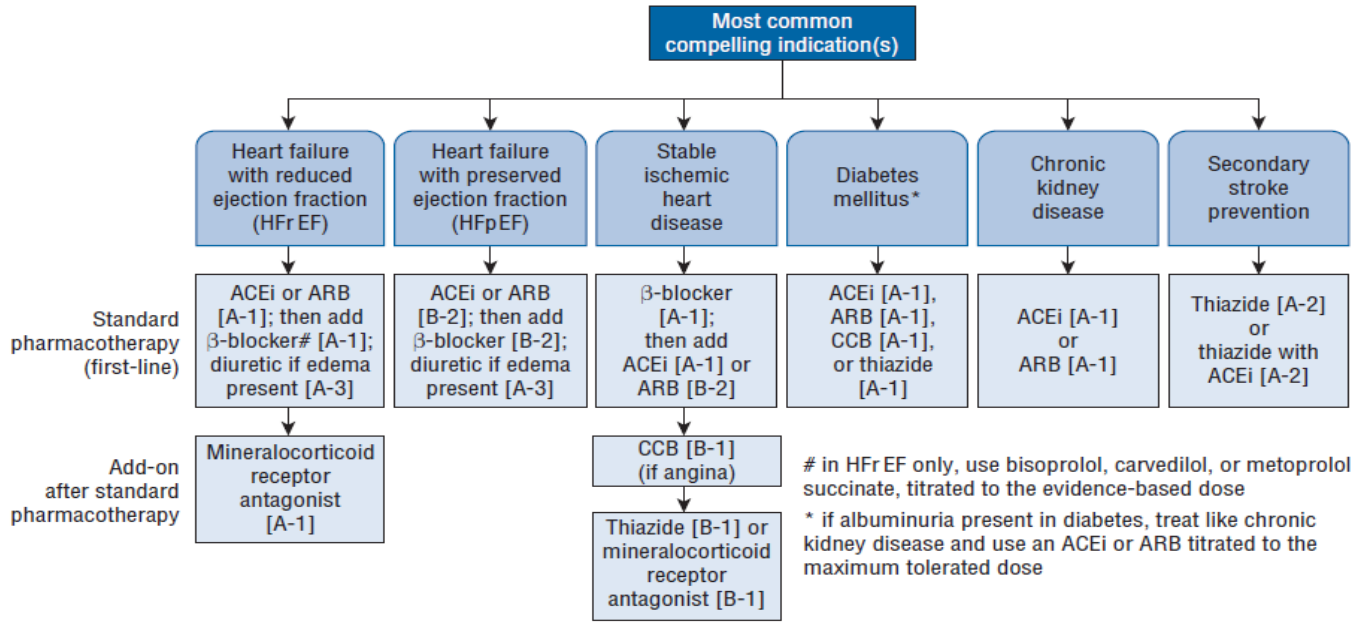
4-The **four first-line options** are angiotensin-converting enzyme (**ACE**) inhibitors, angiotensin II receptor blockers (**ARBs**), calcium channel blockers (**CCBs**), and **thiazide diuretics.**

5-**β-Blockers** should be reserved to treat **a specific compelling indication** or in **combination** with a first-line antihypertensive agent for patients without a compelling indication.

6-**Other antihypertensive** drug classes (α1-blockers, direct renin inhibitors, central α2-agonists, and direct arterial vasodilators) may be used for select patients **after implementing first-line agents.**

Compelling Indications

Compelling indications are **specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication**.



Notes:

1-β-Blockers (without ISA) are first-line therapy in Stable Ischemic Heart Disease (SIHD).

2-For acute coronary syndromes, first-line therapy includes **a β-blocker and ACE inhibitor (or ARB)**.

3-Any first-line agent can be used to control hypertension in patients with diabetes in the absence of albuminuria.

4-In addition to lowering BP, ACE inhibitors and ARBs reduce intraglomerular pressure, which may further slow **chronic kidney disease** progression.

5-The threshold for starting antihypertensive drug therapy in patients **with a history of stroke is when BP is >140/90 mm Hg** (goal of <130/80 mm Hg).

Angiotensin-Converting Enzyme Inhibitors (captopril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, and trandolapril)

1-ACE inhibitors block conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion.

2-**Starting doses should be low with slow dose titration**. Acute hypotension may occur at the onset of therapy.

3-ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. **Hyperkalemia** occurs primarily in patients with CKD or those also taking potassium supplements, potassium-sparing diuretics, mineralocorticoid receptor antagonists, ARBs, or direct renin inhibitors.

4-**AKI is an uncommon but serious side effect**; preexisting kidney disease increases risk. Bilateral renal artery stenosis or unilateral stenosis are particularly susceptible to AKI.

5-Serum creatinine concentrations often increase, but modest elevations (eg, absolute increases <1 mg/dL) **do not warrant treatment changes**. Discontinue therapy or reduce dose if larger increases occur.

6-**Angioedema occurs in <1% of patients**. Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation to support respiration.

7-An **ARB can generally be used in patients with a history of ACE inhibitor-induced angioedema**, with careful monitoring.

8-A **persistent dry cough** occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.

9-**ACE inhibitors (as well as ARBs and direct renin inhibitors) are contraindicated in pregnancy.**

Angiotensin II Receptor Blockers (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan)

1-The ARBs directly block the angiotensin II type 1 receptor that mediates the effects of angiotensin II.

2-Unlike ACE inhibitors, **ARBs do not block bradykinin breakdown and this accounts for the lack of cough as a side effect**.

3-ARBs have a low incidence of side effects. Like ACE inhibitors, they may cause renal **insufficiency, hyperkalemia, and orthostatic hypotension**.

Calcium Channel Blockers

1-Dihydropyridine and nondihydropyridine CCBs are first-line antihypertensive therapies and are also used in addition to or instead of other first-line agents for the compelling indication of ischemic heart disease.

2-Dihydropyridine CCBs may cause reflex sympathetic activation, and all agents (**except amlodipine and felodipine**) may have negative inotropic effects.

3-**Verapamil** produces a negative inotropic effect that may precipitate HF in patients with borderline cardiac reserve. **Diltiazem decreases heart rate to a lesser extent than verapamil.**

4-Both **diltiazem and verapamil** can cause peripheral edema and hypotension. Verapamil causes **constipation** in about 7% of patients.

5-**Dihydropyridines** cause a baroreceptor-mediated **reflex increase in heart rate** because of potent peripheral vasodilating effects. Other side effects of dihydropyridines are dizziness, flushing, headache, gingival hyperplasia, and peripheral edema.

Diuretics

1-**Thiazides are the preferred type of diuretic and are a first-line option for most patients with hypertension**. Chlorthalidone (thiazide-like) is preferred over hydrochlorothiazide, especially in resistant hypertension, because it is more potent on a milligram-per-milligram basis.

2-**Loop diuretics (**Furosemide, Bumetanide and Torasemide**) are more potent for inducing diuresis but are not ideal antihypertensives unless edema treatment is also**

needed. Loop diuretics are sometimes required over thiazides in patients with severe CKD when eGFR is <30 mL/min/1.73 m^2, especially when edema is present.

3-**Potassium-sparing diuretics are weak antihypertensives when used alone**. Their primary use is in combination with another diuretic **to counteract potassium-wasting properties**.

4-Mineralocorticoid receptor antagonists (spironolactone and eplerenone) are also potassium-sparing diuretics that are usually **used to treat resistant hypertension because elevated aldosterone concentrations are prevalent in this setting**. They are also used as add-on agents in patients with **HFrEF** with or without concomitant hypertension.

5-Acutely, diuretics lower BP by causing diuresis. With chronic therapy, **reduced peripheral vascular resistance** is responsible for persistent hypotensive effects.

6-**Side effects of thiazides** include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction.

7-Loop diuretics have less effect on serum lipids and glucose, but hypokalemia is more pronounced, and **hypocalcemia may occur**.

8-Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps, and severe electrolyte abnormalities may result in serious cardiac arrhythmias.

9-**Potassium-sparing diuretics may cause hyperkalemia**, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with a mineralocorticoid receptor antagonist, ACE inhibitor, ARB, direct renin inhibitor, or potassium supplement.

10-**Spironolactone may cause gynecomastia** in up to 10% of patients; this effect occurs rarely with eplerenone.

β-Blockers

1-**Evidence suggests that β-blockers may not reduce CV events as well as ACE inhibitors, ARBs, CCBs, or thiazides when used as the initial drug in patients who do not have a compelling indication for a β-blocker.**

2-β-Blockers are appropriate **first-line agents when used to treat specific compelling indications** or when an ACE inhibitor, ARB, CCB, or thiazide cannot be used.

3-Atenolol, betaxolol, bisoprolol, metoprolol, and nebivolol are β1-cardioselective at low dose. As a result, they are **less likely to provoke bronchospasm and vasoconstriction** and are safer than nonselective β-blockers in patients with asthma or diabetes. Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.

4-Acebutolol, carteolol, and **pindolol** possess **intrinsic sympathomimetic activity** (ISA) or partial β-receptor agonist activity. Theoretically, these drugs may have advantages in select patients with HF or sinus bradycardia. Unfortunately, **they do not reduce CV events as well as other β-blockers and may increase CV risk in patients with SIHD. Thus, agents with ISA are rarely needed and have no role in hypertension management.**

5-**Atenolol and nadolol have relatively long half-lives and are excreted renally**; the dosage may need to be reduced in patients with renal insufficiency.

6-Even though the half-lives of other β-blockers are shorter, once-daily administration still may be effective.

7-**Cardiac side effects** include bradycardia, AV conduction abnormalities, and acute HF. Blocking β2-receptors in arteriolar smooth muscle may cause cold extremities and aggravate intermittent claudication or Raynaud phenomenon because of decreased peripheral blood flow.

8-Increases in serum lipids and glucose appear to be transient and of little clinical significance.

9-**Abrupt cessation of β-blockers should be avoided. The dose should always be tapered gradually over 1–2 weeks before discontinuation**.

α1-Receptor Blockers

1-Prazosin, terazosin, and doxazosin are selective α1-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation and BP lowering.

2-Although they can provide symptomatic benefit in men with benign prostatic hyperplasia, **they should be used to lower BP only in combination with first-line antihypertensive agents**.

Direct Renin Inhibitor

Aliskiren blocks the RAAS at its point of activation, resulting in reduced plasma renin activity and BP. It is approved for monotherapy or in combination therapy. **Its role in the management of hypertension is limited.**

Central α2-Agonists

1-**Clonidine, guanfacine, and methyldopa** lower BP primarily by stimulating α2-adrenergic receptors in the brain, which reduces sympathetic outflow from the vasomotor center.

2-Clonidine is often used in resistant hypertension, and **methyldopa is frequently used for pregnancy-induced hypertension.**

Direct Arterial Vasodilators

Hydralazine and **minoxidil** directly relax arteriolar smooth muscle, resulting in vasodilation and BP lowering.

Special Populations

Older Persons

1-Older patients may present with either isolated systolic hypertension or elevation in both SBP and DBP. **CV morbidity and mortality are more directly correlated to SBP than to DBP in patients aged 50 and older**.

2-First-line antihypertensives provide significant benefits and can be used safely in older patients, **but smaller-than-usual initial doses must be used for initial therapy**.

Children and Adolescents

1-Because **secondary hypertension is more common in children and adolescents** than in adults, an appropriate workup is required if elevated BP is identified.

2-**Nonpharmacologic treatment** is the **cornerstone of therapy for primary hypertension**.

3-ACE inhibitors, ARBs, β-blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.

Pregnancy

1-Preeclampsia (**Further reading 1**) can lead to life-threatening complications for both mother and fetus.

2-**Eclampsia is the onset of convulsions in preeclampsia and is a medical emergency**.

3-Definitive treatment of preeclampsia is **delivery**, and labor induction is indicated if eclampsia is imminent or present. Otherwise, management consists of restricting activity, bed rest, and close monitoring. Salt restriction or other measures that contract blood volume should be avoided.

4-**Antihypertensives are used before induction of labor** if DBP is >105 mm Hg, with a target DBP of 95–105 mm Hg. Intravenous (IV) **hydralazine** is most commonly used; IV labetalol is also effective.

5-**Chronic hypertension** is hypertension that predates pregnancy. **Labetalol, long-acting nifedipine, or methyldopa is recommended as first-line therapy** due to favorable safety profiles. β-Blockers (**except atenolol**) and CCBs are also reasonable alternatives.

Black Patients

CCBs and thiazides are most effective in African Americans and should be first-line in the absence of a compelling indication.

Pulmonary Disease and Peripheral Arterial Disease (PAD)

1-Although β-blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and COPD because of fear of inducing bronchospasm, **cardioselective β-blockers can be used safely.**

2-β-Blockers can theoretically be problematic in patients with PAD because of possible decreased peripheral blood flow secondary to unopposed stimulation of α1-receptors that results in vasoconstriction. However, **available data indicate that β-blockers do not worsen claudication symptoms or cause functional impairment**. Therefore, **antihypertensive treatment for patients with PAD should follow the same general principles as patients without PAD**.

Hypertensive Urgencies and Emergencies

1-Acute administration of a **short-acting oral drug (captopril, clonidine, or labetalol)** is an option.

2-**Hypertensive emergencies require immediate BP reduction with a parenteral agent to limit new or progressing end-organ damage**.

Evaluation of therapeutic outcomes

1-Evaluate **BP response in the clinic 4 weeks after initiating or making changes in therapy** and compare the results to home BP readings.

2-**Once goal BP is obtained, monitor BP every 3–6 months,** assuming no signs or symptoms of acute end-organ damage.

3-**Assess patient adherence with the regimen regularly**.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

Further reading

1-Preeclampsia is defined as **hypertension** (elevated BP ≥140/90 mm Hg on more than two occasions at least 4 hours apart **after 20 weeks' gestation** or ≥160/110 mm Hg confirmed within a short interval) and either **proteinuria** or new onset hypertension with the onset of thrombocytopenia, impaired liver function, new onset renal insufficiency, pulmonary edema, or new onset cerebral or visual disturbances.

Heart Failure

Introduction

1-Heart failure (HF) is a **syndrome associated with signs and symptoms due to abnormalities in cardiac structure or function**

2-HF may be caused by an abnormality in **systolic function**, **diastolic function, or both**.

3-HF with reduced systolic function (ie, reduced left ventricular ejection fraction, LVEF) is referred to as **HF with reduced ejection fraction (HFrEF**).

4-Diastolic dysfunction **with normal LVEF** is termed **HF with preserved ejection fraction** (**HFpEF**).

Pathophysiology

1-**Causes of systolic dysfunction** (decreased contractility) include reduced muscle mass (eg, myocardial infarction [MI])

2-**Causes of diastolic dysfunction** (restriction in ventricular filling) include increased ventricular stiffness, and ventricular hypertrophy.

3-The leading causes of HF are **coronary artery disease and hypertension**.

4-Decreased cardiac output (CO) results **in activation of compensatory responses to maintain circulation:**

(A) **Tachycardia** and **increased contractility** through sympathetic nervous system activation, (B) Increased preload (through **sodium and water retention**) increases **stroke volume**, (C) **vasoconstriction**, and (D) **ventricular hypertrophy and remodeling**.

5-Although these compensatory mechanisms **initially maintain cardiac function**, they are **responsible for the symptoms of HF and contribute to disease progression**.

6-**Chronic activation of the neurohormonal systems** results in a cascade of events that **affect the myocardium**.

7-These events lead to **changes** in ventricular **size** (left ventricular hypertrophy), **shape**, **structure**, and **function** known as **ventricular remodeling.**

Clinical presentation

1-Patient presentation may range from asymptomatic to cardiogenic shock. **Primary symptoms are** dyspnea (especially on exertion) and fatigue, which lead to exercise intolerance.

2-**Other pulmonary symptoms include:** orthopnea, paroxysmal nocturnal dyspnea (PND), tachypnea, and cough. Fluid overload can result in pulmonary congestion and peripheral edema.

3-**Nonspecific symptoms may include** fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite or early satiety, and weight gain or loss.

Diagnosis

1-**Ventricular hypertrophy** can be demonstrated on **chest radiograph** or **electrocardiogram** (**ECG**). Chest radiograph may also show pleural effusions or pulmonary edema.

2-**Echocardiogram** can quantify LVEF to determine if systolic or diastolic dysfunction is present.

3-The New York Heart Association Functional **Classification System** is intended primarily to classify symptoms according to the physician's subjective evaluation.

- **Functional class (FC)-I** patients have no limitation of physical activity.
- **FC-II** patients have slight limitation.
- **FC-III** patients have marked limitation
- **FC-IV** patients are unable to carry on physical activity without discomfort.

Treatment of chronic heart failure

Goals of Treatment: Improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.

General Approach

1-The first step is to **determine the etiology or precipitating factors**. Treatment of underlying disorders (e.g., hyperthyroidism) may obviate the need for treating HF.

2-An international group developed a staging system:

Stage	Description	Recommendation
Stage A	**At risk for HF** (No HF signs or symptoms with No structural heart disease)	Drugs are recommended for HF prevention in select patients
Stage B	**PreHF** (No HF signs or symptoms but with structural heart disease)	Drugs are recommended for HF prevention in select patients
Stage C	**HF** (HF signs or symptoms with structural heart disease)	Most patients with HFrEF in stage C should receive **Guideline directed medical therapy (GDMT)** proven to reduce morbidity and mortality.
Stage D	**Advanced HF** (persistent HF symptoms despite maximally tolerated GDMT)	They should be considered for specialized interventions, including mechanical circulatory support, continuous IV positive inotropic therapy, or cardiac transplantation

Nonpharmacologic Therapy of Chronic Heart Failure

1-Interventions include **restriction of fluid intake and dietary sodium intake** (<2–3 g of sodium/day) with daily weight measurements.

2-In patients with hyponatremia or persistent volume retention despite high diuretic doses and sodium restriction, **limit daily fluid intake** to 2 L/day from all sources.

3-**Revascularization** or anti-ischemic therapy in patients with **coronary disease** may reduce HF symptoms. **Drugs that can aggravate HF should be discontinued if possible**.

Pharmacologic Therapy for Stage C HFrEF

1-In general, patients with stage C HFrEF should receive an **ACE inhibitor**, **ARB**, or **ARNI** **along with β-blocker**, **Sodium Glucose Cotransporter Type 2 (SGLT2) Inhibitors** [4] plus an **aldosterone antagonist**.

2-Administer a **diuretic if there is evidence of fluid retention**. A **hydralazine–nitrate combination, ivabradine, Vericiguat or digoxin may be considered in select patients.**

A-Diuretics

1-**Diuretic** therapy (in addition to sodium restriction) is recommended **for all patients with clinical evidence of fluid retention.**

2-However, because they **do not alter disease progression or prolong survival**, diuretics are not required for patients without fluid retention.

3-**Thiazide** diuretics (eg, hydrochlorothiazide) are relatively weak and **are infrequently used alone in HF**. However, thiazides or the thiazide-like diuretic metolazone can be used **in combination with a loop** diuretic to promote very effective diuresis.

4-**Thiazides** may be preferred over loop diuretics in patients with only **mild fluid retention and elevated BP** because of their more persistent antihypertensive effects.

5-**Loop diuretics** (furosemide, bumetanide, and torsemide) are **usually necessary** to restore and maintain euvolemia in HF.

6-Unlike thiazides, loop diuretics **maintain their effectiveness in the presence of impaired renal function**, although higher doses may be necessary.

7-**Adverse effects of diuretics** include hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, and renal dysfunction.

B-Angiotensin-Converting Enzyme Inhibitors

1-ACE inhibitors improve symptoms, slow disease progression, **and decrease mortality** in patients with HFrEF.

2-**Prior guidelines** recommended that all patients with HFrEF, regardless of whether or not symptoms are present, should receive an ACE inhibitor to reduce morbidity and mortality, unless there are contraindications. However, **recent evidence** suggests that **sacubitril/valsartan is preferred over ACE inhibitors** (or **ARBs**) **for HFrEF** unless other circumstances (eg, affordability) are present in individual patients.

3-Although symptoms may improve within a few days of starting therapy, **it may take weeks to months before the full benefits are apparent**.

4-**The most common adverse effects include** hypotension, renal dysfunction, and hyperkalemia. A dry, nonproductive cough (occurring in 15%–20% of patients) is the most common reason for discontinuation.

5-Because **cough is a bradykinin-mediated effect**, replacement with sacubitril/valsartan or an ARB is reasonable; however, caution is required because **crossreactivity** has been reported.

6-**Angioedema** occurs in approximately 1% of patients and **is potentially life threatening**; ACE inhibitors are contraindicated in patients with a history of angioedema.

7-ACE inhibitors are **contraindicated in pregnancy** due to various congenital defects.

C-Angiotensin Receptor Blockers

1-Because they do not affect the ACE enzyme, ARBs do not affect bradykinin, which is **linked to ACE inhibitor cough and angioedema**.

2-Although ARBs are a guideline recommended alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema, **sacubitril/valsartan is preferred for ACE inhibitor associated cough.**

3-Although numerous ARBs are available, **only candesartan, valsartan, and losartan** are **recommended in the guidelines** because efficacy has been demonstrated in clinical trials.

4-ARBs are **not suitable alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors** because they are just as likely to cause these adverse effects.

5-**Caution** should be exercised when ARBs are used **in patients with angioedema from ACE inhibitors because crossreactivity** has been reported. Similar to ACE inhibitors, ARBs are contraindicated in pregnancy.

D-Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

1-Valsartan/Sacubitril is an ARNI approved for HF. In patients with HFrEF (**Further reading 1)**, the use of ARNi is recommended to reduce morbidity and mortality [(2)].

2-**Neprilysin is an enzyme that degrades bradykinin** and **other endogenous vasodilator and natriuretic peptides**. By reducing neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced, and renin and aldosterone secretion is inhibited.

3-**In patients with HFrEF, ARNI is preferred over either ACE inhibitors or ARBs t**o **improve survival**. Patients receiving ACE inhibitors or ARBs can be switched to ARNI or ARNI can be used as initial treatment in patients with newly detected HFrEF.

4-**Discontinue ACE inhibitors 36 hours prior to initiating the ARNI**; no waiting period is needed in patients receiving an ARB.

5-**Closely monitor** BP, serum potassium, and renal function after the start of therapy and after each titration step.

6-**The most common adverse effects include** hypotension, dizziness, hyperkalemia, worsening renal function, and cough. **Angioedema is most common with sacubitril/valsartan than with enalapril.**

7-Sacubitril/valsartan is **contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB.** It is also **contraindicated in pregnancy** and should **not be used concurrently with ACE inhibitors or other ARBs**.

E-β-Blockers

1-β-Blockers antagonize the effects of the sympathetic nervous systems in HF and slow disease progression. β-**blockers reduce HF mortality, and hospitalizations**.

2-The ACC/AHA guidelines recommend use of β-blockers in **all stable patients** with HFrEF in the absence of contraindications or a clear history of β-blocker intolerance.

3-Patients should receive a β-blocker **even if symptoms are mild or well controlled** with other GDMT.

4-**Carvedilol**, **metoprolol succinate** (CR/XL), and **bisoprolol** are the only β-blockers shown to reduce mortality in large HF trials.

5-Initiate β-blockers in **stable patients who have no or minimal evidence of fluid overload**. **Because of their negative inotropic effects**, start β-blockers in very low doses with slow upward dose titration to avoid symptomatic worsening.

6-**Inform patients that HF symptoms may actually worsen during the initiation period**.

7-**Adverse effects include** bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening HF.

F-Aldosterone Antagonists

1-**Spironolactone** and **eplerenone** block mineralocorticoid receptors, the target for aldosterone.

2-Current guidelines recommend **adding a low-dose aldosterone antagonist** to standard therapy (**Further reading 2)** provided that serum potassium and renal function can be carefully monitored.

3-**Start with low doses**. Avoid aldosterone antagonists in patients with renal impairment, elevated serum potassium, or history of severe hyperkalemia.

4-Spironolactone also interacts with androgen and progesterone receptors, which may lead to **gynecomastia**, **impotence**, and **menstrual irregularities** in some patients.

G-Sodium Glucose Cotransporter Type 2 (SGLT2) Inhibitors

1-SLGT2 inhibitors **inhibit glucose and sodium reabsorption** in the proximal kidney tubules, which leads to **osmotic diuresis and natriuresis**, and **reduction in arterial pressure**

2-In patients with **symptomatic chronic HFrEF**, SGLT2i (**Dapagliflozin** or **empagliflozin**) are recommended to reduce **morbidity** and **mortality**, irrespective of the presence of type 2 diabetes (**with or without diabetes**) [(2)].

3-Patients should be advised to **avoid abrupt changes in position** as orthostasis may occur in the setting of overdiuresis.

H-Nitrates and Hydralazine

1-Isosorbide dinitrate (**ISDN**) is a venodilator that **reduces preload**, whereas **hydralazine** is a direct arterial vasodilator that **reduces systemic vascular resistance** (SVR) and increases stroke volume and CO.

2-Guidelines recommend **addition of hydralazine/ISDN** to **black patients** with HFrEF (**Further reading 3) who are receiving optimal medical therapy** [(2)].

3-The combination can also be useful in patients **unable to tolerate** either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or hypotension.

I-Ivabradine

1-Ivabradine inhibits the **If current** in the sinoatrial node that is responsible for controlling HR, thereby slowing the HR. It does not affect AV conduction, BP, or myocardial contractility.

2-Because of the clear benefits of β-blockers on mortality, clinicians should titrate to the maximum tolerated doses before considering use of Ivabradine (Patients are either on a maximally tolerated dose of a β-blocker or have a contraindication to β-blocker use).

J-Digoxin

1-Studies of digoxin in HF showed either neutral effects or reductions in hospitalizations and either neutral or detrimental effects of digoxin on mortality.

2-So digoxin is **not considered a first-line agent in HF.** In patients with **symptomatic HFrEF despite GDMT** (or who are unable to tolerate GDMT), digoxin might be considered to **improve symptoms and reduce hospitalizations** [(2)].

3-Digoxin may also be considered to **help control ventricular rate** in patients with HFrEF and supraventricular arrhythmias.

K-Vericiguat

1-Vericiguat modulates endothelial dysfunction; **it is a soluble guanylate cyclase activator (sGC) t**hat **enhances the effect of nitric oxide** (NO) and regulate contractility and diastolic function.

2-In a clinical trial, patients with HFrEF receiving vericiguat demonstrated **a significant, but modest, reduction in cardiovascular death or HF hospitalization.**

3-The drug was well tolerated overall, but there was an unexplained **greater incidence of anemia** in patients treated with vericiguat.

4-Vericiguat may be considered **in addition to optimized HF therapy** to **reduce morbidity and mortality** in patients at high risk **with worsening HFrEF** [(2)]**.**

5-It is not indicated in HFpEF due to lack of benefit and safety data.

Pharmacologic Therapy for HFpEF

1-**SGLT2i** should be initiated **in all individuals with HFpEF** lacking contraindications [3].

2-**Diuretics** should be used for symptom relief **in volume overload** [4].

3-The addition of **aldosterone antagonists, ARNIs or ARBs may be considered** (**further reading 4**) [3].

Reference

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.
2-Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Apr 1;145(18).
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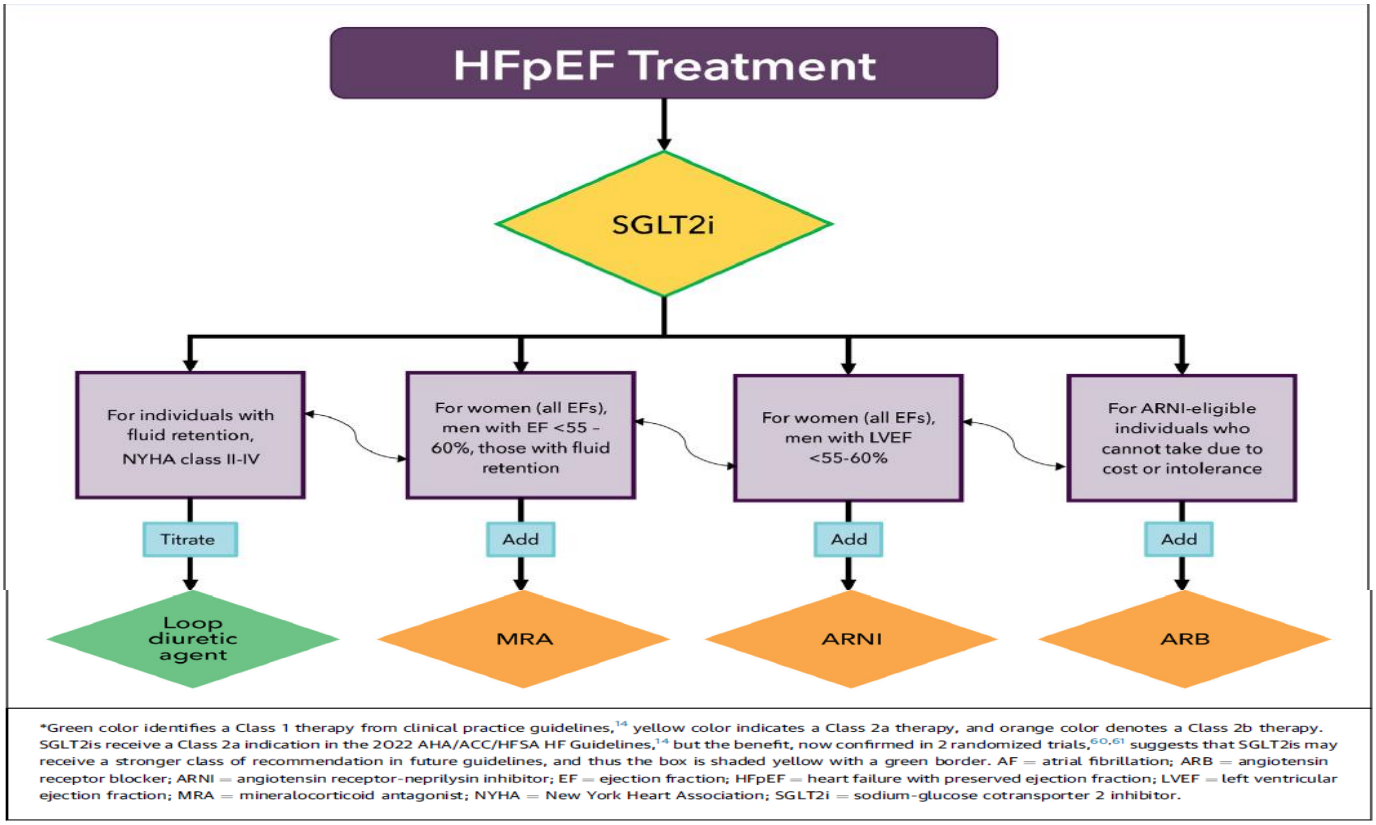
4-ACCP 2023.

Further reading

1-And NYHA class II to III symptoms [2].
2- in (NYHA class II-IV [2]) patients.
3- (NYHA class III or IV) [2].
4-Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF [3].



College of Pharmacy
Fourth year. Clinical Pharmacy

Treatment of acute decompensated heart failure (ADHF)

General Approach

1-**Acute decompensated heart failure** involves patients with **new or worsening signs or symptoms** [often resulting from volume overload and/or low cardiac output (CO)] **requiring medical intervention**, such as emergency department visit or hospitalization.

2-Admission to an **intensive care unit** (ICU) may be required for some cases.

3-**Signs** and s**ymptoms of volume overload** include dyspnea, orthopnea, PND, ascites, GI symptoms (poor appetite, nausea, early satiety), peripheral edema, and weight gain.

4-**Low output signs and symptoms** include altered mental status tachycardia, hypotension (more commonly) or hypertension, cool extremities, pallor and decreased urine output.

5-**If fluid retention** is evident on physical exam, **start aggressive diuresis**, preferably with IV diuretics.

6-In the absence of cardiogenic shock or symptomatic hypotension, strive to continue all GDMT for HF. **β-blockers may be temporarily held or dose reduced** if recent changes are responsible for acute decompensation.

7-Other GDMT **(ACE inhibitors, ARBs, ARNI, and aldosterone antagonists) may also need to be temporarily withheld in the presence of renal dysfunction**, with close monitoring of serum potassium.

8-Place all patients with congestive symptoms **on sodium restriction** (<2 g daily) and consider fluid restriction for refractory symptoms.

9-Consider **noninvasive ventilation** for patients in respiratory distress due to acute pulmonary edema.

10-**Provide pharmacologic thromboprophylaxis** with unfractionated heparin or low-molecular-weight heparin for most patients with limited mobility; **consider mechanical thromboprophylaxis** with intermittent pneumatic compression devices in patients at high risk for bleeding.

11-Temporary **mechanical circulatory support** may be considered for hemodynamic stabilization until the underlying etiology has been corrected or until definitive therapy (e.g., cardiac transplantation).

12-**Cardiac transplantation** is the best option for patients with irreversible advanced HF. New surgical strategies such **myocardial cell transplantation** offer additional options for patients ineligible for device implantation or heart transplantation.

Pharmacologic Therapy for ADHF

A-Loop Diuretics

1-Current guidelines **recommend IV loop diuretics** (furosemide, bumetanide) as first-line therapy for **ADHF patients with volume overload**.

2-Bolus administration **reduces preload** by functional **venodilation** within 5–15 minutes and **later** (>20 minutes) **via sodium and water excretion**, thereby improving pulmonary congestion.

3-**Diuretic resistance may be improved by** administering larger IV **bolus** doses, transitioning from IV bolus to continuous IV **infusions**, or **adding a second diuretic** with a different mechanism of action, such as a distal tubule blocker (eg, oral metolazone, oral hydrochlorothiazide, or IV chlorothiazide).

B-Vasopressin Antagonists

1-Vasopressin receptor antagonists affect one or two AVP (**antidiuretic hormone**) receptors, V1A or V2. Stimulation of V1A receptors (located in vascular smooth muscle cells and myocardium) results in vasoconstriction, and positive inotropic effects. V2 receptors are located in renal tubules, where they regulate water reabsorption.

- **Tolvaptan** selectively binds to and inhibits the V2 receptor. It is an oral agent indicated for hypervolemic and euvolemic **hyponatremia in patients with HF**.

- **Conivaptan** nonselectively inhibits both the V1A and V2 receptors. It is an IV agent indicated for hypervolemic and euvolemic hyponatremia due to a variety of causes but is not indicated for patients with HF.

2-**Monitor patients** closely to avoid an **excessively rapid rise in serum sodium** requiring drug discontinuation.

C-Vasodilators

1-**Venodilators reduce preload** by increasing venous capacitance, and improve symptoms of pulmonary congestion. **Arterial vasodilators decrease afterload and causing increased CO**. **Mixed vasodilators** act on both arterial resistance and venous capacitance vessels, **reducing congestive symptoms while increasing CO.**

2-IV **vasodilators should be considered before positive inotropic** therapy in patients with low CO and elevated systemic vascular resistance (SVR). However, **hypotension may preclude their use in patients with preexisting low BP or SVR.**

3-**IV nitroglycerin is often preferred for preload reduction in ADHF**. Nitroglycerin displays potent coronary vasodilating properties making it the vasodilator of choice for patients with severe HF and ischemic heart disease.

4-**Sodium nitroprusside** is a **mixed arteriovenous vasodilator**. **Hypotension** is an important dose-limiting adverse effect of nitroprusside, and its use should be primarily reserved **for patients with elevated SVR**.

D-Inotropes (Dobutamine, Milrinone**, Norepinephrine** and **dopamine)**

1-Prompt correction of low CO in patients with hypoperfusion is required to **restore peripheral tissue perfusion and preserve end-organ function**.

2-**Inotropes should be considered only as a temporizing measure to maintain end-organ perfusion** in patients with cardiogenic shock or severely depressed CO and low systolic BP (ie, ineligible for IV vasodilators).

Evaluation of therapeutic outcomes

Chronic Heart Failure

1-Ask patients about the **presence and severity of symptoms** and how symptoms affect daily activities.

2-**Evaluate efficacy of diuretic treatment by** disappearance of the signs and symptoms of excess fluid retention.

3-**Body weight** is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes of (1.4–2.3 kg) to their healthcare provider so adjustments can be made in diuretic doses.

4-**Symptoms may worsen initially on β-blocker therapy**, and it may take weeks to months before patients notice symptomatic improvement.

5-**Routine monitoring of** serum electrolytes (especially potassium and magnesium) and renal function (BUN, serum creatinine, eGFR) is mandatory in patients with HF.

Acute Decompensated Heart Failure

1-**Assess the efficacy of drug therapy with daily** monitoring of weight, strict fluid intake and output measurements, and HF signs/symptoms.

2-**Monitor frequently for** electrolyte depletion, symptomatic hypotension, and renal dysfunction. Assess vital signs frequently throughout the day.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

Ischemic Heart Disease

Introduction

1-Ischemic heart disease (IHD) is defined **as lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction**.

2-It may present as **acute coronary syndrome** (**ACS**) [which includes unstable angina and non–ST-segment elevation (**NSTE**) or ST-segment elevation (**STE**) myocardial infarction (MI)], **chronic stable exertional angina**, **ischemia without symptoms**, **microvascular angina**, or **ischemia due to coronary artery vasospasm** (**variant or Prinzmetal angina**).

Pathophysiology

1-Angina pectoris usually results **from increased myocardial oxygen demand** in the setting of a **fixed decrease in myocardial oxygen supply because of atherosclerotic plaque.**

2-Coronary plaques that occupy less than 50%–70% of the vessel luminal diameter rarely produce ischemia or angina. However, **smaller plaques have a lipid-rich core and thin fibrous cap and are more prone to rupture and cause acute thrombosis**.

3-When the luminal diameter of epicardial vessels is **reduced by 70% or more**, minimal physical exertion may result in a flow deficit with myocardial ischemia and often angina.

4-Patients **with variant (Prinzmetal) angina usually do not have a coronary flow-obstructing plaque** but instead have significant reduction in myocardial oxygen supply due to **vasospasm in epicardial vessels**.

Clinical presentation

1-Patients typically complain of **chest pain precipitated by exertion** or activities of daily living that is described as squeezing, crushing, heaviness, or chest tightness. It can also be more **vague and described as a numbness or burning in the chest**.

2-The location is often **substernal and may radiate to the right or left shoulder or arm** (left more commonly), **neck**, **back**, or **abdomen**. Ischemic symptoms may be associated with **diaphoresis, nausea, vomiting, and dyspnea**.

3-Chest pain generally **lasts from 5 to 20 minutes** and is usually **relieved by rest or sublingual nitroglycerin (SL NTG).**

4-Some patients (especially **women and older individuals**) present with **atypical chest pain. Patients with diabetes mellitus may have decreased pain sensation due to neuropathy**.

5-Patients with **variant (Prinzmetal)** angina are typically **younger** and may present with **chest pain at rest**, often early in the **morning**.

Diagnosis

1-Obtain the **medical history** to identify the quality and severity of chest pain, precipitating factors, location, duration, pain radiation, and response to nitroglycerin or rest.

2-Assess **nonmodifiable risk factors for coronary artery disease** (CAD): age, sex, and family history of premature atherosclerotic disease in first degree relatives (male onset before age 55 or female before age 65).

3-Identify the presence of **modifiable CAD risk factors**: hypertension, diabetes mellitus, dyslipidemia, and cigarette smoking.

4-Cardiac **troponin concentrations are not typically elevated in stable IHD**.

5-**Resting ECG is normal in at least half of patients with angina who are not experiencing acute ischemia.** About 50% of patients develop ischemic ECG changes during an episode of angina, which can be observed on the ECG during an **exercise stress test.**

6-**Coronary angiography** is the most accurate test for confirming CAD but is invasive and requires arterial access. Myocardial **perfusion imaging**, **cardiac magnetic resonance**, and **CT angiography** can also be used to detect CAD.

Treatment

Goals of Treatment:

1-A primary goal of therapy is complete (or nearly complete) **elimination of anginal chest pain and return to normal activities**.

2-Long-term goals are to **slow progression of atherosclerosis and prevent complications** such as MI, heart failure, stroke, and death.

Nonpharmacologic Therapy

1-**Lifestyle modifications** include daily physical activity, weight management, dietary therapy (reduced intake of saturated fats, and cholesterol), smoking cessation, psychological interventions (eg, screening and treatment for depression if appropriate), limitation of alcohol intake, and avoiding exposure to air pollution.

2-**Surgical revascularization** options for select patients include coronary artery bypass grafting (**CABG**) or percutaneous coronary intervention (**PCI**) with or without stent placement.

Pharmacologic Therapy

1-Guideline-directed **medical therapy** (GDMT) **reduces the rates of death and MI similar to revascularization therapy.**

2-Approaches to **risk factor modification** include the following recommendations:

- **Dyslipidemia**: Use moderate- or high-dose **statin** therapy in addition to lifestyle changes. Addition of ezetimibe (first) or a PCSK9 inhibitor (second) is reasonable for patients who do not tolerate statins or do **not attain a 50% decrease in LDL cholesterol (or LDL remains above 70–100 mg/dL).**
- **Blood pressure**: If BP is ≥130/80 mm Hg, institute drug therapy in addition to or after a trial of lifestyle modifications.

- **Diabetes mellitus**: Pharmacotherapy to achieve a target A1C of ≤7% is reasonable for select patients (eg, short duration of diabetes and long life expectancy). An A1C goal of <8% is reasonable for other patients, such as those with micro- or macrovascular complications or coexisting medical conditions.
- **Annual influenza vaccinations** are recommended.

Antithrombotic Therapy

1-**Aspirin** reduced platelet activation and aggregation. A small percentage of patients are nonresponsive to aspirin's antiplatelet effects.

2-The ACC/AHA guidelines contain the following recommendations for stable IHD:

- **Aspirin**: 75–162 mg daily should be continued indefinitely in the absence of contraindications.
- **Clopidogrel**: 75 mg daily is a suitable alternative for patients unable to take aspirin due to allergy or intolerance.

3-**Patient responsiveness to clopidogrel is highly variable**, with estimates of nonresponsiveness ranging from 5% to 44% of patients. The most common cause of nonresponsiveness is **nonadherence**, but **genetic polymorphisms** to CYP2C19 may contribute in some patients.

4-**Dual antiplatelet therapy** (DAPT) with aspirin plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is beneficial **after PCI with coronary stent placement** and after **treatment for ACS**. The combination of aspirin (75–162 mg daily) and clopidogrel 75 mg daily may be reasonable in **certain high-risk patients**.

5-**Rivaroxaban (low-dose)**, a direct factor Xa inhibitor, has demonstrated benefit (**reduction of major adverse cardiovascular events**) **in patients with CAD when added to aspirin therapy (further reading A)** [(2)].

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

1-**ACE inhibitors have not been shown to improve symptomatic ischemia or reduce chest pain episodes**.

2-The ACC/AHA guidelines for **stable IHD** recommend the following strategies:

- **Use ACE inhibitors in patients who also have** hypertension, diabetes, heart failure with reduced ejection fraction (HFrEF), or chronic kidney disease, unless contraindicated.
- **ARBs** are recommended for the same populations if patients are **intolerant to ACE inhibitors.**

β-Adrenergic Blockers

1-β-Blockers competitively inhibit the effects catecholamines on β-adrenoceptors. Blockade of β1-receptors in the heart reduces HR, contractility, and BP, thereby decreasing **oxygen demand**.

2-β-**Blockers are recommended over calcium channel blockers** (CCBs) for initial control of angina episodes in patients with stable IHD.

3-The target is to lower the **resting HR to 50–60 beats/min** and the **exercise HR to <100 beats/min.** For patients (eg, **elderly**) who cannot tolerate these ranges, the target HR should be as low as can be tolerated above 50 beats/min.

4-**β-Blockers may be combined** with CCBs or long-acting nitrates when initial treatment with β-blockers alone is unsuccessful.

5-**Only the β-blockers carvedilol**, **metoprolol** succinate, and **bisoprolol** should be used in patients with **HFrEF**.

6-β1-Selective agents are preferred in patients with chronic obstructive pulmonary disease, peripheral arterial disease (PAD), diabetes, dyslipidemia, and sexual dysfunction.

7-Drugs with combined α1- and β-blockade are effective for IHD, but **agents with intrinsic sympathomimetic activity provide little to no reduction in resting HR and are not preferred except perhaps in patients with PAD or dyslipidemia.**

8-If β-blocker therapy must be discontinued, doses should be tapered over 2–3 weeks to prevent abrupt withdrawal, which can significantly increase **oxygen demand** and induce ischemia and even MI because of up-regulation of β-receptors in the myocardium.

Calcium Channel Blockers

1-All CCBs reduce **oxygen demand** by reducing wall tension via lowering arterial BP and (to a minor extent) depressing contractility. CCBs also provide some increase in supply by inducing coronary vasodilation and preventing vasospasm.

2-CCBs or long-acting nitrates should be prescribed for relief of symptoms **when β-blockers are contraindicated or cause unacceptable side effects.**

3-**Dihydropyridine CCBs** (eg, nifedipine, amlodipine, isradipine, and felodipine) primarily affect vascular smooth muscle with little effect on the myocardium.

4-Short-acting agents should not be used because of their greater propensity to cause reflex tachycardia. Other side effects of these CCBs include hypotension, headache, gingival hyperplasia, and peripheral edema.

5-Although most CCBs are contraindicated in patients with HFrEF, **amlodipine and felodipine are considered safe options in these patients.**

6-**Nondihydropyridine CCBs** (**verapamil** and **diltiazem**) mostly affect the myocardium with minimal effects on vascular smooth muscle. These agents should be avoided in patients with concomitant HFrEF due to negative inotropic effects.

7-**Verapamil may cause constipation** in ~8% of patients.

Colchicine (Further reading B)

Nitrates

1-Nitrates cause vasodilation. **Most vasodilation occurs on the venous side**, leading to reduced preload, myocardial wall tension, and **oxygen demand**.

2-**All patients should have access to sublingual (SL) NTG tablets or spray** to treat acute angina episodes. Relief typically occurs within 5 minutes of administration.

3-**SL nitrates can also be used to prevent acute episodes if given 2–5 minutes before activities known to produce angina**; protection can last for up to 30 minutes with SL NTG and up to 1 hour with SL isosorbide dinitrate (ISDN).

4-Long-acting nitrates (or CCBs) should be prescribed for relief of symptoms **when β-blockers are contraindicated or cause unacceptable side effects.**

5-**Transdermal patches** and **isosorbide mononitrate (ISMN)** are most commonly prescribed for **long-term prevention of angina episodes**. **ISDN** is also effective, but the **three times daily regimen** requires dosing every 4–5 hours during the day to provide a nitrate-free interval.

6-**Chronic nitrate use should incorporate a 10- to 14-hour nitrate-free interval each day to reduce nitrate tolerance.** Because this approach places the patient at risk for angina episodes, the **nitrate-free interval is usually provided during the nighttime hours** when the patient has a reduced **oxygen demand** while sleeping.

7-The **extended-release ISMN products** that are dosed **twice daily** should **be given 7 hours apart (**eg, 7:00 AM and 2:00 PM). An extended-release, once daily ISMN product is available that provides 12 hours of nitrate exposure followed by a 12-hour nitrate-free interval.

8-**Transdermal NTG patches** are typically prescribed as "on in the AM and off in the PM" but patients should be given specific application and removal times (eg, apply at 8:00 AM and remove at 8:00 PM).

9-**Nitrates should not be used routinely as monotherapy for stable IHD** because of the **lack of angina coverage during the nitrate-free interval**, and potential for reflex tachycardia.

10-**Concomitant β-blocker or diltiazem therapy** can prevent rebound ischemia during the nitrate-free interval.

11-**Common nitrate side effects include** headache, flushing, nausea, postural hypotension, and syncope. **Headache can be treated with acetaminophen** and usually resolves after about 2 weeks of continued therapy.

12-**Transdermal NTG may cause skin erythema and inflammation**. Initiating therapy with smaller doses and/or rotating the application site can minimize transdermal nitroglycerin side effects.

Ranolazine

1-Ranolazine reduces ischemic episodes by selective inhibition of late **sodium current (INa)**, which reduces intracellular sodium concentration and improves myocardial function and perfusion.

2-**It does not impact HR, BP, the inotropic state, or increase coronary blood flow**. Ranolazine is effective as monotherapy for relief of angina symptoms but should only be used **if patients cannot tolerate traditional agents**.

3-Because it does not substantially affect HR and BP, it is recommended as add-on therapy to traditional antianginal agents for **patients who achieve goal HR and BP and still have exertional angina symptoms, patients who cannot achieve these hemodynamic goals due to adverse effects, and patients who reach maximum doses of traditional agents but still have angina symptoms.**

Treatment of Variable Threshold Angina and Prinzmetal Angina

1-Patients with **variable threshold angina require pharmacotherapy for vasospasm**. Most patients respond well to **SL NTG for acute attacks.**

2-Both **CCBs (**Nifedipine, verapamil, and diltiazem) **and nitrates are effective for chronic therapy**. **CCBs may be preferred** because they are dosed less frequently.

3-**Patients unresponsive to CCBs alone may have nitrates added. β-Blockers are not useful for vasospasm** because they may induce coronary vasoconstriction and prolong ischemia.

Evaluation of therapeutic outcomes

1-Assess for symptom improvement by **number of angina episodes, weekly SL NTG use, and increased exercise capacity or duration of exertion needed to induce angina.**

2-**Once patients have been optimized on medical therapy, symptoms should improve over 2–4 weeks and remain stable until the disease progresses**. Patients may require evaluation **every 1–2 months until target endpoints are achieved**; follow-up **every 6–12 months thereafter is appropriate.**

3-**Monitor for adverse drug effects such as headache and dizziness** with nitrates; fatigue and lassitude with β-blockers; and peripheral edema, constipation, and dizziness with CCBs.

Reference

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.
2-Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: A report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. Circulation. 2023 Jul 20;148(9).

Further reading

A-Addition of **low-dose rivaroxaban** 2.5 mg twice daily to aspirin 81 mg daily [(2)].

B-Colchicine:

1-**Inflammation is a key component in the development of atherosclerosis**. As a result, using select anti-inflammatory agents may have a role in improving cardiovascular outcomes [(2)].

2-**Colchicine** exhibits **anti-inflammatory** properties [(2)].

3-In patients with **chronic coronary disease** (CCD), **the addition of low dose colchicine** (0.5 mg daily) for secondary prevention may be considered to **reduce recurrent atherosclerotic cardiovascular disease (ASCVD) events** (myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death) [(2)].

College of Pharmacy
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Infectious Diseases

Urinary Tract Infections

Introduction

1-Infections of the urinary tract represent a wide variety of clinical syndromes including **urethritis**, **cystitis**, **prostatitis**, and **pyelonephritis**.

2-**A urinary tract infection (UTI)** is defined as the **presence of microorganisms** in the urine that **cannot be accounted for by contamination**.

3-**Lower tract infections** include **cystitis** (bladder), **urethritis** (urethra), **prostatitis** (prostate gland), and **epididymitis**.

4-**Upper tract infections** involve the **kidney** and are referred to as **pyelonephritis**.

5-**Uncomplicated UTIs** are **not associated with structural or functional abnormalities** that may interfere with the normal flow of urine or the voiding mechanism.

6-**Complicated UTIs** are the **result of a predisposing lesion of the urinary tract**, such as an abnormality of the urinary tract, stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses.

7-**Recurrent UTIs**, **two or more UTIs occurring within 6 months** or **three or more within 1 year,** are characterized by multiple symptomatic episodes with asymptomatic periods occurring between these episodes.

8-These infections are due to **reinfection** or to **relapse**. **Reinfections** are caused by a **different organism** and account for the majority of recurrent UTIs. **Relapse** represents the development of **repeated infections caused by the same initial organism**.

Pathophysiology

1-The bacteria causing UTIs usually originate from bowel flora of the host. Organisms typically gain entry into the urinary tract via **three routes**: the **ascending**, **hematogenous** (**descending**), and **lymphatic pathways**.

2-The most common cause of **uncomplicated UTIs is E. coli**, accounting for more than 80%–90% of community-acquired infections.

3-**Additional causative organisms are** Staphylococcus saprophyticus, Klebsiella pneumoniae, Proteus spp., Pseudomonas aeruginosa, and Enterococcus spp.

4-The urinary pathogens in **complicated or nosocomial infections** may include E**. coli**, which accounts for **less than 50% of these infections**, Proteus spp., K. pneumoniae, Enterobacter spp., P. aeruginosa, staphylococci, and enterococci. **Enterococci represent the second most frequently isolated organisms in hospitalized patients.**

5-**Most UTIs are caused by a single organism**; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, **multiple organisms may be isolated.**

Clinical presentation

1-The typical signs and symptoms of urinary tract infections are:

- **Lower UTI**: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness, and gross hematuria.
- **Upper UTI**: Flank pain, fever, nausea, vomiting, malaise and **costovertebral** tenderness.

NOTE: The handbook put the costovertebral tenderness with the lower UTI while the text put it with the Upper UTI (which is more accurate) .

2-**Symptoms alone are unreliable for the diagnosis of bacterial UTIs**. The key to the diagnosis of a UTI is the ability to demonstrate significant numbers of microorganisms present in urine specimen.

3-**Older patients frequently do not experience specific urinary symptoms**, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms.

4-The **most reliable** method of diagnosing UTIs is by **quantitative urine culture**.

Treatment

Goals of Treatment:

1-Eradicate the invading organisms, prevent or treat systemic consequences of infection, prevent recurrence of infection, and decrease the potential for collateral damage with excessively broad antimicrobial therapy.

2-The initial selection of an antimicrobial agent for the treatment of UTI is primarily based on the **severity of the presenting signs and symptoms**, the **site of infection**, and whether the infection is determined to be **complicated** or **uncomplicated**.

3-Other considerations include **antibiotic susceptibility**, **side-effect potential**, **cost**, current **antimicrobial exposure**, and the comparative **inconvenience of different therapies**.

Pharmacologic Therapy

1-Eradication of bacteria from the urinary tract is directly related to the **sensitivity** of the **organism** and the **achievable concentration** of the antimicrobial agent in the **urine**.

2-Most E. coli remain susceptible to trimethoprim–sulfamethoxazole, although resistance is increasing. In light of rising resistance and in order to decrease the overuse of broad-spectrum antimicrobials, **agents such as nitrofurantoin and fosfomycin are considered first-line treatments along with trimethoprim–sulfamethoxazole in acute uncomplicated cystitis.**

3-**Table 1** presents an overview of various therapeutic options for outpatient therapy for UTI. **Table 2** describes empiric treatment regimens for specific clinical situations.

Table 1: Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Oral Dose	Interval[a]	Duration
Lower tract infections				
Uncomplicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	3 days
	Nitrofurantoin monohydrate	100 mg	Twice a day	5 days
	Fosfomycin trometamol	3 g	Single dose	1 day
	Ciprofloxacin	250 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin–clavulanate Pivmecillinam	500 mg 400 mg	Every 8 hours Twice a day	5–7 days 3 days
Complicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	7–10 days
	Ciprofloxacin	250–500 mg	Twice a day	7–10 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	7–10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	Trimethoprim–sulfamethoxazole	1/2 SS tablet	Once a day	6 months
Acute pyelonephritis	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
		1000 mg ER	Once a day	7 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	14 days

a Dosing intervals for normal renal function. **DS**, double strength; **SS**, single strength.

Table 2: Evidence-Based Empirical Treatment of UTIs and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	*Escherichia coli*, *Staphylococcus saprophyticus*	1. Nitrofurantoin × 5 days (A,I)[a] 2. Trimethoprim–sulfamethoxazole × 3 days (A,I)[a] 3. Fosfomycin trometamol × 1 dose (A,I)[a] 4. Fluoroquinolone × 3 days (A,I)[a] 5. β-Lactams × 3–7 days (B,I)[a] 6. Pivmecillinam × 3–7 days (A,I)	Short-course therapy more effective than single dose Reserve fluoroquinolones as alternatives to development of resistance (A-III)[a] β-Lactams as a group are not as effective in acute cystitis than trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin[a] Pivmecillinam not available in the United States

Pregnancy	As above	1. Amoxicillin–clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim–sulfamethoxazole × 7 days	Avoid trimethoprim–sulfamethoxazole during the third trimester
Acute pyelonephritis			
Uncomplicated	*E. coli*	1. Fluoroquinolone × 7 days (A,I)[a] 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A,I)[a]	Can be managed as outpatient
	Gram-positive bacteria	1. Amoxicillin or amoxicillin–clavulanic acid × 14 days	
Complicated	*E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *Enterococcus faecalis*	1. Quinolone × 14 days 2. Extended-spectrum penicillin plus aminoglycoside	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	*E. coli* *K. pneumoniae* *Proteus* spp. *P. aeruginosa*	1. Trimethoprim–sulfamethoxazole × 4–6 weeks 2. Fluoroquinolone 4–6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

Acute Uncomplicated Cystitis

1-These infections are **predominantly caused by E. coli**, and antimicrobial therapy should be directed against this organism initially.

2-**Short-course** therapy **(3-day therapy)** with trimethoprim–sulfamethoxazole or a fluoroquinolone (eg, ciprofloxacin or levofloxacin, but not moxifloxacin) **is superior to single-dose therapy for uncomplicated infection.**

3-**Fluoroquinolones** should be reserved for patients with suspected or possible **pyelonephritis due to the collateral damage risk**. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a **one-time dose of fosfomycin** should be considered as first-line therapy.

4-In areas where there is more than 20% resistance of E. coli to **trimethoprim–sulfamethoxazole**, **nitrofurantoin or fosfomycin should be utilized**.

Complicated Urinary Tract Infections

Acute Pyelonephritis

1-The presentation of **high-grade fever** (>38.3°C) and severe flank pain should be treated as acute pyelonephritis, and aggressive management is warranted.

2-**Severely ill p**atients with **pyelonephritis** should be h**ospitalized and IV drugs administered initially. Milder cases may be managed with oral antibiotics in an outpatient setting.**

3-At the **time of presentation**, a **Gram stain of the urine** should be performed, along with urinalysis, culture, and sensitivities.

4-In the **mild to moderately symptomatic patient** for whom **oral therapy** is considered, an effective agent should be administered **for 7–14 days**, depending on the agent used.

5-**Fluoroquinolones** (ciprofloxacin or levofloxacin) **orally for 7–10 days** are the **first-line choice in mild-tomoderate pyelonephritis**. Other options include trimethoprim–sulfamethoxazole for 14 days.

6-If a Gram stain reveals **gram-positive cocci**, **Streptococcus faecalis should be considered** and treatment directed against this pathogen (**ampicillin**).

7-In **the seriously ill patient**, the traditional initial therapy is **an IV fluoroquinolone**, an aminoglycoside with or without ampicillin, or an extended spectrum cephalosporin with or without an aminoglycoside.

8-If the patient has been **hospitalized in the last 6 months, has a urinary catheter, or is in a nursing home, the possibility of P. aeruginosa and enterococci infection, as well as multiple-resistant organisms, should be considered.** In this setting, ceftazidime, ticarcillin–clavulanic acid, piperacillin, aztreonam, meropenem, or imipenem, in combination with an aminoglycoside, is recommended.

9-**Follow-up urine cultures** should be **obtained 2 weeks after the completion of therapy** to ensure a satisfactory response and to detect possible relapse.

Urinary Tract Infections in Men

1-**Therapy in men requires prolonged treatment**. A **urine culture should be obtained before treatment**, because the cause of infection in men is not as predictable as in women.

2-If **gram-negative bacteria are presumed**, **trimethoprim–sulfamethoxazole or a fluoroquinolone is a preferred agent**. Initial therapy is for **10–14 days.**

3-For **recurrent infections in men**, cure rates are much higher with **a 6-week regimen of trimethoprim–sulfamethoxazole.**

Recurrent Infections

1-Recurrent episodes of UTI (reinfections and relapses) **account for a significant portion** of all UTIs.

2-These patients are most **commonly women** and can be divided into **two groups**: those **with fewer than two or three episodes per year** and those who develop **more frequent infections.**

3-In patients with **infrequent infections** (ie, fewer than three infections per year), **each episode should be treated as a separately occurring infection.** Short-course therapy should be used in symptomatic female patients with lower tract infection.

4-In patients who have **frequent symptomatic infections**, **long-term prophylactic antimicrobial therapy may be instituted**. Therapy is **generally given for 6 months**, with urine cultures followed **monthly**.

5-In females who experience **symptomatic reinfections in association with sexual activity**, **voiding after intercourse** may help prevent infection. Also, **self-administered, single-dose prophylactic therapy with trimethoprim–sulfamethoxazole** taken after intercourse significantly reduces the incidence of recurrent infection in these patients.

6-Females who **relapse after short-course therapy should receive a 2-week course** of therapy.

7-In patients **who relapse after 2 weeks**, therapy should be c**ontinued for another 2–4 weeks.**

8-If **relapse occurs after 6 weeks of treatment**, **urologic examination** should be performed, and **therapy for 6 months or even longer may be considered**.

Special conditions

Urinary Tract Infection in Pregnancy

1-In females with **significant bacteriuria**, **symptomatic or asymptomatic treatment is recommended** to avoid possible complications during the pregnancy.

2-Therapy should consist of an **agent with a relatively low adverse-effect potential** (cephalexin, amoxicillin, or amoxicillin/clavulanate) administered for **7 days**.

3-**Tetracyclines** should be **avoided** because of teratogenic effects and **sulfonamides** should **not be administered during the third trimester** because of the possible development of kernicterus and hyperbilirubinemia. Also, the **fluoroquinolones should not be given** because of their potential to inhibit cartilage and bone development in the newborn.

Catheterized Patients

1-When **bacteriuria occurs in asymptomatic**, short-term catheterized patients **(<30 days**), the use of **systemic antibiotic therapy should be withheld** and the **catheter removed** as soon as possible. If the patient becomes **symptomatic**, the **catheter should again be removed**, and **treatment as described for complicated infections should be started.**

2-The use of **prophylactic systemic antibiotics** in patients with short-term catheterization reduces the incidence of infection over the first 4–7 days.

3-In **long-term catheterized patients**, however, antibiotics only postpone the development of bacteriuria and lead to emergence of resistant organisms.

Reference:

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

College of Pharmacy
Fourth year. Clinical Pharmacy

Infectious Diseases

Tuberculosis

Introduction

1-**Tuberculosis** (TB) is a **communicable infectious disease** caused by *Mycobacterium tuberculosis.* It can produce silent, **latent infection**, as well as progressive, **active disease**.

2-In 2019, there were about 10 million new cases and 1.2 million deaths from TB reported.

Pathophysiology and etiology

1-M. tuberculosis is transmitted from person to person **by coughing** or other activities that cause the organism to be aerosolized. Close contacts of TB patients are most likely to become infected.

2-**Human immunodeficiency virus (HIV) is the most important risk factor** for progressing to active TB. An HIV-infected individual with TB infection is over **100-fold more likely** to develop active disease than an HIV-seronegative patient.

3-Occasionally, **a massive inoculum of organisms may be introduced into the bloodstream**, causing widely disseminated disease and granuloma formation known as **miliary TB.**

Clinical presentation

1-Patients with TB typically present with **cough**, **weight loss**, **fatigue**, **fever**, and **night sweats**. Symptom onset may be gradual.

2-Frank **hemoptysis** usually occurs late in the course of disease but may present earlier.

3-**Sputum smear** is done to **detect mycobacteria**. **Chest radiograph** is also important.

4-Clinical features associated with **extrapulmonary TB vary depending on the organ system(s) involved but typically consist of slowly progressive decline of organ function** with low-grade fever and other constitutional symptoms.

5-Patients with **HIV may have atypical presentation**. HIV-positive patients are **less likely to have positive skin tests, or fever. They have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease**.

6-The most widely used s**creening method for tuberculous infection is the tuberculin skin test**, which uses purified protein derivative (PPD).

7-When active TB is suspected, attempts should be made to **isolate M. tuberculosis from the infected site**. Daily sputum collection over 3 consecutive days is recommended.

8-Tests to measure release of **interferon-γ** in the patient's blood in response to TB antigens may provide **quick and specific results for identifying M. tuberculosis**.

Treatment

1-**Goals of Treatment**: (1) Rapid **identification** of a new TB case; (2) **Initiation** of specific anti-TB treatment; (3) **Eradicating** M. tuberculosis infection; (4) Achievement of a **noninfectious** state in the patient, thus ending isolation; (5) **Preventing** the development of **resistance**; (6) **Adherence** to the treatment regimen by the patient; and (7) **Cure** of the patient as quickly as possible (generally at least 6 months of treatment).

2-Patients with active disease should be isolated to prevent spread of the disease.

3-Drug treatment is the cornerstone of TB management. A minimum of **two drugs, and generally three or four drugs, must be used simultaneously.**

4-Directly observed therapy (**DOT**) by a healthcare worker is a cost-effective way to ensure completion of treatment and is considered the standard of care.

5-Drug treatment is continued for **at least 6 months**, and **18–24 months for cases of multidrug-resistant TB** (MDR-TB).

6-**Surgery may be needed** to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

Pharmacologic Therapy

Latent Infection

1-Chemoprophylaxis should be initiated in patients **to reduce the risk of progression to active disease.**

2-There are **three recommended treatment regimens for latent tuberculosis infection (LTBI): 3 months of once weekly isoniazid plus rifapentine**, **4 months of daily rifampin,** or **3 months of daily isoniazid plus rifampin**.

3-The Centers for Disease Control and Prevention (CDC) recommends the 12week isoniazid/rifapentine regimen **as an equal alternative to 9 months of daily isoniazid for treating LTBI** in otherwise healthy patients aged 12 years or older who have greater likelihood of developing active TB.

4-Pregnant women, alcoholics, and patients with poor diets who are **treated with isoniazid should receive pyridoxine, 10–50 mg daily,** to reduce the incidence of central nervous system (CNS) effects or **peripheral neuropathies**.

Treating Active Disease

1-Table 1 lists options for treatment of culture-positive pulmonary TB caused by drug-susceptible organisms.

2-The standard TB treatment regimen is **isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months**, followed by **isoniazid and rifampin for 4 months** (**a total of 6 months of treatment**). Ethambutol can be stopped if susceptibility to isoniazid, rifampin, and pyrazinamide is shown.

3-Appropriate samples should be sent for culture and susceptibility testing **prior to initiating therapy** for all patients with active TB. The data should guide the initial drug selection for the new patient.

Table 1: Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug Susceptible Organisms

Initial Phase			Continuation Phase		
Regimen	Drugs[a]	Interval and Doses (Minimal Duration)[b]	Drugs	Interval and Doses[a]	Comments[b,c]
1	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily for 8 weeks, 7 days/week for 56 doses or 5 days/week for 40 doses[d]	Isoniazid/Rifampin	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)[c]	This is preferred regimen for patient with newly diagnosed pulmonary TB.
2	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily for 8 weeks, 7 days/week for 56 doses or 5 days/week for 40 doses[d]	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)[e]	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times weekly for 8 weeks (24 doses)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.
4	Isoniazid Rifampin Ethambutol Pyrazinamide	Daily for 2 weeks, then twice weekly for 6 weeks. 7 days/week for 14 doses, then twice weekly for 12 doses[e]	Isoniazid/Rifampin	Twice weekly for 36 doses (18 weeks)	Do not use twice weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.

DOT, directly observed therapy; **EMB**, ethambutol; **HIV**, human immunodeficiency virus; **INH**, isoniazid; **PZA**, pyrazinamide; **RIF**, rifampin.

aWhen DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days/week.

bBased on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7month (31week) continuation phase.

cPyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

dFive-day-a-week administration is always given by DOT.

4-If the patient is being evaluated for the retreatment of TB, **it is imperative to know what drugs were used previously and for how long.**

Drug Resistance

1-If the organism is drug resistant, **the aim is to introduce two or more active agents that the patient has not received previously**. With MDR-TB, no standard regimen can be proposed.

2-It is critical to **avoid monotherapy or adding only a single drug** to a failing regimen.

3-Drug resistance should be suspected in the following situations:

- Patients who have received **prior therapy for TB**
- Patients from **geographic areas** with a high prevalence of resistance (South Africa, Mexico, Southeast Asia, the Baltic countries, and the former Soviet states)
- Patients who are **homeless**, institutionalized, IV drug abusers, and/or infected with HIV
- Patients who **still have acid-fast bacilli–positive** sputum smears after 2 months of therapy
- Patients who **still have positive cultures** after 2–4 months of therapy
- Patients who **fail therapy or relapse after retreatment**
- Patients known to **be exposed to MDR-TB cases**

Special Populations

Tuberculous Meningitis and Extrapulmonary Disease

1-In general, **isoniazid**, **pyrazinamide**, **ethionamide**, **cycloserine** and **linezolid penetrate the cerebrospinal fluid readily.**

2-Patients with **CNS TB** are often **treated for longer periods (9–12 months).**

3-**Extrapulmonary TB of the soft tissues** can be treated **with conventional regimens**. TB of the **bone** is typically treated **for 9 months**, occasionally with surgical debridement.

Children

1-TB in children may be treated with regimens similar to those used in adults, although some **physicians still prefer to extend treatment to 9 months**.

2-**Pediatric doses** of drugs should be used.

Pregnant Women

1-The usual treatment of pregnant women is **isoniazid**, **rifampin**, and **ethambutol for 9 months.**

2-Women with TB should be **cautioned against becoming pregnant**, as the disease poses a risk to the fetus as well as to the mother.

3-**Isoniazid** or **ethambutol is relatively safe** when used during pregnancy. Supplementation **with B vitamins** is particularly important during pregnancy.

4-**Rifampin** has been **rarely associated with birth defects**, but those seen are occasionally severe, including limb reduction and CNS lesions.

5-**Pyrazinamide has not been studied in a large number of pregnant women**, but anecdotal information suggests that it may be safe.

6-**Ethionamide** may be associated with premature delivery, congenital deformities, and Down syndrome when used during pregnancy, so it cannot be recommended in pregnancy.

7-**Cycloserine** is not recommended during pregnancy. **Fluoroquinolones** should be avoided in pregnancy and during nursing.

Renal Failure

In nearly all patients, **isoniazid and rifampin do not require dose modifications** in renal failure. **Pyrazinamide** and **ethambutol** typically **require a reduction in dosing frequency from daily to three times weekly.**

Evaluation of therapeutic outcomes

1-**The most serious problem with TB therapy is nonadherence** to the prescribed regimen. **The most effective way to ensure adherence is with DOT**.

2-Patients should have **blood urea nitroge**n, serum **creatinine**, **aspartate transaminase** or **alanine transaminase**, and a **complete blood count** determined at **baseline** and **periodically**, depending on the presence of other factors that may increase the likelihood of toxicity (advanced age, alcohol abuse, and possibly pregnancy).

3-**Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL**. At this point, the offending agent(s) should be discontinued and alternatives selected.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

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Infectious Diseases

Central Nervous System Infections

Introduction

1-Central nervous system (CNS) infections include a wide variety of clinical conditions and etiologies: **meningitis**, **meningoencephalitis**, **encephalitis**, **brain and meningeal abscesses**, and **shunt infections**. The focus of this lecture is **meningitis**.

2-CNS infections may be caused by a variety of **bacteria**, **fungi**, **viruses**, and **parasites**. **The most common causes of bacterial meningitis** are **Streptococcus pneumoniae**, group B **Streptococcus**, **Neisseria meningitidis**, **Haemophilus influenzae**, and **Listeria monocytogenes**

Pathophysiology

1-The critical **first step** in the acquisition of acute bacterial meningitis is **nasopharyngeal colonization** of the host by the bacterial pathogen.

2-Most cases of acute bacterial meningitis probably **occur following bacteremia**, but the high incidence of pneumococcal meningitis in patients with sinusitis and otitis media suggests that **direct spread to the CNS can also occur**.

3-The **neurologic sequelae of meningitis** occur due to the activation of host inflammatory pathways.

4-These events **lead to cerebral edema**, **elevated intracranial pressure**, **decreased cerebral blood flow**, **cerebral ischemia**, and **death**.

5-Passive and active exposure to **cigarette smoke** and the presence of a **cochlear implant** that includes a positioner both **increase the risk of bacterial meningitis**.

Clinical presentation

1-**Signs and symptoms of acute bacterial meningitis include** fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia, and severe headache.

2-**Up to 95% of patients exhibit at least two of the following symptoms:** fever, nuchal rigidity, headache, and altered mental status.

3-**Kernig** and **Brudzinski** signs may be present but are poorly sensitive and **frequently absent in children**.

4-Clinical signs and symptoms in **young children** may include bulging fontanelle, apnea, purpuric rash, and convulsions.

5-**Purpuric and petechial skin** lesions typically indicate **meningococcal involvement,** although the lesions may be present with H. influenza meningitis. Rashes rarely occur with pneumococcal meningitis.

6-Meningitis causes **changes in CSF fluid**, and these changes can be used as diagnostic markers of infection (**Table1**).

7-**CSF culture is the gold standard for diagnosis** of bacterial meningitis .

8-**Gram stain is a rapid, inexpensive, and accurate method to assess the presence of bacteria in CSF**. However, prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose.

9-Polymerase chain reaction (**PCR**) techniques can rapidly diagnose CNS infections and may be **particularly useful in patients who have received antimicrobial therapy** before lumbar puncture.

Table 1: Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm^3 or 10^6/L)	<5 (<30 in newborns)	1000–5000	50–1000	20–500	25–500
Differential[a]	Monocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
Protein (mg/dL)	<50 (<500 mg/L)	Elevated	Mild elevation	Elevated	Elevated
Glucose (mg/dL)	45–80 (2.5–4.4 mmol/L)	Low	Normal	Low	Low
CSF/blood glucose ratio	50%–60%	Decreased	Normal	Decreased	Decreased

aInitial cerebrospinal fluid (CSF), white blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs). In CNS infection due to tuberculosis, "therapeutic paradox" may occur in which a lymphocytic predominance becomes neutrophilic during antituberculous treatment.

Treatment

1-**Goals of Treatment**: Effective eradication of infection, amelioration of signs and symptoms, and reduction of morbidity and mortality.

2-Key elements include initiating **appropriate antimicrobials**, providing **supportive care**, and **preventing disease** through timely introduction of vaccination and chemoprophylaxis.

3-Administration of **fluids**, **electrolytes**, **antipyretics**, and **analgesics** may be indicated for patients presenting with a possible CNS infection.

4-Additionally, **venous thromboembolism prophylaxis**, **antiepileptic therapy**, and **ICP monitoring may be needed.**

Pharmacologic Therapy

1-**Empiric antimicrobial therapy** should be instituted as soon as possible to eradicate the causative organism (**Table-2**). Antimicrobial therapy should **last at least 48–72 hours** or **until the diagnosis of bacterial meningitis can be ruled out.**

2-**The time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour**.

Table 2: Bacterial Meningitis: Most Likely Etiologies and Empiric Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy[a]
<1 month	*S. agalactiae* Gram-negative enterics[b] *L. monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1–23 months	*S. pneumoniae* *N. meningitidis* *H. influenzae* *S. agalactiae*	Vancomycin[c] + third generation cephalosporin (cefotaxime *or* ceftriaxone)
2–50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[c] + third generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[b] *L. monocytogenes*	Vancomycin[c] + ampicillin + third generation cephalosporin (cefotaxime *or* ceftriaxone)

3-**Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.**

4-With increased meningeal inflammation, there will be greater antibiotic penetration (**Table-3**). **Problems of CSF penetration** can be overcome by direct **instillation of antibiotics intrathecally or intraventricularly.**

5-Advantages of direct instillation, however, must be weighed against the **risks of invasive CNS procedures and adverse effects**. **Intraventricular delivery** may be necessary in patients who have **shunt infections that are difficult to eradicate** .

6-See (**Table-4**) for **antimicrobial agents of first choice and alternatives** for treatment of meningitis caused by gram-positive and gram-negative microorganisms.

Table 3: Penetration of Anti-infective Agents into the CSF

Therapeutic Levels in CSF With or Without Inflammation of Meninges	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin
Flucytosine	Pyrazinamide
Foscarnet	Rifampin
Fosfomycin	Sulfonamides
Ganciclovir	Trimethoprim
Isoniazid	Voriconazole

Therapeutic Levels in CSF With Inflammation of Meninges	
Ampicillin ± sulbactam	Imipenem
Aztreonam	Meropenem
Cefepime	Nafcillin
Cefotaxime	Ofloxacin
Ceftazidime	Penicillin G
Ceftriaxone	Piperacillin/Tazobactam[b]
Cefuroxime	Pyrimethamine
Colistin	Quinupristin/Dalfopristin
Daptomycin	Ticarcillin ± clavulanic acid[b]
Ethambutol	Vancomycin

Nontherapeutic Levels in CSF With or Without Inflammation of Meninges	
Aminoglycosides	Cephalosporins (second generation)[d]
Amphotericin B	Doxycycline[e]
β-Lactamase inhibitors[c]	Itraconazole[f]
Cephalosporins (first generation)	

a Using recommended CNS dosing and compared to MIC of target pathogens. **b** May not achieve therapeutic levels against organisms with higher MIC, as in P. aeruginosa. Tazobactam does not penetrate the blood-brain barrier. **c** Includes clavulanic acid, sulbactam, and tazobactam. **d** Cefuroxime is an exception. **e** Documented effectiveness for B. burgdorferi. **f** Achieves therapeutic concentrations for Cryptococcus neoformans therapy.

7-Meningitis caused by **S. pneumoniae** has been treated successfully with **10–14 days** of antibiotic therapy, while cases caused by **N. meningitidis** or **H. influenzae** usually can be treated with a **7-day course**.

8-In contrast, a longer duration (**21 days or more**) has been recommended for patients with **L. monocytogenes**, **Gram-negative or pseudomonal meningitis**.

Table 4: Antimicrobial Agents of First Choice and Alternative Choice for Treating Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Gram-Positive Organisms			
Streptococcus pneumoniae[a]			10–14 days
Penicillin susceptible MIC ≤0.06 mcg/mL (mg/L)	Penicillin G or ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), cefepime (B-II), or meropenem (B-II)	
Penicillin resistant MIC >0.06 mcg/mL (mg/L)	Vancomycin[b,c] + cefotaxime or ceftriaxone (A-III)	Moxifloxacin (B-II)	
Ceftriaxone resistant MIC >0.5 mcg/mL (mg/L)	Vancomycin[b,c] + cefotaxime or ceftriaxone (A-III)	Moxifloxacin (B-II)	

Staphylococcus aureus			14–21 days
Methicillin susceptible	Nafcillin or oxacillin (A-III)	Vancomycin (A-III) or meropenem (B-III)	
Methicillin resistant	Vancomycin[b,c] (A-III)	Trimethoprim-sulfamethoxazole or linezolid (B-III)	
Group B *Streptococcus*	Penicillin G or ampicillin (A-III) ± gentamicin[b,c]	Ceftriaxone or cefotaxime (B-III)	14–21 days
S. epidermidis	Vancomycin[b,c] (A-III)	Linezolid (B-III)	14–21 days[d]
L. monocytogenes	Penicillin G or ampicillin ± gentamicin[b,c,e] (A-III)	Trimethoprim-sulfamethoxazole (A-III), meropenem (B-III)	≥21 days
Gram-Negative Organisms			
Neisseria meningitis			7–10 days
Penicillin susceptible	Penicillin G or ampicillin (A-III)	Cefotaxime or ceftriaxone (A-III)	
Penicillin resistant	Cefotaxime or ceftriaxone (A-III)	Meropenem or moxifloxacin (A-III)	
Haemophilus influenzae			7–10 days
β-lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), cefepime (A-III) or moxifloxacin (A-III)	
β-lactamase positive	Cefotaxime or ceftriaxone (A-I)	Cefepime (A-I) or moxifloxacin (A-III)	
Enterobacteriaceae[f]	Cefotaxime or ceftriaxone (A-II)	Cefepime (A-III), moxifloxacin (A-III), meropenem (A-III) or aztreonam (A-III)	21 days
Pseudomonas aeruginosa	Cefepime or ceftazidime (A-II) ± tobramycin[b,c] (A-III)	Ciprofloxacin (A-III), meropenem (A-III), piperacillin plus tobramycin[a,b] (A-III), colistin sulfomethate[g] (B-III), aztreonam (A-III)	21 days

Dexamethasone as an Adjunctive Treatment for Meningitis

1-In addition to antibiotics, **dexamethasone is a commonly used adjunctive therapy** in the treatment of acute bacterial meningitis to **immunomodulate the inflammatory response**.

2-Recommendations call for the use of adjunctive dexamethasone in **infants and children** (6 weeks of age and older) **with H. influenzae meningitis**. The recommended intravenous dose is 0.15 mg/kg every 6 hours for **2–4 days**, initiated **10–20 minutes prior to or concomitant with the first dose of antibiotics.**

3-In infants and children with **pneumococcal meningitis**, adjunctive dexamethasone may be considered **after weighing the potential benefits and possible risks**.

4-If **pneumococcal meningitis** is suspected or proven, **adults should receive dexamethasone** 0.15 mg/kg (up to 10 mg) every 6 hours for 2–4 days with the first dose administered **10–20 minutes prior to first dose of antibiotics**.

Neisseria meningitidis (Meningococcus)

1-**N. meningitidis is a leading cause of bacterial meningitis** among children and young adults around the world. It is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions.

2-The presence of **petechiae** may be the primary clue that the underlying pathogen is N. meningitidis. Patients may also have disseminated **intravascular coagulation** (DIC).

3-**Deafness** unilaterally, or more commonly bilaterally, may develop early or late in the disease course.

4-**Third-generation cephalosporins** (ie, cefotaxime and ceftriaxone) are the recommended empiric treatment for meningococcal meningitis.

5-**Penicillin G or ampicillin is recommended for penicillin-susceptible isolates**. The recommended duration of therapy is typically **7 days** if there is good clinical response.

6-Antimicrobial **chemoprophylaxis** of close contacts should be started as soon as possible (ideally <24 hours after identification of the patient). Ciprofloxacin and rifampin are the two most used chemoprophylactic agents.

Streptococcus pneumoniae (Pneumococcus or Diplococcus)

1-Streptococcus group B is **a leading cause of community acquired bacterial meningitis in patients 2 months of age or older.**

2-Coma, hearing impairment, and seizures are common neurologic complications.

3-The combination of **vancomycin** and **ceftriaxone** can be used as empirical treatment until antimicrobial susceptibility data are available.

Haemophilus influenzae

1-Widespread vaccination of infants and children has effectively decreased the incidence of bacterial meningitis due to **Hib** in children between the ages of 1 month and 5 years, resulting in a significant decline in all cases of bacterial meningitis.

2-**Third-generation cephalosporins** (cefotaxime and ceftriaxone) are the drugs of choice for empirical therapy for H. influenzae type b meningitis as they are active against β-lactamase–producing and non-β-lactamase–producing strains. **Cefepime** and **fluoroquinolones are suitable alternatives** regardless of β-lactamase activity.

3-Recommended duration of treatment is **7 days (adults) or 7–10 days (children).**

4-**Dexamethasone** is beneficial for treatment of **infants and children with Hib meningitis** to diminish the risk of hearing loss, if given **before or concurrently** with the first dose of antimicrobial agent(s).

5-**Chemoprophylaxis with rifampin** is indicated to reduce the risk of secondary invasive Hib disease in close contacts.

6-Rifampin should be administered orally, **once a day for 4 days** (20 mg/kg/dose; maximum, 600 mg).

Listeria monocytogenes

1-L. monocytogenes is implicated in approximately 10% of meningitis cases in patients **older than 65 years of age** and carries a case-fatality rate of approximately 18% in the United States.

2-Treatment of L. monocytogenes meningitis should consist of **penicillin G or ampicillin**. **The addition of aminoglycoside is also recommended in proven infection in both children and adults.**

3-Patients should be treated **a minimum of 21 days**. **Trimethoprim–sulfamethoxazole and meropenem may be effective alternatives** because adequate CSF penetration is achieved with these agents.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

College of Pharmacy
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Rheumatologic Disorders

Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, **progressive autoimmune condition** that primarily affects joints and the synovium but can **also have systemic manifestations**.

Pathophysiology

1-RA results from a combination of **genetic** susceptibility, **nongenetic** factors, and a **triggering event**. An **unknown infectious process is thought to be the primary trigger**.

2-**Activated T cells stimulate B cells to produce autoantibodies**. **Antibodies to immunoglobulin G (IgG) are known as rheumatoid factor** (RF) and have a strong correlation to the pathogenesis and **poor prognosis of RA.**

3-B cells also produce **proinflammatory cytokines**, including tumor necrosis factor (**TNF**) and the interleukin (**IL**) system, which induce further enhance T-cell proliferation and differentiation, and encouraging cell migration.

4-**Overexpression of tumor suppressor gene p53** increased anticitrullinated protein antibodies (**ACPA**). ACPA positivity is associated with a **worse prognosis** in patients with RA.

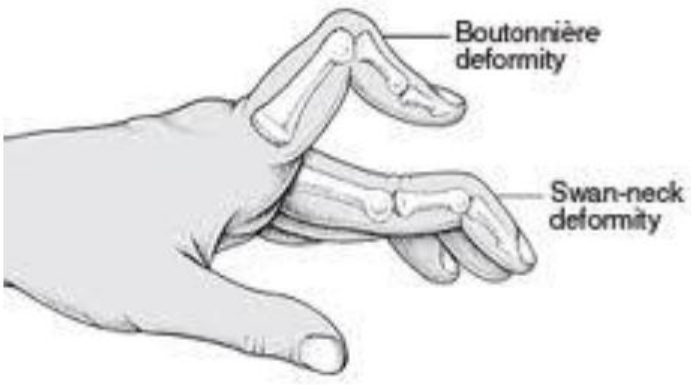
5-The inflamed, fibrotic synovium (**pannus**) **invades cartilage and bone around it**, promoting further destruction and dysregulation.

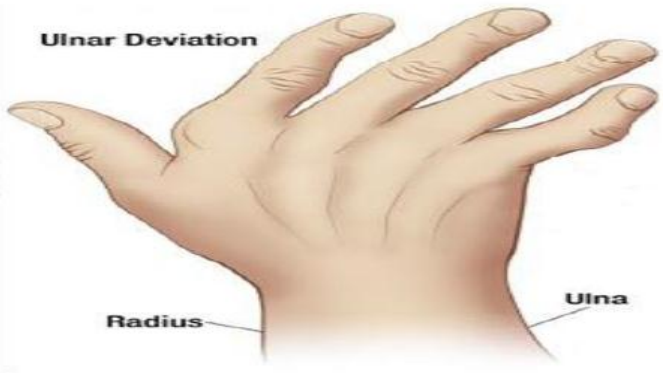
Clinical presentation

1-**Nonspecific prodromal symptoms** developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain.

2-Joint involvement tends to be **symmetric and affects small joints** of the hands, feet, wrists, and ankles; elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be affected.

3-**Joint stiffness is typically worse in the morning, usually exceeds 30 minutes, and may persist all day**. Tissue warm, and may be erythematous.





4-If **left untreated, long-term joint inflammation may lead to** bony erosions and **deformities of** joints (**swan neck deformity, boutonnière deformity, and ulnar deviation**).

5-**Extra-articular involvement may include** rheumatoid nodules, interstitial lung disease, pleural effusions, vasculitis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.

6-RF is detected in 70%–80% of patients; **higher titers generally reflect a more severe disease course**. **ACPA antibodies generally predict a more aggressive disease course**.

7-**Normocytic anemia, thrombocytosis or thrombocytopenia, and leukopenia may also be present**.

Diagnosis

1-The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010.

2-The criteria use a scoring system with a combined **score of 6 or more out of 10 indicating that the patient has definite RA.**

Treatment

Goals of Treatment: The ultimate goal is **to induce complete remission or low disease activity**. Additional goals are to reduce inflammation and symptoms, maintain ability to function in daily activities, slow destructive joint changes, and delay disability.

Nonpharmacologic Therapy

1-**Patient education** about the disease and medications (e.g., potential adverse effects, self-administration of injectable agents) is important.

2-**Physical therapy** can reduce pain and inflammation while preserving joint function. Exercise and physical activity (including **aerobic activity** and **muscle-strengthening exercises)** can improve disease outcomes.

3-**Assistive devices and orthoses** such as braces and supports are useful to improve pain and function. **Occupational therapy** can provide benefits such as appropriate footwear and splinting.

4-**Weight loss** can help decrease stress on joints. **Surgical options** (e.g., joint replacements) are reserved for patients with more severe disease with significant cartilage loss.

Pharmacologic Therapy

General Approach

1-Therapies to **treat RA and slow disease progression** include conventional and biologic disease-modifying antirheumatic drugs (DMARDs) and the small-molecule oral Janus-kinase (JAK) inhibitors.

- **Conventional DMARDs** include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine.

- **Biologic DMARDs** include **TNF inhibitors** (adalimumab, certolizumab, etanercept, golimumab, and infliximab) and **non-TNF biologics** (abatacept, sarilumab, tocilizumab, rituximab, and anakinra).
- **JAK inhibitors** include baricitinib, tofacitinib, and upadacitinib.

2-Current RA treatment guidelines recommend **initiating conventional DMARDs irrespective of disease activity once a diagnosis is established**.

3-**The preferred conventional DMARD is methotrexate unless a contraindication exists**.

4-For patients with early RA (<6 months duration) and **low disease activity, DMARD monotherapy is recommended**. **Double or triple DMARD therapy is recommended for moderate or high disease activity.**

5-**A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity**.

6-**A JAK inhibitor is an alternate** option if disease activity remains moderate or high with combination conventional DMARDs.

7-**If disease activity remains moderate or high** despite conventional DMARDs or biologics, **a low-dose glucocorticoid** (prednisone ≤10 mg/day or equivalent) can be added for the shortest duration necessary.

8-**If patients achieve remission, DMARDs and biologic agents can be tapered**, but patients should remain on DMARD therapy at some dosage level.

9-Dual biologic therapy should be avoided due to the risk of infection associated with immunosuppression.

10-**Because DMARDs can take weeks to months to take effect**, NSAIDs, **glucocorticoids**, and other **analgesics** (eg, acetaminophen) can be used to provide more rapid symptomatic relief ("**bridge therapy**").

11-**NSAIDs do not slow disease progression**, and g**lucocorticoids can have serious side effects**, making **both drug classes less desirable for long-term use**.

Conventional DMARDs

1-Methotrexate inhibits dihydrofolate reductase. Injectable (subcutaneous [**SC**], intramuscular [**IM**]) methotrexate **has higher bioavailability than oral methotrexate** and thus provides superior clinical efficacy; it is typically **better tolerated** with **less potential to cause gastrointestinal (GI) side effects as well.**

2-Oral methotrexate doses >15 mg weekly may not have significant added clinical benefit; **changing to SC methotrexate may increase bioavailability and clinical benefit in this situation.**

3-Clinical benefit can be seen 3–6 weeks after starting therapy. Methotrexate has numerous adverse effects; **concomitant folic acid 1–5 mg/day may reduce some adverse effects without loss of efficacy.**

4-**Methotrexate is teratogenic**, and patients should use contraception and discontinue the drug if conception is planned.

5-**Leflunomide ***** efficacy for RA is similar to that of methotrexate.

6-Sulfasalazine ***** use is limited by GI adverse effects**.

7-**Hydroxychloroquine *****: Its main advantage is that **it does not require frequent, routine laboratory monitoring because it is not generally associated with infection risk or hepatic, renal, or blood cell abnormalities.** GI side effects can sometimes be mitigated by taking the **medication with food or splitting the dose** into two doses. **Periodic ophthalmologic examinations are necessary** for early detection of **irreversible retinal toxicity**.

*****: Can be used alone or in combination with DMARDs**

Biologic DMARDs (given i.v or s.c)

1-Biologic agents are **genetically engineered** . They are categorized as **either TNF inhibitors or non-TNF biologics**. They may be effective **when conventional DMARDs fail** to achieve adequate disease control but are considerably **more expensive**.

2-**Biologic DMARDs are associated with an increased risk of infection** due to immunosuppressive effects. A **tuberculin skin test** or interferon gamma release assay (IGRA) blood test should be obtained before starting a biologic **to detect and treat latent or active tuberculosis.**

3-Patients should also be **screened for hepatitis B** before starting biologic therapy because of the risk for reactivation.

4-Biologics can be used in **combination with conventional DMARDs**, but **multiple biologics should not be used** concomitantly due to additive immunosuppressive effects.

5-In general, if **patients are switched from one biologic to another, the new agent should be initiated when the patient is due for a dose of the previous biologic**.

6-Because of immunosuppressive effects, **patients taking biologics should notify their providers if they are being treated for an infection or plan to undergo major surgery**. Treatment may need to be held u**ntil appropriate postsurgical healing and/or resolution of infection** can be confirmed. **Live vaccines should not be given** to patients taking biologic agents.

7-**Biosimilars are biologic products that have been verified to have no clinically meaningful differences compared to an FDA-approved reference biologic product**. These agents can increase access to RA treatment because **their costs are lower** than the originator products.

A-TNF-α Inhibitors (Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab)

1-They **should not be used in patients with moderate-to-severe heart failure** (New York Heart Association [NYHA] class III/IV) because new-onset and worsening heart failure have been reported.

2-These agents increase **the risk of serious infection and malignancies** (eg, lymphoma, skin cancers), and new-onset or exacerbation of demyelinating disorders such as multiple sclerosis has been observed.

3-**To prevent formation of an antibody response to Infliximab, methotrexate must be given orally** in doses used to treat RA for as long as the patient continues infliximab. **Premedication with an antihistamine**, **acetaminophen**, and/or a **glucocorticoid** can decrease development of **infusion-related reactions**.

B-Costimulation Modulator

Abatacept *** inhibits the activation of T cells. Abatacept is indicated for moderate-to-severe RA .

C-IL-6 Receptor Antagonists

1-**Sarilumab ***** is indicated for treatment of patients with moderate-to-severe RA who have had an incomplete response or intolerance to one or more DMARDs.

2-**Tocilizumab ***** can be used for patients with moderate-to-severe RA who have had an incomplete response to one or more DMARDs.

D-Anti-CD20 Monoclonal Antibody

1-**Rituximab** is a monoclonal antibody that binds the CD20 antigen on the surface of B cells. Binding of rituximab to B cells results in nearly complete depletion of peripheral B cells, with a gradual recovery over several months.

2-Rituximab can be initiated in patients **with moderate to-severe RA who have had an incomplete response to one or more TNF inhibitors**. **Methotrexate should be given concurrently** in the usual doses for RA to achieve optimal outcomes.

3-**Methylprednisolone** 100 mg IV is recommended 30 minutes before each infusion as well as **acetaminophen** and an **antihistamine** to reduce the incidence and severity of **infusion reactions.**

E-IL-1 Receptor Antagonist

1-**Anakinra***** is an IL-1 receptor antagonist; **it is less effective than other biologics**, is used **infrequently**, and is not included in the current ACR treatment recommendations.

2-However, it can be used in patients with moderate-to-severe RA who have failed one or more DMARDs.

Janus-Kinase Inhibitors

1-Baricitinib, tofacitinib, and upadacitinib are **oral**, small-molecule, **nonbiologic** JAK inhibitors.

2-**Baricitinib ***** is FDA approved for adults with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors.

3-**Tofacitinib*** and upadacitinib ***** have FDA approval for treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

4-**JAK inhibitors should not be given concomitantly with biologic**. Labeling for all JAK inhibitors includes black-box warnings about serious infections, lymphomas, and other malignancies. **Live vaccinations should not be given during treatment**.

5-Patients should be **tested and treated for latent tuberculosis** before starting therapy.

*****: Can be used alone or in combination with DMARDs**

Nonsteroidal Anti-inflammatory Drugs

1-NSAIDs possess both analgesic and anti-inflammatory properties and reduce stiffness, but **they do not slow disease progression or prevent bony erosions or joint deformity** and should not be used as monotherapy for RA treatment.

2-They have a more rapid onset of action than DMARDs and may be beneficial to "**bridge**" **patients while DMARDs take effect**.

Glucocorticoids

1-Glucocorticoids have anti-inflammatory and immunosuppressive properties; although they have been shown to slow RA progression, **glucocorticoids should not be used as monotherapy for RA due to the potential for serious, long-term adverse effects**.

2-They should be used at the **lowest effective dose for the shortest period of time**. According to the ACR, short-term glucocorticoid therapy is **defined as <3 months**, and low-dose glucocorticoid is defined as **prednisone ≤10 mg/day (or equivalent).**

3-Similar to NSAIDs, oral glucocorticoids (eg, prednisone, methylprednisolone) can be used to **"bridge" patients while DMARDs take effect**. They can also be used **as adjuncts** to DMARDs at the lowest dose possible in patients with refractory disease.

4-**High-dose, short-term bursts can** be used as needed **for acute flares of RA symptoms**, **followed by tapering** to the lowest effective dose to control symptoms or until discontinued over several days.

5-**The IM route may be useful in nonadherent patients**. **Depot forms** (triamcinolone and methylprednisolone) **provide 2–6 weeks of symptom control**. **Onset of effect may be delayed for several days**.

6-The **depot effect provides a physiologic taper**, avoiding hypothalamic–pituitary axis suppression.

7-**Intra-articular injections may be useful when only a few joints are involved**. Injections should **not be repeated more often than every 3 months** because of the potential for accelerated loss of joint cartilage.

Evaluation of therapeutic outcomes

1-**Assess disease activity at baseline and at each follow-up visit to evaluate therapeutic response**.

2-**Laboratory monitoring** of acute phase reactants such as **CRP** and **ESR** can be useful in assessing inflammation.

3-It is important to monitor and assess for **clinical and laboratory adverse effects** of the medications used to treat RA which may include [**complete blood count** (CBC) with differential to detect hematological toxicity, **SCr** to detect renal toxicity, liver function tests (**LFTs**): (**ALT**, **AST**) to detect hepatic toxicity]and **ophthalmologic examination** (for patient taking hydroxychloroquine) to detect ocular toxicity.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

College of Pharmacy
Fourth year. Clinical Pharmacy

Rheumatologic Disorders

Osteoarthritis

Introduction

Osteoarthritis (OA) is a common, progressive **disorder affecting primarily weight-bearing diarthrodial joints**, characterized by progressive **destruction of articular cartilage**, osteophyte formation, pain, limitation of motion, deformity, and disability.

Pathophysiology

1-**Primary (idiopathic) OA, the more common type, has no known cause**. **Secondary OA is associated with a known cause** such as trauma.

2-**OA usually begins with damage to articular cartilage** through injury, excessive joint loading from obesity or other reasons, or joint instability.

3-Cartilage loss causes **joint space narrowing** and painful, deformed joints. **New bone formations (osteophytes**) at joint margins are thought to help stabilize affected joints.

4-**Inflammatory changes can occur in the joint capsule and synovium**. **Inflammatory changes result in synovial effusions and thickening**.

Clinical presentation

1-**Risk factors include** increasing age, obesity, sex, certain occupations and sports activities, history of joint injury or surgery, and genetic predisposition.

2-**The predominant symptom** is pain in affected joints. Pain accompanies joint activity and decreases with rest.

3-**Joints most commonly affected are** the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hand, first carpometacarpal joint, knees, hips, cervical and lumbar spine, and first metatarsophalangeal (MTP) joint of the toe.

4-Limitation of motion, stiffness, **crepitus**, and deformities may occur.

5-Upon arising, **joint stiffness typically lasts less than 30 minutes** and resolves with motion. Presence of warm, red, and tender joints suggests inflammatory synovitis.

6-Physical examination of affected joints reveals **tenderness**, **crepitus**, and possibly enlargement. **Heberden** and **Bouchard** nodes are bony enlargements (osteophytes) of the DIP and PIP joints, respectively.

Diagnosis

1-Diagnosis is made through patient **history**, **physician examination**, **radiologic** findings, and **laboratory testing**.

2-American College of Rheumatology criteria for classification of OA of the hips, knees, and hands include presence of **pain**, **bony changes on examination**, **normal erythrocyte sedimentation rate** (ESR), and **radiographs showing osteophytes** or joint **space narrowing.**

Treatment

Goals of Treatment: (**1**) Educate the patient, family members, and caregivers; (**2**) relieve pain and stiffness; (**3**) maintain or improve joint mobility; (**4**) limit functional impairment; and (**5**) maintain or improve quality of life.

Nonpharmacologic Therapy

1-**Educate** the patient about the disease process and extent, prognosis, and treatment options. Promote dietary counseling, exercise, and a weight loss program for overweight patients.

2-**Physical therapy**—with heat or cold treatments and an exercise program—helps maintain range of motion and reduce pain and need for analgesics.

3-**Assistive and orthotic devices** (canes, walkers, braces, heel cups, and insoles) can be used during exercise or daily activities.

4-**Surgical procedures** (e.g., osteotomy, arthroplasty, joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy

Pharmacologic Therapy

General Approach

Drug therapy is targeted at relief of pain. Apply an individualized approach (Figs. 1 and 2). **Continue appropriate nondrug therapies when initiating drug therapy**.

Knee and Hip OA

1-**Acetaminophen** is a **preferred first-line treatment**; it may be less effective than oral NSAIDs but has a lower risk of serious gastrointestinal (GI) and cardiovascular (CV) events.

2-**Acetaminophen** is usually well tolerated, but potentially fatal **hepatotoxicity** with overdose is well documented. It should be avoided in chronic alcohol users or patients with liver disease.

3-Nonselective NSAIDs or cyclooxygenase-2 (COX-2) selective inhibitors (eg, celecoxib) are recommended **if a patient fails acetaminophen**.

4-Nonselective NSAIDs may cause minor GI complaints such as nausea, dyspepsia, anorexia, abdominal pain, and diarrhea. **They may cause gastric and duodenal ulcers** and bleeding through direct (topical) or indirect (systemic) mechanisms.

5-**Risk factors for NSAID-associated ulcers and ulcer complications** (perforation, gastric outlet obstruction, and GI bleeding) **include** longer duration of NSAID use, higher dosage, age older than 60 years, past history of peptic ulcer disease of any cause, history of alcohol use, and concomitant use of glucocorticoids or anticoagulants.

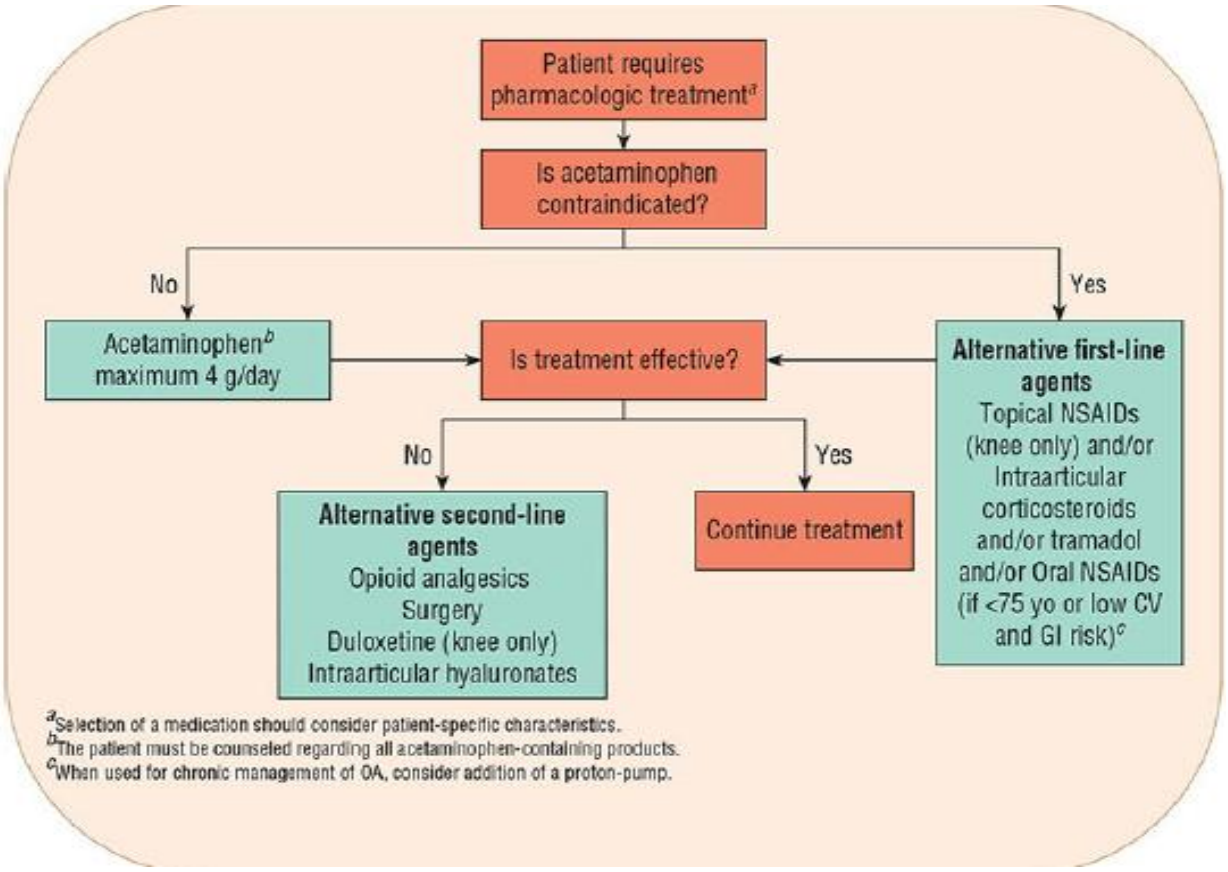


Figure 1: Treatment recommendations for knee and hip osteoarthritis.

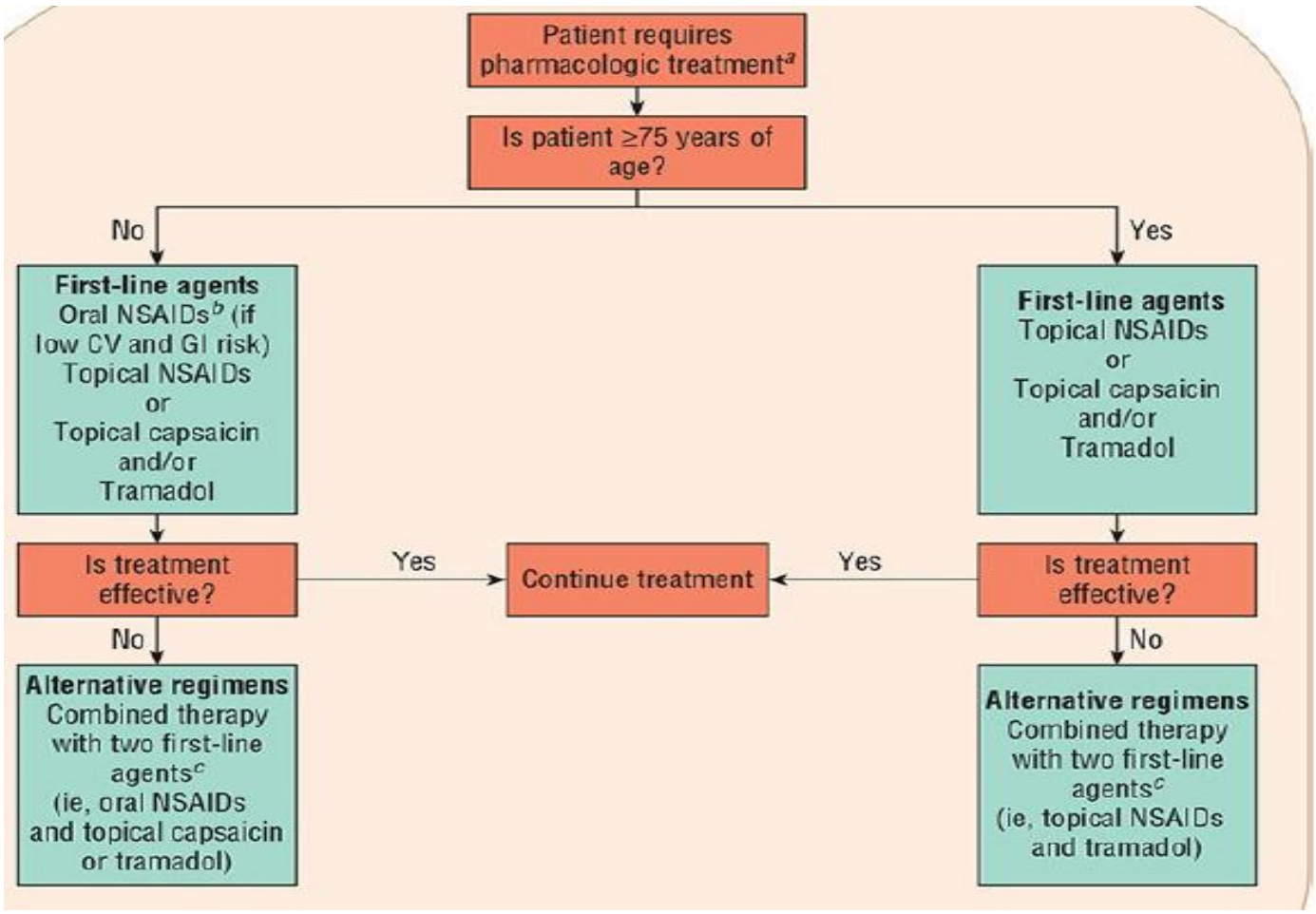


Figure 2: Treatment recommendations for hand osteoarthritis.

6-Options for reducing the GI risk of nonselective NSAIDs include using (1) the **lowest dose** possible and only when needed, (2) **misoprostol** with the NSAID, and (3) a **PPI** or **H2-receptor antagonist** daily with the NSAID.

7-**COX-2 inhibitors** pose **less risk for adverse GI events** than nonselective NSAIDs, but this advantage is substantially **reduced for patients taking aspirin**. **Both nonselective and selective NSAIDs are associated with an increased risk for CV events** (hypertension, stroke, myocardial infarction, and death).

8-Unlike aspirin, **celecoxib and nonspecific NSAIDs inhibit thromboxane formation reversibly, with normalization of platelet function 1–3 days after drug discontinuation**. Avoid NSAIDs in late pregnancy because of risk of premature closure of the ductus arteriosus.

9-**Topical NSAIDs are recommended for knee OA if acetaminophen fails**, and they are preferred over oral NSAIDs in patients older than 75 years.

10-Topical NSAIDs provide **similar pain relief with fewer adverse GI events** than oral NSAIDs but may be associated with adverse events at the application site (e.g., dry skin, pruritus, and rash).

11-**Patients using topical products should avoid oral NSAIDs** to minimize the potential for additive side effects. Use of topical NSAIDs has not been linked with increased risk of CV events.

12-**Intra-articular (IA) corticosteroid injections** are recommended for both hip and knee OA **when analgesia with acetaminophen or NSAIDs is suboptimal**. They can provide excellent pain relief, particularly when joint effusion is present.

13-**Local anesthetics** such as lidocaine or bupivacaine are commonly combined with corticosteroids to provide rapid pain relief. Injections may also be given with concomitant oral analgesics for additional pain control. **Local adverse effects** can include infection, osteonecrosis, tendon rupture, and skin atrophy at the injection site.

14-Do not administer injections more frequently than **once every 3 months** to minimize systemic adverse effects. **Systemic corticosteroid therapy is not recommended in OA**, given lack of proven benefit and well-known adverse effects with long-term use.

15-**Tramadol** is recommended for hip and knee OA in patients who have failed acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive IA corticosteroids.

16-**Tramadol can be added to partially effective** acetaminophen or oral NSAID therapy. Tramadol is associated with opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence.

17-**The most serious adverse event is seizures**. Tramadol is classified as a Schedule IV controlled substance due to its potential for dependence, addiction, and diversion.

18-**Duloxetine** can be used as adjunctive **treatment of knee** (not hip) OA in patients with partial response to first-line analgesics (acetaminophen, oral NSAIDs). **It may be a**

preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain.

19-**IA hyaluronic acid (sodium hyaluronate)** is not routinely recommended because injections have **shown limited benefit for knee OA and have not been shown to benefit hip OA.**

20-**Glucosamine and/or chondroitin** and topical **rubefacients** (e.g, methyl salicylate, trolamine salicylate) lack uniform improvement in pain control or functional status for hip and knee pain and **are not preferred treatment options**.

Hand OA

1-**Topical NSAIDs are a first-line option for hand OA**. Efficacy with topical NSAIDs typically occurs with 1–2 weeks.

2-**Oral NSAIDs** are **an alternative first-line treatment** for patients who cannot tolerate the local skin reactions or who received inadequate relief from topical NSAIDs.

3-**Capsaicin cream** is **an alternative first-line treatment**. It is a reasonable option for patients unable to take oral NSAIDs. Capsaicin must be used regularly to be effective, and it **may require up to 2 weeks to take effect**. Adverse effects are primarily local.

4-Tramadol is **an alternative first-line treatment** and is a reasonable option for patients who do not respond to topical therapy and are not candidates for oral NSAIDs because of **high GI, CV, or renal risks**.

5-Tramadol may also be used **in combination with partially effective** acetaminophen, topical therapy, or oral NSAIDs.

Evaluation of therapeutic outcomes

1-To monitor **efficacy**, assess baseline **pain with a visual analog scale**, and **assess range of motion** for affected joints with **flexion**, or **extension**.

2-Depending on the joint(s) affected, measurement of **grip strength and 50-ft walking time** can help assess hand and hip/knee OA, respectively.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

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Fourth year. Clinical Pharmacy

Rheumatologic Disorders

Gout and Hyperuricemia

Introduction

Gout involves an **inflammatory response to precipitation of monosodium urate (MSU) crystals in both articular and nonarticular tissues**.

Acute gouty arthritis : pathophysiology

1-An increased urate pool in individuals with gout may result from **overproduction** or **underexcretion**.

2-Overproduction of uric acid may result from **abnormalities in enzyme systems that regulate purine metabolism**. Cytotoxic drugs can result in overproduction of uric acid due to **lysis and the breakdown of cellular matter**.

3-Dietary purines are insignificant in generating hyperuricemia without some derangement in purine metabolism or elimination.

4-**Two-thirds of uric acid produced daily is excreted in urine**. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion leads to hyperuricemia.

5-Some drugs **decrease renal uric acid clearance like** diuretics.

6-Deposition of urate crystals in synovial fluid results in **inflammation**.

7-**Uric acid nephrolithiasis occurs in ~10% of patients with gout**. Predisposing factors include excessive urinary excretion of uric acid, acidic urine (pH <6), and highly concentrated urine.

8-**In acute uric acid nephropathy**, acute kidney injury occurs because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. **Chronic urate nephropathy** is caused by long-term deposition of urate crystals in the renal parenchyma.

9-**Tophi** (**urate deposits**) are uncommon and are a late complication of hyperuricemia.

Clinical presentation

1-**Acute gout attacks are characterized by** rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, most often affecting the first metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows.

2-Attacks commonly begin at **night**, with the patient awakening with excruciating pain. Affected joints are erythematous, warm, and swollen.

3-**Fever** and l**eukocytosis** are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.

4-**Acute attacks may occur without provocation or be precipitated by** stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid-lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

Diagnosis

1-Definitive diagnosis requires **aspiration of synovial fluid from the affected joint** and identification of intracellular MSU crystals in synovial fluid leukocytes.

2-When joint aspiration is not feasible, the diagnosis can be made based on **presence of characteristic signs and symptoms as well as the response to treatment.**

Treatment

Goals of Treatment: **Terminate the acute attack**, **prevent recurrent attacks**, and **prevent complications** associated with chronic deposition of urate crystals in tissues.

Nonpharmacologic Therapy

1-**Local ice** application is the most effective adjunctive treatment.

2-Dietary **supplements** (eg, flaxseed, cherry, celery root) **are not recommended.**

Pharmacologic Therapy

Most patients are treated successfully with **NSAIDs**, **corticosteroids**, or **colchicine**. Treatment should begin **as soon as possible after the onset of an attack**.

A-NSAIDS

1-NSAIDs have **excellent efficacy and minimal toxicity** with short-term use. Indomethacin, naproxen, and sulindac have FDA approval for gout, **but others are likely to be effective**.

2-Start therapy **within 24 hours of attack** onset and **continue until complete resolution** (usually 5–8 days). Tapering may be considered after resolution.

3-**Selective cyclooxygenase-2 inhibitors** (e.g., celecoxib) **may be an option** for patients unable to take nonselective NSAIDs, but the cardiovascular risk must be considered.

B-Corticosteroids

1-Corticosteroid efficacy is equivalent to NSAIDs; **they can be used systemically or by intra-articular (IA) injection**. If only one or two joints are involved, either IA or oral corticosteroids are recommended. **Systemic therapy is necessary for polyarticular attacks**.

2-**Tapering** is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.

3-**IA corticosteroids should be used with an oral NSAID**, **colchicine**, or **corticosteroid therapy**. Alternatively, **IM corticosteroid monotherapy** may be considered in patients with multiple affected joints who cannot take oral therapy.

4-Avoid long-term use because of risk for osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.

C-Colchicine

1-Colchicine is **highly effective** in relieving acute gout attacks; **when it is started within the first 24 hours of onset**, about two-thirds of patients respond within hours.

2-Colchicine causes **dose-dependent GI adverse effects** (nausea, vomiting, and diarrhea). **Non-GI effects include** neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (e.g., statins) or with impaired kidney function.

3-Use colchicine with **caution in patients taking P-glycoprotein or strong CYP450 3A4 inhibitors** (e.g., **clarithromycin**) due to increased plasma colchicine levels and potential toxicity; colchicine dose reductions may be required.

Hyperuricemia in gout

Recurrent gout attacks can be prevented by maintaining low uric acid levels, but nonadherence with nonpharmacologic and pharmacologic therapies is common.

Nonpharmacologic Therapy

1-Promote **weight loss** through caloric restriction and exercise in all patients to enhance renal urate excretion.

2-**Alcohol restriction** is important because increased consumption has been associated with an increased risk of gout attacks.

3-**Dietary recommendations** include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) which have been linked to uric acid elevation.

4-**Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels**. **Low-dose aspirin for cardiovascular prevention should be continued** because aspirin has a negligible effect on elevating serum uric acid.

Pharmacologic Therapy

1-After the first attack of acute gout, **prophylactic pharmacotherapy is recommended** if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated.

2-**Other indications include** presence of tophi, and radiographic evidence of damage attributable to gout.

3-Urate-lowering therapy can be started during an acute attack **if anti-inflammatory prophylaxis has been initiated.**

4-**Xanthine oxidase inhibitors are recommended first-line therapy**, with uricosurics reserved for patients with a contraindication or intolerance to xanthine oxidase inhibitors.

5-In refractory cases, **combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties** (probenecid, losartan, or fenofibrate) is suggested.

6-**Pegloticase** may be used in **severe cases** in which the patient cannot tolerate or is not responding to other therapies.

7-The ACR guideline goal of urate-lowering therapy is to achieve and maintain serum uric **acid <6 mg/Dl.** Urate lowering should be prescribed for long-term use.

A-Xanthine Oxidase Inhibitors

1-Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid.

2-Because they are effective in both overproducers and underexcretors of uric acid, **they are the most widely prescribed agents for long-term prevention of recurrent gout attacks**.

3-**Mild adverse effects of allopurinol include** skin rash, leukopenia, GI problems, headache, and urticaria. A **more severe adverse reaction known as allopurinol hypersensitivity syndrome**, which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), occurs rarely but is associated with **a 20%–25% mortality rate.**

4-**Febuxostat**: also lowers serum uric acid in a dose dependent manner. Clinical trial evidence demonstrated an **increase in all cause and cardiovascular mortality compared to allopurinol**, resulting in a warning that febuxostat should be reserved for patients unable to take allopurinol.

B-Uricosurics

1-Uricosuric drugs increase renal clearance of uric acid by inhibiting renal tubular reabsorption of uric acid.

2-Patients with a **history of urolithiasis should not receive uricosurics**. **Maintaining adequate urine flow and urine alkalinization** during the first several days of therapy may also decrease likelihood of uric acid stone formation.

C-Pegloticase

1-Pegloticase is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble.

2-Pegloticase is indicated for antihyperuricemic therapy in **adults refractory to conventional therapy.**

3-Because of potential **infusion-related allergic reactions**, patients must be pretreated with antihistamines and corticosteroids.

4-Pegloticase is substantially **more expensive than first-line urate-lowering therapies**. The **ideal duration of pegloticase therapy is unknown**. Patients may develop pegloticase antibodies that result in loss of efficacy after several months.

5-**Because of its limitations**, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.

D-Miscellaneous Urate-Lowering Agents

1-**Fenofibrate** is thought to increase clearance of hypoxanthine and xanthine, leading to a susained reduction in serum urate concentrations of 20%–30%. **However, ACR guidelines**

recommend against changing cholesterol lowering agents to fenofibrate because it is not a preferred therapy in current lipid guidelines.

3-**Losartan** inhibits renal tubular reabsorption of uric acid **and increases urinary excretion**, properties that are not shared with other angiotensin II receptor blockers. It also **alkalinizes the urine**, which helps reduce the risk for stone formation. Guidelines recommend **choosing losartan preferentially as antihypertensive therapy in patients with gout when feasible**.

Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy

1-**Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations**.

2-**Prophylactic anti-inflammatory therapy is recommended to prevent such gout attacks.**

3-The ACR guidelines strongly recommend **low dose oral colchicine**, **low dose NSAIDs, or prednisone 10 mg daily** during the **first 3 to 6 months of urate lowering therapy initiation**, and longer as needed if gout flares persist.

Evaluation of therapeutic outcomes

1-**Check the serum uric acid level** in patients suspected of having an acute gout attack, however, acute gout can occur with normal serum uric acid concentrations.

2-**Monitor patients with acute gout for symptomatic relief** of joint pain.

3-**Because of the high rates of comorbidities associated with gout** (diabetes, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, and stroke), elevated serum uric acid concentrations or gout should prompt **evaluation for cardiovascular disease and the need for appropriate risk reduction measures.**

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

College of Pharmacy
Fourth year. Clinical Pharmacy

Rheumatologic Disorders

Osteoporosis

Introduction

Osteoporosis is a bone disorder characterized **by low bone density**, **impaired bone architecture**, and **compromised bone strength** predisposing to **fracture**.

Pathophysiology

1-Bone loss occurs **when resorption exceeds formation** (when the bone resorption greatly exceeds the ability of osteoblasts to form new bone).

2-Men and women begin to lose bone mass **starting in the third or fourth decade because of reduced bone formation**. **Estrogen deficiency during menopause increases osteoclast activity,** increasing bone resorption more than formation.

3-**Men are at a lower risk for developing osteoporosis** and osteoporotic fractures. Male osteoporosis results from aging or secondary causes.

4-**Age-related osteoporosis results from** hormone, calcium, and vitamin D deficiencies; less exercise; and other factors.

5-**Drug-induced osteoporosis** may result from systemic corticosteroids, excessive thyroid hormone replacement, antiepileptic drugs (eg, phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other agents.

Clinical presentation

1-**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.

2-The most common fractures involve **vertebrae**, **proximal femur**, and **distal radius** (wrist or Colles fracture).

3-Multiple vertebral fractures decrease height and sometimes curve the spine (**kyphosis** or **lordosis**).

4-Patients with a **nonvertebral fracture frequently present with severe pain**, swelling, and reduced function and mobility at the fracture site.

Diagnosis

1-Physical examination findings may include bone pain, postural changes (ie, kyphosis), and loss of height (>1.5 in [3.8 cm]).

2-**Bone mineral density** (BMD) is measured by dual-energy x-ray absorptiometry (**DXA) scan.**

Treatment

Goals of Treatment:

1-The primary goal of osteoporosis care is **prevention**.

2-After low bone mass or **osteoporosis develops**, the objective is to stabilize or improve bone mass and strength and **prevent fractures**.

3-Goals in patients with **osteoporotic fractures** include **reducing pain and deformity**, and improving quality of life

Nonpharmacologic Therapy

1-All individuals should have **a balanced diet with adequate intake of calcium and vitamin** D. Protein is required for bone formation.

2-**Smoking cessation, and reduced alcohol and caffeine consumption** are recommended.

3-**Weight-bearing aerobic** and **strengthening exercises** can decrease risk of falls and fractures by improving muscle strength.

4-**Fall prevention programs** can decrease falls and fractures.

5-**Vertebroplasty** and **kyphoplasty** involve injection of cement into fractured vertebra(e) for patients with debilitating pain from compression fractures. Research demonstrated **only short term benefit** with no major pain relief and the potential for post-procedure complications.

Pharmacologic Therapy

General Approach

1-Alendronate, risedronate, zoledronic acid, and denosumab reduce both hip and vertebral fracture risks.

2-Abaloparatide, calcitonin, ibandronate, raloxifene, romosozumab, and teriparatide reduce vertebral but not hip fracture risks.

3-**Calcitonin** is **last-line therapy**. **Estrogen** and **testosterone** are **not used for osteoporosis treatment but can have a positive bone effect when prescribed for other conditions.**

Antiresorptive Therapy

Calcium Supplementation

1-There are insufficient data to support using calcium and vitamin D supplementation to reduce fracture incidence.

2-Because the **fraction of calcium absorbed decreases with increasing dose**, maximum single doses of 600 mg or less of elemental calcium are recommended.

3-**Calcium carbonate is the salt of choice** because it contains the highest concentration of elemental calcium (40%) and is typically least expensive. **It should be ingested with meals** to enhance absorption in an acidic environment.

4-**Calcium citrate** (21% calcium) has **acid-independent absorption and need not be taken with meals.** It may have fewer GI side effects than calcium carbonate.

5-**Tricalcium phosphate** contains 38% calcium. It may be useful in **patients with hypophosphatemia that cannot be resolved with increased dietary intake.**

6-**Constipation is the most common calcium-related adverse reaction**; treat with increased water intake, dietary fiber , and exercise.

7-Calcium carbonate can sometimes cause flatulence or upset stomach. Calcium causes kidney stones rarely.

8-Calcium can **decrease the oral absorption of some drugs** including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Vitamin D Supplementation

1-Supplementation is usually provided with **daily** nonprescription cholecalciferol (**vitamin D3**) products. Higher-dose prescription ergocalciferol (**vitamin D2**) regimens given weekly, monthly, or quarterly may be used for replacement and maintenance therapy.

2-Current guidelines recommend treating patients with osteoporosis to a 25-hydroxyvitamin D concentration of at least 20 ng/mL or 30–50 ng/mL.

3-Because the **half-life of vitamin D is about 1 month**, **recheck the vitamin D concentration after about 3 months of therapy.**

Bisphosphonates

1-Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor. Therapy leads to decreased osteoclast maturation, number, recruitment, and life span.

2-Incorporation into bone gives bisphosphonates **long biologic half-lives of up to 10 years**.

3-**Ibandronate is not a first-line therapy** because of the lack of hip fracture reduction data.

4-BMD increases are dose dependent **and greatest in the first 12 months of therapy**. After discontinuation, the increased BMD is sustained for a prolonged period that varies per bisphosphonate.

5-Oral bisphosphonates must be **administered correctly** to optimize clinical benefit and minimize adverse GI effects.

A-Each oral tablet should be **taken in the morning with at least** (180 mL) of **plain water** (not coffee, juice, mineral water, or milk) **at least 30 minutes** (60 minutes for oral ibandronate) **before consuming any food**, supplements, or medications.

B-An exception is **delayed-release risedronate, which is administered immediately after breakfast** with at least (120 mL) of plain water.

C-The patient **should remain upright** (**sitting or standing**) **for at least 30 minutes** after alendronate and risedronate and **1 hour after ibandronate** to prevent esophageal irritation and ulceration.

D-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. If a patient **misses a monthly** dose, it can be taken up to 7 days before the next scheduled dose.

6-The most common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. **Esophageal, gastric, or duodenal irritation,** perforation, ulceration, or bleeding may occur.

7-The most common adverse effects of **IV bisphosphonates** include **fever**, **flu-like symptoms**, and **local injection-site reactions.**

8-**The optimal duration of bisphosphonate therapy is unknown**.

Denosumab

1-Denosumab is a RANK ligand inhibitor that **inhibits osteoclast formation** and **increases osteoclast apoptosis**. It is indicated for treatment of osteoporosis in women and men.

2-Denosumab is **contraindicated in patients with hypocalcemia until the condition is corrected**.

Mixed Estrogen Agonists/Antagonists and Tissue-Selective Estrogen Complexes

1-**Raloxifene** is an estrogen agonist/antagonist that is **an estrogen agonist on bone receptors** but an antagonist at breast receptors, with minimal effects on the uterus.

2-It is approved for prevention and treatment of **postmenopausal osteoporosis** .

3-**Bazedoxifene** is an estrogen agonist/antagonist that is an **agonist at bone** and antagonist at the uterus and breast; however, reduction in breast cancer risk has not yet been demonstrated. The proprietary product **Duavee** is combined with conjugated equine estrogens (**CEE**), making it a tissue-selective estrogen complex. It **is approved for prevention of postmenopausal osteoporosis and vasomotor menstrual symptoms**.

Calcitonin

Calcitonin is FDA approved for osteoporosis treatment for women at least 5 years past menopause. **Calcitonin is considered as a last line therapy** because there are more effective treatment options.

Hormone Therapies

1-Estrogen therapy is FDA approved for prevention of postmenopausal osteoporosis but not for treatment. Estrogen therapy can be a good choice for **women going through early menopause when protection against bone loss is needed** in addition to reduction of vasomotor symptoms.

2-**Testosterone** is used to treat hypogonadism in men, **but an osteoporosis medication should be added when risk for osteoporotic fracture is high.**

Formation Medications

Parathyroid Hormone Analogs

1-**Abaloparatide** is an analog of parathyroid hormone-related peptide (PTHrP), and **teriparatide** is an analogs of parathyroid hormone (PTH); these agents are indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

2-**Transient hypercalcemia** can occur. PTH analogs should **not be used in patients with hypercalcemia**.

Formation and Antiresorptive Medication

Romosozumab

1-Romosozumab **prevent inhibition of bone formation** and **decrease bone resorption**, an activity that differentiates this medication from other anabolic therapies.

2-It indicated for postmenopausal women at high risk for fracture.

Sequential and Combination Therapy

1-In sequential therapy, **an anabolic agent is given first to increase bone mass, followed by an antiresorptive agent**.

2-**Combination therapy is rarely used** because of no documented fracture benefit, increased cost, and potential for more adverse effects.

Glucocorticoid-induced osteoporosis

1-Glucocorticoids decrease bone formation through decreased proliferation and differentiation as well as enhanced apoptosis of osteoblasts. They also increase the number of osteoclasts, increase bone resorption, decrease calcium absorption, and increase renal calcium excretion.

2-All glucocorticoid doses and formulations have been associated with increased bone loss and fractures; however, **risk is much greater with oral prednisone doses ≥5 mg daily** (or equivalent) and **oral therapy** compared to inhaler or intranasal therapy.

3-**All patients starting or receiving systemic glucocorticoid** therapy (any dose or duration) **should practice a bone-healthy lifestyle and ingest 1000–1200 mg elemental calcium and 600–800 units of vitamin D daily** to achieve therapeutic 25-hydroxyvitamin D concentrations.

4-Use **the lowest possible corticosteroid dose** and **duration**.

5-**Alendronate**, **risedronate**, **zoledronic** acid, **denosumab**, and **teriparatide** are FDA approved for glucocorticoid-induced osteoporosis.

6-**Oral bisphosphonates are recommended first-line**, although **IV bisphosphonates can be used in nonadherent** patients or those unable to take the oral preparations.

7-**Teriparatide is recommended for patients who cannot use a bisphosphonate**, and **denosumab** is recommended if neither a bisphosphonate nor teriparatide can be used.

8-Denosumab is not recommended as first-line therapy due to **limited safety data in this population.**

Evaluation of therapeutic outcomes

1-Assess **medication adherence** and **tolerability** at each visit.

2-Ask patients about **possible fracture symptoms** (eg, bone pain, disability) at each visit.

3-Obtain a central DXA BMD measurement after 1–2 years or 3–5 years after initiating a medication therapy to monitor response.

4-Repeat a central **DXA every 2 years until BMD is stable**, at which time the reassessment interval can be lengthened.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

College of Pharmacy
Fourth year. Clinical Pharmacy

Hematologic Disorders

Anemias

Introduction

1-Anemia is a group of diseases characterized by a **decrease in either hemoglobin** (Hb) or the **volume of red blood cells** (RBCs), resulting in **decreased oxygen-carrying capacity** of blood.

2-The World Health Organization defines anemia as Hb **less than 13 g/dL in men** or **less than 12 g/dL in women.**

Pathophysiology

1-The functional classification of anemias is found in **Fig. -1**.

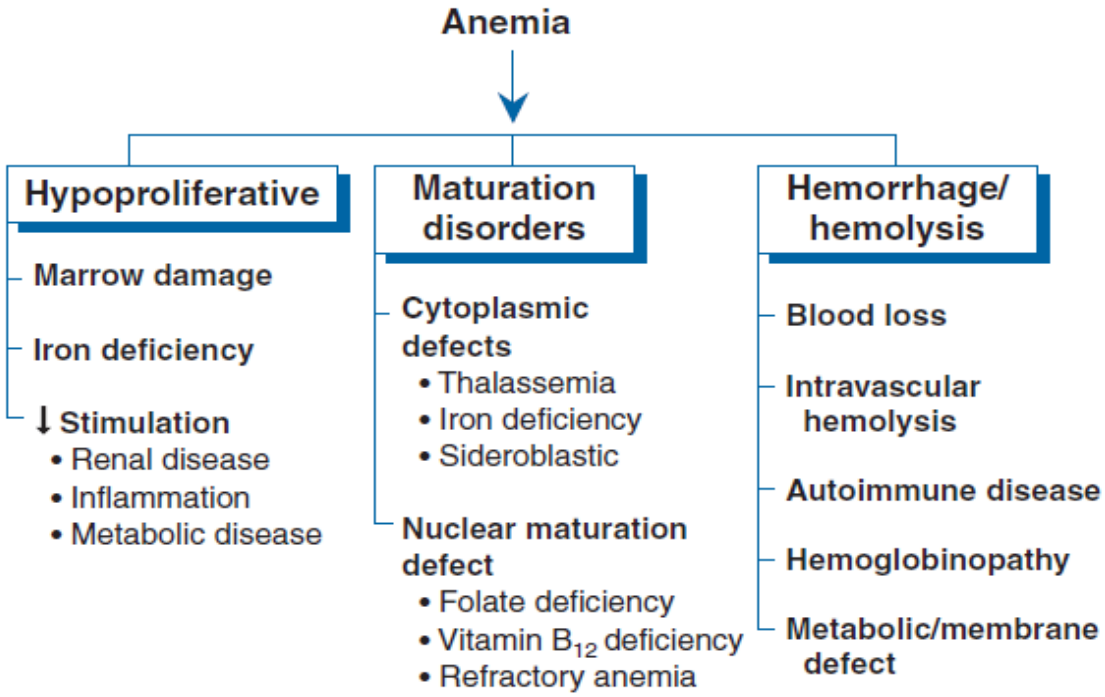

Figure -1. Functional classification of anemia.

2- **Morphologic classifications** are based on **cell size**.

A-Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B12 or folic acid.

B-Microcytic cells are smaller than normal and are associated **with iron deficiency**, whereas **normocytic anemia** may be associated with **recent blood loss or chronic disease.**

3-**Iron-deficiency anemia (IDA),** characterized by **decreased levels** of **ferritin** (most sensitive marker) and serum **iron**, and decreased **transferrin saturation**, can be caused by inadequate dietary intake, inadequate gastrointestinal (GI) absorption, increased iron demand (eg, pregnancy), blood loss, and chronic diseases.

4-Vitamin B12– and folic acid–deficiency anemias, macrocytic in nature, can be caused by inadequate dietary intake, malabsorption syndromes, and inadequate utilization.

A-**Deficiency of intrinsic factor** causes decreased absorption of **vitamin B12** (ie, **pernicious anemia**).

B-Folic acid–deficiency anemia can be caused by hyperutilization due to pregnancy, hemolytic anemia, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt.

C-Drugs can cause anemia by reducing absorption of folate (eg, phenytoin) or through folate antagonism (eg, methotrexate).

5-Anemia of inflammation (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness.

A-AI is an anemia that traditionally has been associated with malignant, infectious, or inflammatory processes, tissue injury, and conditions associated with release of proinflammatory cytokines.

B-Serum iron is decreased but in contrast to IDA, the **serum ferritin concentration is normal or increased**.

Clinical presentation

1-**Acute-onset anemia** is characterized by **cardiorespiratory symptoms** such as palpitations, angina, orthostatic light-headedness, and breathlessness.

2-**Chronic anemia** is characterized by weakness, fatigue, headache, orthopnea, dyspnea on exertion, vertigo, faintness, cold sensitivity, and pallor.

3-**IDA is characterized by** glossal pain, smooth tongue, reduced salivary flow, **pica** (compulsive eating of nonfood items), and **pagophagia** (compulsive eating of ice).

4-**Neurologic effects** (eg, numbness and paraesthesisas) **of vitamin B12 deficiency** may precede hematologic changes. Psychiatric findings, including irritability, depression, and memory impairment, may also occur with vitamin B12 deficiency. **Anemia with folate deficiency is not associated with neurologic symptoms.**

Diagnosis

1-Rapid diagnosis is essential because anemia is often **a sign of underlying pathology.** Severity of symptoms does not always correlate with the degree of anemia.

2-Initial evaluation of anemia involves a **complete blood cell count** (CBC), **reticulocyte index**, and **examination of the stool for occult blood**.

3-The earliest and most sensitive laboratory change for IDA is **decreased serum ferritin** (storage iron).

4-**In macrocytic anemias**, mean corpuscular volume is usually elevated. **Vitamin B12 and folate concentrations can be measured t**o differentiate between the two deficiency anemias.

5-In AI, **serum iron is usually decreased**, but, unlike IDA, **serum ferritin is normal or increased**. The peripheral smear reveals **normocytic anemia**.

Treatment

Goals of Treatment: The goals are to return hematologic parameters to normal, restore normal function and quality of life, and prevent long-term complications.

Iron-deficiency anemia

1-**Oral iron therapy** with soluble ferrous iron salts, which are **not enteric coated** and **not slow or sustained release**, is recommended at a daily dosage of 150–200 mg elemental iron in two or three divided doses.

2-Iron is best absorbed from meat, fish, and poultry. **Administer iron at least 1 hour before meals** because food interferes with absorption, but administration with **food may be needed to improve tolerability.**

3-Consider **parenteral iron for patients with** iron malabsorption, intolerance of oral iron therapy, or nonadherence.

4-**Iron dextran**, sodium ferric gluconate, **iron sucrose**, ferumoxytol, and ferric carboxymaltose are available parenteral iron preparations **with similar efficacy** but different pharmacokinetics, bioavailability, and **adverse effect profiles**.

Vitamin B12‑deficiency anemia

1-**Oral vitamin B12 supplementation** is as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B12 absorption pathway is independent of intrinsic factor.

2-Parenteral therapy acts more rapidly than oral therapy and **is recommended if neurologic symptoms are present**. Initiate daily **oral** cobalamin administration after symptoms resolve.

3-Continue vitamin **B12 for life** in patients with **pernicious anemia**.

Folate-deficiency anemia

1-Oral folic acid, 1 mg daily for 4 months, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected.

2-If malabsorption is present, a dose of 1–5 mg daily may be necessary. Parenteral folic acid is available but rarely necessary.

Anemia of inflammation

1-Treatment of AI is less specific than that of other anemias and should **focus on correcting reversible causes**. Reserve **iron therapy for an established IDA**; **iron is not effective when inflammation is present**. RBC transfusions are effective but should be limited to Hb of 7–8 g/dL.

2-**Erythropoiesis-stimulating agents** (ESAs) can be considered, but response can be impaired in patients with AI. Iron, cobalamin, and folic acid supplementation may improve response to ESA treatment.

3-Potential toxicities of exogenous ESA administration include **increases in blood pressure**, nausea, headache, fever, bone pain, and fatigue. Hb must be monitored during ESA therapy. **An increase in Hb greater than 12 g/dL with treatment or a rise of**

greater than 1 g/dL every 2 weeks has been associated with increased mortality and cardiovascular events.

4-In patients with anemia of **critical illness**, **parenteral iron** is often used but is associated with **a theoretical risk of infection.**

Anemia in pediatric populations

1-**Infants aged 9–12 months:** Administer ferrous sulfate 3–6 mg/kg/day (elemental iron) divided once or twice daily between meals for 4 weeks. Continue for two additional months in responders to replace storage iron pools.

2-The dose and schedule of vitamin B12 should be titrated according to clinical and laboratory response. The daily dose of folic acid is 1 mg.

Evaluation of therapeutic outcomes

1-IDA: Positive response to oral iron therapy is characterized by an increase in Hb **seen at 2 weeks**. Hb should return to normal after 2 months; **continue iron therapy until iron stores are replenished and serum ferritin normalized** (up to 12 months).

2-Megaloblastic anemia: Signs and symptoms usually improve within a few days after starting vitamin B12 or folic acid therapy.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

Respiratory disorders

Asthma

Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease **usually characterized by chronic airway inflammation**. It is defined by a history of **respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough** that vary over time and in intensity, together with variable expiratory airflow limitation.

Pathophysiology

1-There is a **variable degree of airflow obstruction**. In acute inflammation, inhaled allergens in allergic patients **cause activation of inflammatory cells (mast cells, neutrophils and macrophages)**

2-After rapid activation, **inflammatory cells release proinflammatory mediators such as histamine** and eicosanoids that induce **contraction of airway smooth muscle (bronchospasm), mucus secretion, edema, and exudation of plasma in the airways**.

Clinical presentation

A-Chronic asthma

Signs and symptoms include episodes of **shortness of breath, chest tightness, dry coughing** (particularly at **night**), **wheezing, or a whistling** sound when breathing. These often occur with exercise but may occur spontaneously or in association with known allergens.

B-Acute severe asthma

1-Uncontrolled asthma can progress to an **acute state**. Patients may be anxious in acute distress and **complain of severe dyspnea, shortness of breath, chest tightness, or burning**. They may **be able to say only a few words** with each breath. **Symptoms are unresponsive to usual measures (ie, SABAs).**

2-Signs include **dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis;** and **hyperinflated chest** with **intercostal and supraclavicular retractions.**

Diagnosis

A-Chronic asthma

1-Diagnosis is made primarily by **history** and confirmatory spirometry.

2-**Spirometry demonstrates obstruction** (forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] **<80%)** with **reversibility after inhaled β2-agonist** administration.

B-Acute severe asthma

1-**Peak expiratory flows (PEF) and FEV1 are <40%** of normal predicted values. Pulse oximetry reveals decreased arterial oxygen **and O2 saturations**.

2-Arterial blood gases may reveal **metabolic acidosis** and low partial pressure of oxygen (PaO2).

Treatment

Goals of Treatment: The GINA long-term goals for asthma management include:
(1) achieve good control of symptoms and maintain normal activity levels.
(2) minimize future risk of exacerbations, and side effects.

For acute severe asthma, the primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and providing rapid treatment.

Nonpharmacologic Therapy

1-**Patient education** is mandatory to improve medication adherence, self-management skills, and use of healthcare services.

2-Routine PEF monitoring is generally recommended only **for patients with severe asthma or poor symptom perception.**

3-**Avoidance of known allergenic triggers** can improve symptoms, and reduce medication use. Smokers should be encouraged to quit.

4-**In acute asthma exacerbations, initiate oxygen therapy**.

5-Correct **dehydration if present**.

Pharmacologic Therapy

General Approach

1-Figure 1 summarizes GINA recommendations for **initial treatment** in adults and adolescents with asthma (**further reading**).

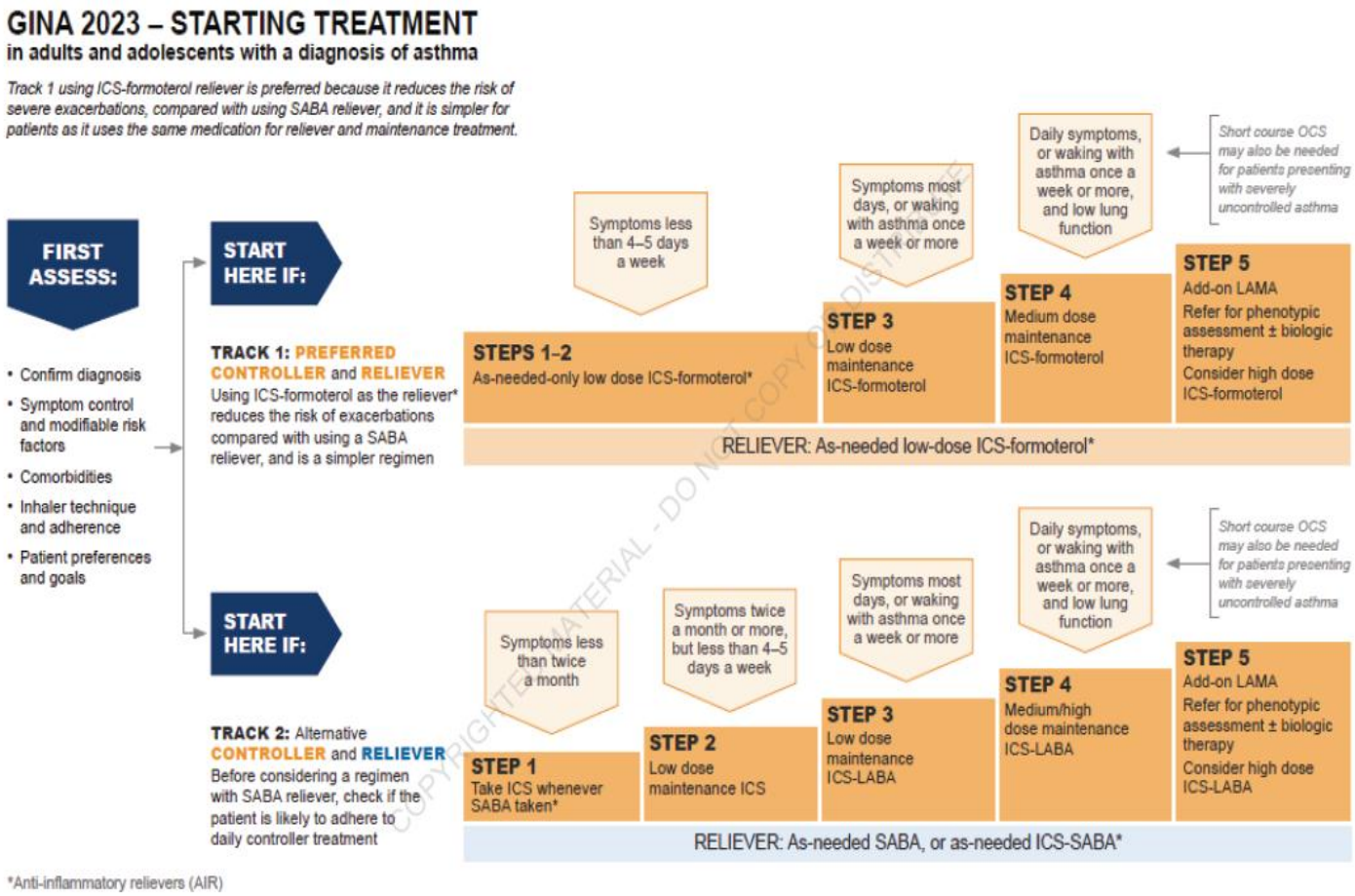

Figure 1: GINA recommendations for initial treatment in adults and adolescents

2-Despite the addition of inhaled corticosteroid-short acting β2 agonist (**ICS-SABA**) reliever in track 2, **GINA track 1 with as-needed ICS- formoterol remains the preferred treatment for adults and adolescents** [(2)].

[Single Maintenance and Reliever Therapy (**SMART**) also called Maintenance and Reliever Therapy (**MART**) in GINA guidelines: SMART therapy with ICS-formoterol **significantly reduces the risk of severe exacerbation** compared with using a SABA reliever, with similar symptom control] [(2)].

3-Depending on the inflammatory phenotype (e.g. allergic asthma, eosinophilic asthma) and other clinical features, add-on treatment for severe asthma include **long acting muscarinic antagonist** (LAMA), **leukotriene receptor antagonists** (LTRA), and **biologic agents** [(2)].

4-Low-dose maintenance oral corticosteroid (OCS) should be considered only as a last resort if no other options are available, because of their long-term side effects [(2)].

5-Once good asthma control has been achieved and maintained **for 2-3 months**, consider **stepping down gradually** to find the patient's lowest treatment that controls both symptoms and exacerbations [(2)].

6-The **primary therapy of acute exacerbations includes** inhaled **SABAs** and (depending on severity) **systemic corticosteroids**, inhaled **ipratropium**, intravenous (IV) **magnesium** sulfate, and **oxygen**. Treatments are typically administered concurrently to facilitate rapid improvement.

β2-Agonists

1- SABAs (eg, albuterol) **are the treatment of first choice for managing acute severe asthma**. A SABA is also indicated for **as needed** treatment of intermittent episodes of bronchospasm (e.g., exercise induced bronchospasm).

2-Aerosol administration enhances bronchoselectivity and provides more rapid response **than systemic administration**.

3-Two **long-acting β2-agonists** (**LABAs**), **formoterol** and **salmeterol**, provide bronchodilation for 12 hours or longer and **are dosed twice daily**. When **combined with an ICS, formoterol may be dosed on a daily and as needed basis** (thus, more frequently than twice daily).

Corticosteroids

1-**ICS are the preferred long-term control therapy for persistent asthma** because of potency and consistent effectiveness; they are the only therapy shown to reduce risk of dying from asthma.

2-**Response to ICS is delayed**.

3-**Systemic toxicity of ICS is minimal with low-to-moderate doses**, but risk of systemic effects increases with high doses (e.g., growth suppression in children, osteoporosis, cataracts, dermal thinning, adrenal insufficiency).

4-**Local adverse effects include** dose-dependent oropharyngeal candidiasis and dysphonia, which can be **reduced by using a spacer device.**

5-**Systemic corticosteroids** are indicated in all patients **with acute severe asthma** not responding completely to initial inhaled β2-agonist administration and should be administered within 1 hour of presentation.

6-**IV therapy offers no advantage over oral administration** except in patients unable to take oral medications.

Anticholinergics

1-Anticholinergics **reverse cholinergic mediated bronchoconstriction** and are effective bronchodilators in asthma.

2-**Ipratropium bromide** is useful **as adjunctive therapy in acute severe asthma not completely responsive to SABA alone.**

3-Patients with persistent asthma who are **intolerant to short acting β2agonists** may be **prescribed ipratropium for rescue inhaler use**.

4-**Tiotropium bromide** is a **long acting inhaled anticholinergics** with a duration of 24 hours. Tiotropium may be considered an **add on therapy in patients whose asthma is not well controlled with ICS and LABA combination therapy.**

Leukotriene Modifiers

1-**Zafirlukast** and **montelukast** are oral leukotriene receptor antagonists (LTRA) that reduce the proinflammatory and bronchoconstriction effects of leukotriene D4.

2-**They are less effective than ICS**, and they are **less effective than LABAs when added to ICS**. They are **not used** to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods.

3-Use of **montelukast and zafirlukast has fallen out of favor due to increased observance of unusual adverse effects and modest therapeutic efficacy.**

4-Because of reports of **adverse neuropsychiatric** events especially within a few weeks of starting therapy, **monitor patients for signs of irritability, aggressiveness, and sleep disturbances**; suicidality has also been reported rarely.

5-There have been reports of fatal **hepatic failure associated with zafirlukast**.

6-**Zileuton** is a 5-lipoxygenase inhibitor; **its use is limited due to potential for elevated hepatic enzymes and inhibition of metabolism** of drugs metabolized by CYP3A4 (eg, theophylline, warfarin).

Biologic Agents

1-**These agents target the IgE pathway (Omalizumab) or (IL-4, IL-13) (Dupilumab), and IL-5 pathways** (**Mepolizumab, Benralizumab and reslizumab**).

A-Omalizumab is approved for treatment of allergic asthma.

B-**Mepolizumab, Benralizumab, Dupilumab and reslizumab** are indicated for patients with an "**eosinophilic phenotype".**

Magnesium Sulfate

1-Magnesium sulfate is a moderately potent **bronchodilator**, producing relaxation of smooth muscle by blocking calcium ion influx into smooth muscles; it may also have anti-inflammatory effects.

2-For patients with **severe asthma exacerbations**, a single 2 g IV infusion may reduce hospital admissions

3-**Adverse effects include** hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, and CNS and respiratory depression.

Methylxanthines

1-Methylxanthines **are rarely used today** because of the high risk of severe life-threatening toxicity, numerous drug interactions, and decreased efficacy compared with ICS, LABAs, and biologics.

2-Theophylline is available for oral and IV administration. Theophylline dosing requires **monitoring of serum concentrations** for both efficacy and toxicity, including seizures and death.

3-In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP P450 microsomal enzymes, **and drug interactions affecting metabolism significantly affect blood concentrations.**

Evaluation of therapeutic outcomes

1-All patients on inhaled drugs should have **their inhalation technique evaluated monthly initially and then every 3–6 months.**

2-After initiation of anti-inflammatory therapy or increase in dosage, **most patients should experience decreased symptoms within 1–2 weeks and achieve maximum improvement within 4–8 weeks.**

Reference

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.
2-GINA guideline. 2023.

Further reading

Table 1: Initial asthma-treatment recommended options for adults and adolescents [2].

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g., less than twice a month and no risk factors for exacerbations, including no exacerbations in the last 12 months (Box 2-2B, p.38)	**As-needed low-dose ICS-formoterol** (Evidence B)	**Low-dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B)
Asthma symptoms or need for reliever twice a month or more	**As-needed low-dose ICS-formoterol** (Evidence A)	**Low-dose ICS plus as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Troublesome asthma symptoms most days (e.g., 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B, p.38)	**Low-dose ICS-formoterol maintenance and reliever therapy** (MART) (Evidence A)	**Low-dose ICS-LABA plus as-needed SABA** (Evidence A) or plus as-needed ICS-SABA (Evidence B), **OR** Medium-dose ICS plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B). Consider likely adherence with daily maintenance treatment.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	**Medium-dose ICS-formoterol maintenance and reliever therapy** (MART) (Evidence D). A short course of oral corticosteroids may also be needed.	**Medium- or high-dose ICS-LABA** (Evidence D) plus as-needed SABA or plus as-needed ICS-SABA. Consider likely adherence with daily maintenance treatment. A short course of oral corticosteroids may also be needed. High-dose ICS plus as-needed SABA is another option (Evidence A) but adherence is weak compared with combination ICS-LABA.

College of Pharmacy
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Respiratory disorders

Chronic Obstructive Pulmonary Disease

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by **chronic respiratory symptoms** (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of **the airways** (**bronchitis**, bronchiolitis) and/or **alveoli** (**emphysema**) that cause **persistent**, **often progressive, airflow obstruction** [3].
It includes **two** principal conditions:

A-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**.

B-Emphysema: Abnormal, **permanent enlargement of the airspaces** distal to the terminal bronchioles, accompanied by **destruction of their walls, without fibrosis**.

Pathophysiology

1-The **most common cause of COPD is exposure to tobacco smoke.**

2-Inhalation of noxious particles and gases **activates inflammatory cells to release inflammatory mediators**. Inflammatory cells and mediators lead to widespread **destructive changes in airways resulting in chronic airflow limitation.**

3-Chronic hypoxemia and changes in pulmonary vasculature lead to increases in pulmonary pressures. **Sustained elevated pulmonary pressures can lead to right-sided heart failure (cor pulmonale)** characterized by right ventricle hypertrophy in response to increased pulmonary vascular resistance.

Clinical presentation

1-Initial symptoms include **chronic cough and sputum production**; patients may experience cough for several years before dyspnea develops.

2-**Dyspnea** (described by patients as "**increased effort to breathe**" or "**air hunger**") [2] is worse with exercise and **progressive over time**, with decreased exercise tolerance or decline in physical activity. Chest tightness or wheezing may be present.

3-When airflow limitation progresses, patients may have **shallow breathing**, increased **resting respiratory rate**, "**barrel chest" due to lung hyperinflation**, **pursed lips during expiratio**n, use of **accessory respiratory muscles**, and **cyanosis of mucosal membranes**.

Diagnosis

1-Diagnosis is based **on patient symptoms**, **history** of exposure to risk factors such as tobacco smoke and occupational substances, and **confirmation by pulmonary function testing, such as spirometry (Spirometry assesses lung volumes and capacities**. Forced vital capacity (**FVC**) is the total volume of air exhaled after maximal inhalation, and **FEV1** is the total volume of air exhaled in 1 second).

2-The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest a four-grade classification of airflow limitation: **mild** (GOLD 1), **moderate** (GOLD 2), severe (GOLD 3), or **very severe (**GOLD 4).

Treatment

Goals of Treatment: Prevent or slow disease progression, relieve symptoms, improve exercise tolerance, improve overall health status, prevent and treat exacerbations, prevent and treat complications, and reduce morbidity and mortality **(Further reading 1**).

Nonpharmacologic Therapy

1-**Smoking cessation** is the most important intervention to prevent development and progression of COPD.

2-**Reducing exposure to occupational dust and fumes** as well as other environmental toxins is also important.

3-**Pulmonary rehabilitation programs** include exercise training, breathing exercises, and psychosocial support.

4-Administer the **influenza vaccine annually** during each influenza season. Vaccination against pneumococcal infection is recommended for all adults with COPD.

5-Some patients with severe COPD required **long-term O2 therapy** (by **nasal cannula).**

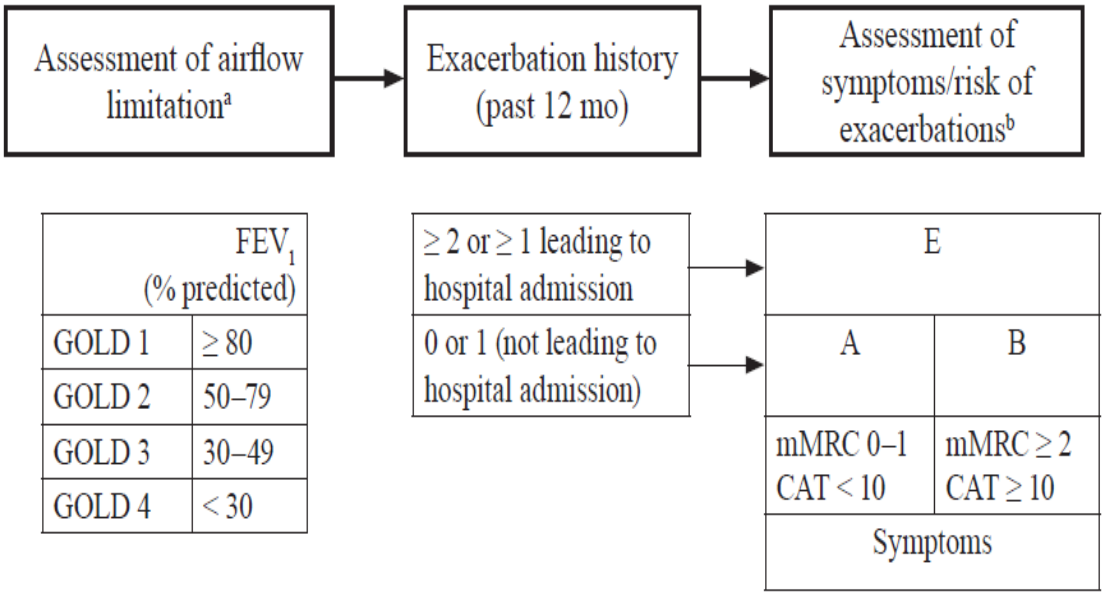
Pharmacologic Therapy

1-Bronchodilators are the mainstay of drug therapy; classes include short- and long-acting **β2-agonists**, short- and long-acting **muscarinic antagonists** (anticholinergics), and **methylxanthines**.

2-Short-acting inhaled bronchodilators **relieve symptoms** (e.g., dyspnea). Long acting inhaled bronchodilators **relieve symptoms and reduce exacerbation frequency**.

Patient assessment and selection of therapy

GOLD guidelines combine **symptoms** (by **questionnaires**) and **frequency of exacerbations** in the previous 12 months to determine patient risk group **and recommend initial treatment** (Figure 1 and 2) [(2)].



[a]Post-bronchodilator FEV_1 should be used.

[b]CAT score is preferred, but any can be used.

CAT = COPD Assessment Test (validated questionnaire); GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council breathlessness scale (validated questionnaire).

Figure 1. GOLD guidelines: refined assessment of COPD severity and risk [2].

Initial pharmacological management

1-**Rescue short-acting bronchodilators** should be prescribed **to all patients for immediate symptom relief** [3].

2-**Group A:** All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be **either a short- or a long-acting bronchodilator** [3].

3-Group B: Treatment should be initiated with a **LABA+LAMA combination.**

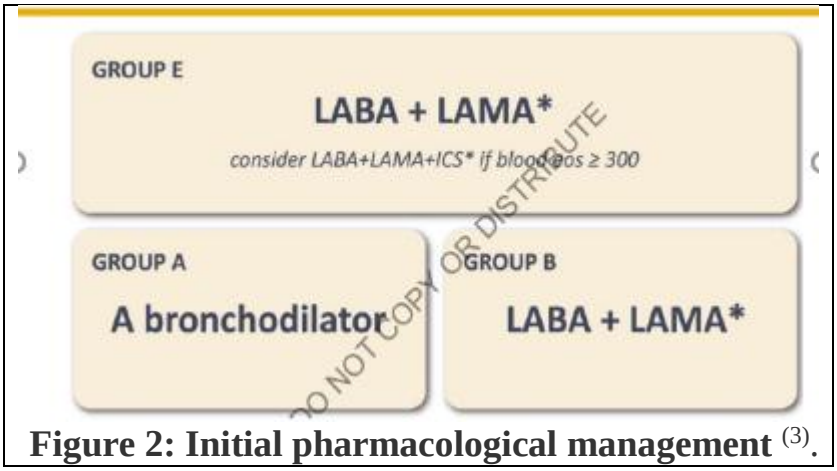


Figure 2: Initial pharmacological management [3].

4-Group E ("E" for "Exacerbations"):

A-**LABA+LAMA** is the preferred choice for initial therapy in group E patients.

B-Consider **LABA+LAMA+ICS** in group E if eosinophil count ≥ 300 cells/µL.

Maintenance therapy

Maintenance therapy adjustments are recommended according to the **predominant treatable trait** of **dyspnea** (Figure 3 left column); or **exacerbations** (Figure 3 right column). If **both exacerbations and dyspnea need to be targeted**, the **exacerbation pathway** should be followed [2, 3].

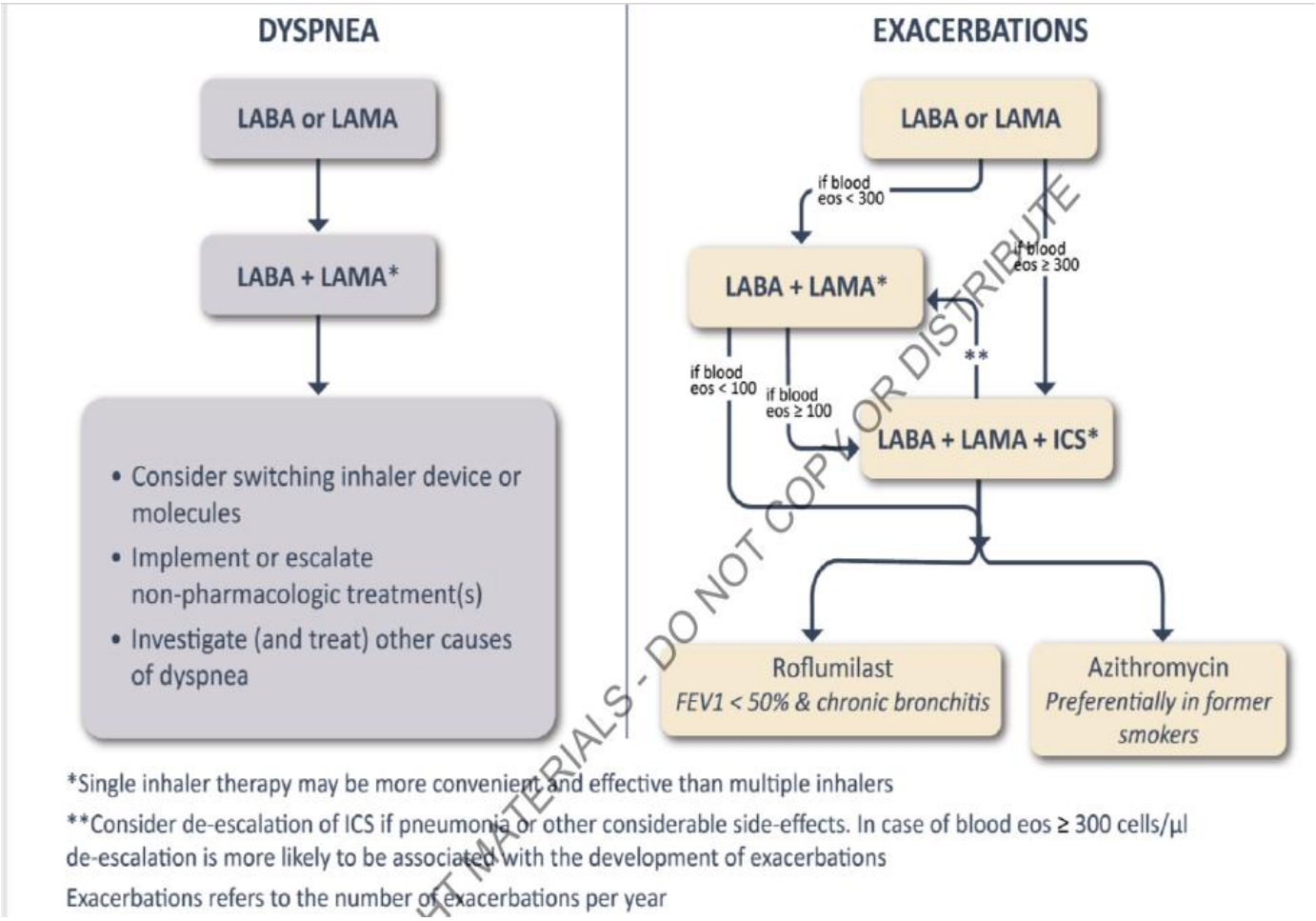


Figure 3: Maintenance therapy of COPD [3].

Dyspnea (patients with persistent dyspnea)

For patients with persistent breathlessness or exercise limitation on bronchodilator monotherapy, **the use of two long acting bronchodilators is recommended** [3].

Exacerbations [patients continuing to have exacerbations (with or without persistent dyspnea)]

1-For patients with persistent exacerbations on bronchodilator monotherapy:

A-Escalation **to LABA+LAMA+ICS** may be considered **if blood eosinophil count ≥ 300 cells/µL**[3].

B-If blood **eosinophil count < 300 cells/µL escalation to LABA+LAMA is recommended** [3].

2-In patients on LABA+LAMA and still have exacerbations, Escalation to LABA+LAMA+ICS if eosinophil counts ≥ 100 cells/ml may be considered [3].

3-In patients on LABA+LAMA and eosinophil counts < 100 cells/ **µL** who still have exacerbations, or patient treated with LABA+LAMA+ICS and still have exacerbations, the following options may be considered [3]:

A-Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis [3].

B-Add azithromycin (especially in those who **are not current smokers**) [3].

Short-Acting Bronchodilators

1-**Either a short- or long-acting bronchodilator** is recommended initially for patients with occasional symptoms (**category A**).

2-Short acting bronchodilators are also recommended **for all patients (categories A–E) as rescue or as-needed therapy to manage symptoms.**

3-Choices among short-acting bronchodilators include **short-acting β2-agonists** (**SABAs**) or **short-acting muscarinic antagonists** (**SAMAs**). Both drug classes have a relatively rapid onset of action, **relieve symptoms** to a similar degree, and **improve exercise tolerance** and lung function.

4-Short-acting bronchodilators **do not reduce the frequency or severity of COPD exacerbations.**

5-If a patient does not achieve adequate symptom control with one agent, **combining a SABA with a SAMA is reasonable.**

6-The SABA choices include albuterol and levalbuterol. **Inhalation** is the preferred route for SABAs, and administration via metered-dose or dry powder inhalers (**MDIs**, **DPIs**) is at least as effective as nebulization therapy and is more convenient and less costly.

7-**Inhaled SABAs are generally well tolerated**; **they can cause** sinus tachycardia and rhythm disturbances rarely in predisposed patients. **Skeletal muscle tremors** can occur initially but generally subside as tolerance develops. Older patients may be more sensitive and experience palpitations, tremors, and "jittery" feelings.

8-**Ipratropium bromide** is the most commonly prescribed SAMA. Improvements in pulmonary function are similar to inhaled SABAs, **although ipratropium has a slower onset of action (15–20 minutes vs. 5 minutes for albuterol) and more prolonged effect.**

9-Because of its slower onset, **ipratropium may be less suitable for as needed use but is often prescribed in this manner.**

10-The most frequent **patient complaints** are dry mouth, nausea, and occasionally metallic taste.

Long-Acting Bronchodilators

1-Therapy can be administered as an inhaled **long-acting β2-agonist (LABA**) or **muscarinic antagonist (LAMA).** There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

2-The available LABA **formoterol**, has an onset of action similar to albuterol (<5 minutes), whereas **salmeterol** has a slower onset (15–20 minutes); **however, none of these agents are recommended for acute relief of COPD symptoms.**

3-The available LAMA: **tiotropium** has an onset of action (80 minutes) and is not recommended for acute relief of symptoms.

Methylxanthines (Theophylline and aminophylline)

1-Methylxanthines have a limited role in COPD therapy because of the availability of LABAs and LAMAs as well as **significant methylxanthine drug interactions and interpatient variability in dosage requirements**.

2-Theophylline may be considered in patients **intolerant of or unable to use inhaled bronchodilators.**

3-**Sustained-release theophylline preparations** are most appropriate for long-term COPD management. Caution should be used in **switching from one sustained-release preparation to another** because of variability in sustained-release characteristics.

4-**Common theophylline side effects** include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. Arrhythmias and seizures may occur, especially at toxic concentrations.

Corticosteroids

1-The clinical benefits of ICS therapy **have been observed with combination therapy**. **ICS monotherapy is not recommended for patients with COPD.**

2-Short-term systemic corticosteroids may **also be considered for acute exacerbations**. **Chronic systemic corticosteroids should be avoided in COPD** because of questionable benefits and high risk of toxicity.

Roflumilast

1-Roflumilast is a **phosphodiesterase 4 (PDE4) inhibitor** that relaxes airway smooth muscle.

2-Roflumilast is recommended for patients with recurrent exacerbations **despite treatment with triple inhalation therapy (LAMA/LABA/ICS) or [dual therapy (LAMA/LABA) who are not candidates for ICS** (eosinophil count <100 cells/ **µL**)**].**

3-Because theophylline and roflumilast have similar mechanisms of action, **they should not be used together.**

Azithromycin

1-Chronic **azithromycin was associated with a lower rate of COPD exacerbation** but also with colonization with macrolide resistant bacteria and hearing deficits.

2-In addition, the azithromycin product labeling includes **a precaution about QT prolongation.**

3-Current guidelines recommend to consider **adding chronic azithromycin only for patients with recurrent exacerbations despite optimal therapy (especially in those who are not current smokers)** [(3)].

COPD exacerbations

1-A COPD exacerbation is defined as **a change in the patient's baseline symptoms (dyspnea, cough, or sputum production) (**worsening dyspnea, increased sputum volume, or increased sputum purulence**) sufficient to warrant a change in management**.

2- Classification [2]:

A. Mild: SA bronchodilators only
B. Moderate: SA bronchodilators plus antibiotics and/or oral corticosteroids
C. Severe: hospitalization or emergency department (ED) visits

3-**Goals of Treatment:** (1) Minimize the negative consequences of the acute exacerbation (i.e., reduce symptoms, prevent hospitalization, shorten hospital stay, prevent acute respiratory failure or death) and (2) prevent future exacerbations.

Nonpharmacologic therapy

1-**Provide oxygen therapy for patients with significant hypoxemia**.

2-**Noninvasive positive-pressure ventilation** (**NPPV**) provides ventilatory support with oxygen using a face or nasal mask **without endotracheal intubation**.

3-**Intubation and mechanical ventilation** may be needed in patients failing NPPV or who are poor candidates for NPPV.

Pharmacologic Therapy

The three classes of medications most commonly used for COPD exacerbations are bronchodilators, corticosteroids, and antibiotics [3].

A-Bronchodilators

1-It is recommended that inhaled SABAs are the initial bronchodilators for acute treatment of a COPD exacerbation [3]. **SABAs are preferred** because of rapid onset of action. **Muscarinic antagonists may be added** if symptoms persist despite increased doses of β2-agonists.

2-Bronchodilators may be administered via **MDI**, **DPI**, or **nebulization** with equal efficacy. **Nebulization** may be considered for patients with severe dyspnea **who are unable to hold their breath after actuation of an MDI.**

3-Methylxanthines are not recommended due to increased side effect profiles. [**I.V methylxanthines (theophylline or aminophylline) are not recommended due to significant side effects] [3].**

B-Corticosteroids

Although the optimal corticosteroid dose and duration are unknown, **prednisone 40 mg orally daily (or equivalent) for 5 days is effective for many patients.**

C-Antimicrobial Therapy

1-In order to limit unnecessary use, antibiotics should be initiated in any of these clinical situations:

(1) patients presenting **with three cardinal symptoms** of acute exacerbation (worsening dyspnea, increased sputum volume, or increased sputum purulence).
(2) patients presenting with **two cardinal symptoms** as long as one is **increased sputum purulence**.
(3) patients requiring **mechanical ventilation** regardless of symptoms.

2-The most common pathogens in COPD exacerbations are ***Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*** [(2)].

3-The choice of the antibiotic should be **based on the local bacterial resistance pattern**. Usually, initial empirical treatment is **an aminopenicillin with clavulanic acid**, **macrolide**, **tetracycline** or, in selected patients, **quinolone** [(3)].

3-**Continue antimicrobial therapy for at least 5–7 days**. If the patient deteriorates or does not improve as anticipated, hospitalization may be necessary, and more aggressive attempts should be made to identify potential pathogens responsible for the exacerbation.

Evaluation of therapeutic outcomes

1-**In chronic stable COPD**, **assess pulmonary function tests annually** and with any treatment additions or discontinuations.

2-**In acute exacerbations of COPD**, assess white blood cell count, vital signs, chest x-ray, and changes in frequency of dyspnea, sputum volume, and sputum purulence at the onset and throughout treatment of the exacerbation.

3-**In more severe exacerbations**, ABG and SaO2 should also be monitored.

Reference

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.
2-ACCP 2023
3-Global Initiative for Chronic Obstructive Lung Disease. GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2023 Report. Global Initiative for Chronic Obstructive Lung Disease - GOLD. 2023.

Further reading

Pharmacological and non-pharmacological therapies with evidence of efficacy in reducing the mortality of COPD patients include [Triple combinations (LABA+LAMA+ICS), Smoking cessation, Pulmonary rehabilitation, Long term oxygen therapy, Non-invasive positive pressure ventilation, Lung transplantation and lung volume reduction surgery] [(3)].

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Gastrointestinal disorders

Peptic Ulcer Disease

Introduction

1-**Peptic ulcer disease** (PUD) refers to **ulcerative disorders of the upper gastrointestinal (GI) tract** that **require acid and pepsin for their formation.**

2-The **three common etiologies** include (1) **Helicobacter pylori** infection, (2) nonsteroidal anti-inflammatory drug (**NSAID**) use, and (3) **stress-**related mucosal damage (SRMD).

Pathophysiology

1-Most **duodenal ulcers** occur **in the first part of the duodenum** (duodenal bulb).

2-Pathophysiology is determined by **the balance between aggressive factors** (gastric acid and pepsin) and **protective factors** (Mucus and bicarbonate secretion, mucosal blood flow normally).

3-**Increased acid** secretion may be involved in **duodenal ulcers**, but patients with **gastric ulcers** usually have **normal or reduced acid secretion** (hypochlorhydria).

4-**Nonselective NSAIDs** (including aspirin) cause gastric mucosal damage by two mechanisms: (1) **direct or topical irritation** of the gastric epithelium, and (2) **systemic inhibition** of endogenous mucosal PG synthesis (the **primary mechanism**).

5-**COX-2 selective inhibitors** have a lower risk of ulcers and related GI complications than nonselective NSAIDs. **Addition of aspirin to a selective COX-2 inhibitor reduces its ulcer-sparing benefit** and increases ulcer risk.

6-**Use of corticosteroids alone does not increase risk of ulcer or complications**, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.

7-**Cigarette smoking** has been linked to PUD, impaired ulcer healing, and ulcer recurrence. Risk is proportional to amount smoked per day.

8-**Psychological stress has not been shown to cause PUD**, but ulcer patients may be adversely affected by stressful life events.

9-**Carbonated beverages**, **coffee**, **tea**, **beer**, **milk**, **and spices may cause dyspepsia but do not appear to increase PUD risk**. Ethanol ingestion in high concentrations is associated with acute gastric mucosal damage and upper GI bleeding but is not clearly the cause of ulcers.

Clinical presentation

1-**Abdominal pain is the most frequent PUD symptom**. Pain is often epigastric and described as burning but can present as vague discomfort, abdominal fullness, or cramping.

2-**Nocturnal pain** may awaken patients from sleep, especially between **12 AM and 3 AM**.

3-Pain from **duodenal ulcers often occurs 1–3 hours after meals** and is usually **relieved by food**, whereas **food may precipitate or accentuate ulcer pain in gastric ulcers**. Antacids provide rapid pain relief in most ulcer patients.

4-Presence or absence of epigastric pain does not define an ulcer, and ulcer healing does not necessarily render the patient asymptomatic. **Conversely**, **absence of pain does not preclude an ulcer diagnosis,** especially in **older persons**, who may present with a "**silent**" ulcer complication.

5-Ulcer **complications** include upper GI **bleeding**, **perforation** into the peritoneal cavity, penetration into an adjacent structure (eg, pancreas, biliary tract, or liver), and **gastric outlet obstruction.**

6-**Bleeding may be occult or present as melena or hematemesis**. **Perforation** is associated with sudden, sharp, severe **pain**.

7-**Symptoms of gastric outlet obstruction typically occur over several months** and include **early satiety, bloating, anorexia, nausea, vomiting, and weight loss**.

Diagnosis

1-Routine blood tests are not helpful in establishing a diagnosis of PUD. Hematocrit, hemoglobin, and stool guaiac tests are used **to detect bleeding**.

2-**Diagnosis of PUD depends on visualizing the ulcer crater**; upper GI **endoscopy** has replaced radiography as the procedure of choice because it provides a more accurate diagnosis and permits direct visualization of the ulcer.

3-**Diagnosis of H. pylori infection** can be made using **endoscopic** or **nonendoscopic** (urea breath test [UBT], serologic antibody detection, and fecal antigen) tests.

4-**Endoscopic biopsy-based tests, UBT, and fecal antigen tests are the recommended tests to verify H. pylori eradication** but must be delayed until at least **4 weeks after completion of antibiotic treatment and after proton pump inhibitor (PPI) therapy has been discontinued for 2 weeks** to avoid confusing **bacterial suppression with eradication**.

Treatment

1-Goals of Treatment: Overall goals are to relieve ulcer pain, heal the ulcer, prevent ulcer recurrence, and reduce ulcer-related complications.

2-In H. pylori-positive patients with an ulcer**, goals are to eradicate H. pylori**, **heal the ulcer**, and **cure the disease with a cost-effective drug regimen.**

3-The primary goal for a patient with an NSAID-induced ulcer is **to heal the ulcer as rapidly as possible.**

Nonpharmacologic Therapy

1-Lifestyle modifications including **stress reduction** and **smoking cessation** should be implemented. **NSAIDs should be avoided if possible**, and alternative agents such as acetaminophen should be used for pain relief when feasible.

2-**There is no specific recommended diet**, but patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms (e.g., spicy foods, caffeine, and alcohol).

3-Emergent surgery may be required for patients with ulcer related complications (e.g., bleeding, perforation, or obstruction).

Pharmacologic Therapy

1-**Treatment of H. pylori infection** should be effective, well tolerated, convenient, and cost-effective. Drug regimens to eradicate H. pylori are shown **in Table 1**.

2-**Clarithromycin triple therapy** (PPI, clarithromycin, amoxicillin) **is no longer recommended in areas where H. pylori resistance exceeds 15%.** This regimen given for 14 days remains an option in regions where clarithromycin resistance is <15% and no prior macrolide exposure is documented.

3-**Bismuth quadruple therapy** (PPI or H2RA, bismuth subsalicylate, metronidazole, tetracycline) **for 10–14 days** is **the preferred first-line therapy to eradicate H. pylori infection**. PPIs generally produce higher H. pylori eradication rates and are preferred over H2RA. **All medications except the PPI should be taken with meals and at bedtime**. The PPI should **be taken 30–60 minutes before a meal.** The mean eradication rate for a 10-day course is ~90%, but limitations include the need for **four-times-daily therapy** (which can impair adherence), and frequent minor side effects.

4-**Non-bismuth quadruple (or "concomitant") therapy** (PPI, clarithromycin, amoxicillin, metronidazole) **for 10–14 days** is another recommended first-line therapy. "**Concomitant**" therapy means that **all four drugs are given at the same time twice daily** for the entire duration of therapy.

5-**Sequential therapy** involves a PPI plus antibiotics **given in sequence rather than together.** The rationale is to treat initially with antibiotics that rarely promote resistance (eg, amoxicillin) to reduce bacterial load and preexisting resistant organisms and then to follow **with different antibiotics** (eg, **clarithromycin and metronidazole**) to kill any remaining organisms.

6-**Hybrid therapy** combines the strategies of concomitant and sequential therapy; it **involves 7 days of dual therapy** (PPI and amoxicillin) follow**ed by 7 days of quadruple therapy** (PPI, amoxicillin, clarithromycin, metronidazole).

7-**Levofloxacin-based regimens include** (1) triple therapy with amoxicillin and a PPI, (2) modified sequential therapy with 5–7 days of amoxicillin plus a PPI followed by 5–7 days of levofloxacin, and (3) **quadruple therapy** with levofloxacin, omeprazole or another PPI, nitazoxanide (Alinia), and doxycycline ("**LOAD" therapy**).

8-The **LOAD regimen is not currently recommended** due to high cost and lack of efficacy data. In addition, concerns with fluoroquinolone use include development of resistance and adverse effects (eg, tendonitis, hepatotoxicity).

Table 1:Drug Regimens Used to Eradicate Helicobacter pylori

Regimen	Duration	Drug #1	Drug #2	Drug #3	Drug #4
Proton pump inhibitor–based triple therapy[a]	14 days	PPI once or twice daily[b]	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily *or* metronidazole 500 mg twice daily	
Bismuth quadruple therapy[a]	10–14 days	PPI or H2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg four times daily	Metronidazole 250–500 mg four times daily	Tetracycline 500 mg four times daily
Non-bismuth quadruple or "concomitant" therapy[e]	10–14 days	PPI once or twice daily on days 1–10[b]	Clarithromycin 250–500 mg twice daily on days 1–10	Amoxicillin 1 g twice daily on days 1–10	Metronidazole 250–500 mg twice daily on days 1–10
Sequential therapy[e]	10 days	PPI once or twice daily on days 1–10[b]	Amoxicillin 1 g twice daily on days 1–5	Metronidazole 250–500 mg twice daily on days 6–10	Clarithromycin 250–500 mg twice daily on days 6–10
Hybrid therapy[e]	14 days	PPI once or twice daily on days 1–14[b]	Amoxicillin 1 g twice daily on days 1–14	Metronidazole 250–500 mg twice daily on days 7–14	Clarithromycin 250–500 mg twice daily on days 7–14
Levofloxacin triple	10–14 days	PPI twice daily	Levofloxacin 500 mg daily	Amoxacillin 1 g twice daily	
Levofloxacin sequential	10 days	PPI twice daily on days 1–10	Amoxicillin 1 g twice daily on days 1–10	Levofloxacin 500 mg once daily on days 6–10	Metronidazole 500 mg twice daily on days 6–10
LOAD	7–10 days	Levofloxacin 250 mg once daily	Omeprazole (or other PPI) at high dose once	Nitazoxanide (Alinia) 500 mg twice daily	Doxycycline 100 mg once daily
Rifabutin-based triple therapy	14 days	Omeprazole 40 mg every 8 hours	Amoxicillin 1 g every 8 hours	Rifabutin 50 mg every 8 hours	

aAlthough treatment is minimally effective if used for 7 days, 10−14 days is recommended. The antisecretory drug may be continued beyond antimicrobial treatment for patients with a history of a complicated ulcer, for example, bleeding, or in heavy smokers.
bStandard PPI peptic ulcer healing dosages given once or twice daily.
cStandard H2RA peptic ulcer healing dosages may be used in place of a PPI.
dBismuth subcitrate potassium (biskalcitrate) 140 mg, as the bismuth salt, is contained in a prepackaged capsule (Pylera), along with metronidazole 125 mg and tetracycline 125 mg; three capsules are taken with each meal and at bedtime; a standard PPI dosage is added to the regimen and taken twice daily. All medications are taken for 10 days.
e Requires validation as first-line therapy in the United States.
H2RA, H2>-receptor antagonist; PPI, proton pump inhibitor.

9-If initial **treatment fails to eradicate H. pylori**, **second-line (salvage) treatment should**: (1) use antibiotics that **were NOT included in the initial regimen**, (2) be guided by **region-specific or individual antibiotic resistance testing,** and (3) use an **extended treatment duration of 10–14 days.**

10-Patients **failing clarithromycin triple therapy** can be treated with either bismuth quadruple therapy or the levofloxacin triple regimen for 14 days.

11-**Other salvage regimens** may also be successful. Penicillin allergy testing is recommended for patients who report penicillin allergy **because many patients are not truly allergic.**

12-Patients with NSAID-induced ulcers should be tested to determine H. pylori status. If **they are H. pylori positive**, **start treatment with a recommended first-line regimen**. If patients are H. pylori **negative**, **discontinue the NSAID and treat with a PPI, H2RA, or sucralfate.** PPIs are generally preferred due to more rapid symptom relief and ulcer healing.

13-If the NSAID must be continued, **implement cotherapy with a PPI** or **misoprostol**. Patients at highest risk of recurrent ulcers or ulcer-related complications should be switched **to a COX-2 inhibitor**.

14-Limit **maintenance therapy with a PPI or H2RA to high-risk patients** with ulcer complications, patients who fail H. pylori eradication, and those with H. pylori-negative ulcers.

15-Patients with ulcers **refractory** to treatment should **undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and assess H. pylori status**.
H. pylori-positive patients should receive eradication therapy. Refractory ulcers despite a complete standard PPI course should be retreated with **double-dose of PPI**, or consideration can be given to using **a different PPI**.

Evaluation of therapeutic outcomes

1-**Monitor patients for symptomatic relief of ulcer pain**, potential adverse drug effects, and drug interactions.

2-**Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy.** Patients with uncomplicated PUD are usually symptom free after treatment with any of the recommended antiulcer regimens.

3-**Persistent or recurrent symptoms within 14 days after the end of treatment** suggests **failure of ulcer healing or H. pylori eradication** or presence of an **alternative diagnosis** such as gastroesophageal reflux disease.

4-Eradication of H. pylori should be confirmed **after treatment** in all patients, particularly those who are at risk for complications.

Reference: **Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.**

College of Pharmacy
Fourth year. Clinical Pharmacy

Endocrine disorders:
Diabetes Mellitus Part I

Introduction

1-**Diabetes mellitus** (DM) is a **group of metabolic disorders characterized by chronically elevated blood glucose (BG)** and abnormal carbohydrate, fat, and protein metabolism.

2-Without effective treatment, **DM can lead to acute complications such as diabetic ketoacidosis (DKA)** and **hyperosmolar hyperglycemic syndrome** (**HHS**).

3-**Chronic hyperglycemia** can cause **microvascular**, **macrovascular**, and **neuropathic complications.**

Pathophysiology

1-**Type 1 DM** (5%–10% of cases) usually results **from autoimmune destruction of pancreatic β-cells (**islet cell antibody**), leading to absolute deficiency of insulin.**

2-It usually presents **in children and adolescents but can occur at any age**.

3-**Type 2 DM (90%–95% of cases) is characterized by multiple defects:**

- **Impaired insulin secretion**:
- **Reduced incretin effect:** Normally, the gut incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and **stimulate insulin secretion in response to a meal**. **Patients with type 2 DM have a reduced incretin effec**t.
- **Insulin resistance:** This is manifested by excessive hepatic glucose production, decreased skeletal muscle uptake of glucose, and increased lipolysis and free fatty acid production.
- **Excess glucagon secretion.**
- **Sodium-glucose cotransporter-2 (SGLT-2) upregulation in the kidney:** This **increases reabsorption of glucose**, which further contributes to hyperglycemia.

4-**Gestational diabetes** (GDM) is DM **that occurs in women during pregnancy**.

5-**Microvascular complications** include **retinopathy**, **neuropathy**, and **nephropathy**.

6-**Macrovascular complications** include **coronary heart disease** (CHD), **stroke**, and **peripheral vascular disease**.

Clinical presentation

Type 1 Diabetes Mellitus

1-Patients often **have symptoms in the days or weeks preceding the diagnosis**. The most common initial symptoms are **polyuria**, **polydipsia**, **polyphagia**, **weight loss**, **fatigue**, and **lethargy**.

2-Individuals are often **thin** and are **prone to develop DKA** in the absence of an adequate insulin supply; many patients initially present with DKA.

3-Symptom onset can be **triggered by infection, trauma, or psychological stress**.

Type 2 Diabetes Mellitus

1-**Most patients are asymptomatic** or have **only mild fatigue at the time of diagnosis**. Many patients are **incidentally found to have type 2 DM after routine laboratory testing** (eg, plasma glucose or A1C) or development of complications (eg, myocardial infarction, stroke).

2-**Because mild hyperglycemia may exist for years prior to the diagnosis**, microvascular and macrovascular **complications are often present at the time of diagnosis**.

3-**Most patients are overweight** or obese.

Diagnosis

1-Criteria for diagnosis of DM include any one of the following:

1. **A1C ≥6.5%** 2. Fasting (no caloric intake for at least 8 hours) plasma glucose (FPG) **≥126 mg/dL** 3. Oral glucose tolerance test **(OGTT) ≥200 mg/dL** 4. **Random plasma glucose ≥200 mg/dL** with **classic symptoms of hyperglycemia or hyperglycemic crisis.**

2-**Prediabetes** is a condition of abnormal BG that is not sufficiently high to meet the thresholds that define DM but often progresses to the diagnosis.

3-**Screening for type 1 DM in asymptomatic children or adults is not recommended** due to low disease prevalence and the acute onset of symptoms.

4-**Screening for type 2 DM is recommended for asymptomatic adults who are overweight** (BMI ≥25 kg/m^2) and **have at least one other risk factor for developing type 2 DM.**

5-**All adults, even those without risk factors, should be screened every 3 years starting at 45 years old**. Children at risk for developing type 2 DM should undergo screening every 3 years starting at age 10 years.

Treatment

1-**Goals of Treatment:** The **primary goal is** to prevent or delay progression of long-term microvascular and macrovascular complications.

2-**Additional goals are** to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse effects.

3-**General glycemic targets** for most nonpregnant adults with DM are listed in **Table-1.**

Table-1: Glycemic Target Recommendations for Most Nonpregnant Adults with Diabetes

Parameter	American Diabetes Association (ADA)	American Association of Clinical Endocrinologists (AACE)
A1C	<7.0% (53 mmol/mol Hb)	≤6.5% (48 mmol/mol Hb)
Fasting plasma glucose (FPG)	80–130 mg/dL (4.4–7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Postprandial glucose (PPG)	<180 mg/dL (10 mmol/L)	<140 mg/dL (7.8 mmol/L)

4-Glycemic targets should be individualized. More stringent or less stringent goals may be appropriate for some patients.

Nonpharmacologic Therapy

1-Medical nutrition therapy (MNT): Implement a healthy meal plan that is moderate in calories and carbohydrates and low in saturated fat with all of the essential vitamins and minerals. Target an initial weight loss goal of at least 5% in all type 2 DM patients who are overweight or obese through calorie restriction.

2-**Aerobic exercise**: Physical activity goals include at least 150 min/week of moderate intensity exercise spread over at least 3 days/week with no more than 2 days between activity. Resistance/strength training is recommended at least 2 times/week for patients without proliferative diabetic retinopathy.

3-Patients **must be involved in decision making and have strong knowledge of the disease and associated complications.**

Pharmacologic Therapy

Insulin

1-The main advantage of insulin over other antihyperglycemic agents is **that the** dose can be individualized based on glycemic levels.

2-**Disadvantages** include the **risk of hypoglycemia**, **need for injections**, **and weight gain**.

3-Most insulin products are administered **subcutaneously** (SC) **for chronic diabetes management**, except for **inhaled human insulin**, which is a dry powder of regular insulin that is inhaled and absorbed through pulmonary tissue.

4-The **pharmacokinetics of insulin products** is characterized by their onset, peak, and duration of action (**Table**-2).

5-**Basal insulin** (or background insulin) **refers to longer-acting insulins** that regulate BG levels in **between meals**. Options include the following insulins:

- **NPH** is the least ideal product because it **has a distinct peak** and usually requires **twice daily dosing**.
- **Detemir also has a peak** and often lasts <24 hours; it can be given once daily in some patients **but should be dosed twice daily at low doses**.
- **Glargine** and **degludec** are longer acting-agents that have no **peak and are given once daily.**

6-**The longer-acting products have a lower risk of hypoglycemia** (particularly nocturnal hypoglycemia). However, they are more expensive.

7-**Bolus insulin refers to short- or rapid-acting insulins that cover meals** (also called prandial insulin) or glycemic excursions (also called correction insulin).

8-**Basal insulin** is the preferred and most convenient **initial insulin formulation for patients with type 2 DM,** whereas patients with **type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control**.

Table-2: Pharmacokinetics of Select Insulins Administered Subcutaneously

Type of Insulin by Generic (Brand) Name (U-100 unless otherwise noted)	Onset	Peak[a]	Duration[a]
Ultra-rapid acting			
Insulin aspart (Fiasp)	15–20 min[b]	90–120 min	5–7 hours
Insulin lispro aabc (Lyumjev)	15–17 min[c]	120–174 min	4.6–7.3 hours
Insulin human—inhaled (Afrezza)	12 min	35–55 min	1.5–4.5 hours
Rapid-acting			
Insulin aspart (NovoLog)	10–20 min	30–90 min	3–5 hours
Insulin lispro U-100, U-200 (Humalog, Admelog)			
Insulin glulisine (Apidra)			
Short-acting			
Regular (Humulin R, Novolin R)	30–60 min	2–4 hours	5–8 hours
Intermediate-acting			
NPH (Humulin N, Novolin N)	2–4 hours	4–10 hours	10–24 hours
Regular U-500 (Humulin R 500)	15–30 min	4–8 hours	13–24 hours
Long-acting			
Insulin detemir (Levemir)	1.5–4 hours	6–14 hours[c]	16–20 hours
Insulin glargine (Lantus, Basaglar)	2–4 hours	No peak	20–24 hours
Insulin glargine U-300 (Toujeo)	6 hours	No peak	36 hours
Insulin degludec U-100, U-200 (Tresiba)	1 hour	No peak	42 hours
Combination Products			
70% NPH/30% Regular (Humulin 70/30, Novolin 70/30)	30–60 min	Dual	10–16 hours
75% NPL, 25% lispro (Humalog 75/25)	5–15 min		10–16 hours
50% NPL, 50% lispro (Humalog 50/50)	5–15 min		10–16 hours
70% insulin aspart protamine, 30% insulin aspart (NovoLog 70/30)	5–15 min		15–18 hours

9-**Bolus insulin options include**:

- **Aspart**, **lispro**, and **glulisine**, the rapid-onset, short-duration insulins

- Inhaled human insulin, fast-acting insulin aspart (Fiasp®), and insulin lispro (Lyumjev®): the ultrarapid onset insulins

10-Rapid-acting insulins offer a **faster onset and shorter duration of action than regular insulin**, and **ultra-rapid acting insulins offer an even faster onset**; this may more closely **mimic prandial endogenous insulin release**.

11-Rapid-acting insulins have **a modestly lower risk of hypoglycemia** than regular insulin.

12-**Various premixed insulin products** containing both a basal and a prandial component are also available (**Table-2**). However, **these products are limited by fixed mixed formulations, which can make it challenging to tailor the dosing regimen.**

13-**The insulin dose must be individualized.** In type 1 DM, **the average daily requirement** is 0.5–0.6 units/kg, with **approximately 50% given as basal insulin** and the remaining **50% dedicated to meal coverage.**

14-**Hypoglycemia is the most common adverse effects of insulin therapy**. Insulin also causes dose-dependent weight gain.

15-SC administration can result in **lipoatrophy** or **lipohypertrophy**, which can be prevented by **routinely rotating injection sites.**

Biguanides

1-Metformin **decreases hepatic glucose production** and **enhances insulin sensitivity** in peripheral (muscle) tissues, **allowing for increased glucose uptake into muscle cells**.

2-Metformin is recommended **as first-line pharmacotherapy in patients with type 2 DM** (unless a contraindication or intolerability exists).

3-It **does not cause weight gain** and may **lead to a modest (2–3 kg) weight loss.**

4-It has a **low risk of hypoglycemia** because it does not directly increase pancreatic insulin secretion.

5-Metformin **decreases plasma triglycerides** and **low-density lipoprotein cholesterol** (LDL-C) and **modestly increases high-density lipoprotein cholesterol** (HDL-C).

6-**Metformin frequently causes GI side effects** (diarrhea, abdominal discomfort, stomach upset); these effects are usually dose-dependent, transient, mild, and can be **minimized with slow dose titration and taking metformin with or immediately after meals.**

7-**Extended-release metformin** may lessen some of the GI side effects**.**

8-**Metformin may cause a metallic taste and may lower vitamin B12 concentrations**; B12 levels or methylmalonic acid should be measured annually or if a deficiency is suspected, **with vitamin B12 supplementation given if indicated**.

9-**Lactic acidosis occurs rarely**, usually in the setting of **severe illness or acute kidney injury**. **Because symptoms are often nonspecific, the diagnosis must be confirmed by laboratory measurement of high lactic acid levels and acidosis**.

10-Metformin is renally excreted and accumulates in renal insufficiency; Due to the risk of **acute renal failure with use of IV contrast dye**, **withhold metformin therapy starting the day of the procedure and resume it 2–3 days later** if normal renal function has been documented.

11-Metformin can be **used in combination with any other antihyperglycemic therapy** and is often continued when insulin therapy is initiated.

Sodium-Glucose Cotransporter-2 Inhibitors

1-Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin reduce plasma glucose by **preventing the kidneys from reabsorbing glucose back into the bloodstream**, leading to increased glucose excretion in the urine.

2-SGLT-2 inhibitors **lower both FPG and postprandial glucose** (**PPG).**

3-SGLT-2 inhibitors **can be added** to metformin or other second-line agents. **They** can be used as monotherapy in patients who cannot tolerate or take metformin ..

4-They are recommended for patients at high risk for or with established **ASCVD, heart failure, or CKD.**

5-They are **unlikely to cause hypoglycemia** unless combined with medications such as sulfonylureas, meglitinides, or insulin.

6-**The most common adverse effect is genital mycotic infections**, which are more common in women and uncircumcised men. There is also a slightly increased risk of **urinary tract infections**. Polyuria, dehydration, dizziness, or hypotension may occur because of the osmotic diuresis effects.

Glucagon-like Peptide 1 Receptor Agonists (GLP1-RAs)

1-Dulaglutide, exenatide, exenatide XR, lixisenatide, liraglutide, and semaglutide stimulate insulin secretion and suppress inappropriately high postprandial glucagon secretion, decreasing hepatic glucose output. They also slow gastric emptying, increase satiety, and **cause weight loss (average 1–3 kg).**

2-**Short-acting agents** (exenatide, lixisenatide) predominantly **lower PPG levels**, whereas **long-acting agents** (dulaglutide, liraglutide, exenatide XR, semaglutide) **lower both FPG and PPG**, but with larger effects on FPG.

3-Dulaglutide, liraglutide, and semaglutide are FDA approved to reduce the risk of major adverse CV events in adults with type 2 DM and established ASCVD

4-GLP1RAs can be used as monotherapy in patients who cannot tolerate or take first line therapy. Six GLP1RAs are administered SC. Semaglutide is available as SC and oral preparations.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

1-Alogliptin, linagliptin, saxagliptin, and sitagliptin prolong the half-life of endogenously produced GLP-1 and GIP, thereby increasing glucose-dependent insulin secretion from the

pancreas and reducing inappropriate postprandial glucagon secretion, resulting in lower glucose levels **without an increase in hypoglycemia when used as monotherapy**.

2-They do not alter gastric emptying, or cause weight gain/loss.

3-DPP-4 inhibitors are considered **second- or third-line therapy**.

4-Advantages include **once-daily dosing**, **oral administration**, **weight neutrality**, **low risk of hypoglycemia, and good tolerability**.

Thiazolidinediones (TZDs)

1-TZDs bind to the peroxisome proliferator activator receptor-γ (PPAR-γ) located primarily on fat and vascular cells, enhancing insulin sensitivity in muscle, liver, and fat tissues.

2-Maximum effects may **not be seen until 3–4 months of therapy**.

3-TZDs are considered **second- or third-line agents** and can be used in combination with metformin and other commonly prescribed medications for type 2 DM.

4-**Fluid retention may occur**. This may result in **peripheral edema**, HF, **hemodilution** of hemoglobin and hematocrit, **and weight gain.**

5-**TZDs are contraindicated in patients with New York Heart Association Class III or IV HF** and should be used with caution in patients with Class I or II HF.

6-**Weight gain** is dose related and results from both fluid retention and fat accumulation.

Sulfonylureas (e.g. glyburide, glipizide, and glimepiride)

1-Sulfonylureas enhance insulin secretion by binding to the sulfonylurea receptor SUR1 on pancreatic β-cells.

2-Sulfonylureas are widely used because they have an extensive record of safety and effectiveness, are given orally, and are inexpensive. **However, current treatment guidelines either discourage their use or suggest caution due to the risk of hypoglycemia and weight gain.** In addition, **tachyphylaxis** to the insulin secretion effect occurs, leading to poor long-term durability of response in most patients.

3-**The most common side effect is hypoglycemia**.

4-**Weight gain is common** (typically 1–2 kg). **Patients with sulfa allergy rarely experience crossreactivity with sulfonylureas.**

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.

Endocrine disorders

Diabetes Mellitus Part II

α-Glucosidase Inhibitors

1-**Acarbose** and **miglitol delay the breakdown of sucrose and complex carbohydrates** in the small intestine, prolonging carbohydrate absorption.

2-Good candidates for these drugs are patients who are **near target A1C levels** with near-normal FPG but **high PPG levels**.

3-The most common side effects **are flatulence, abdominal pain, and diarrhea**, which can be reduced by slow dosage titration.

Meglitinides

1-**Nateglinide** and **repaglinide** stimulate insulin secretion from pancreatic β-cells by binding to a site adjacent to the sulfonylurea receptor.

2-They are similar to sulfonylureas except that they have **a faster onset and shorter duration** of action.

3-Similar to sulfonylureas, the main side effects **are hypoglycemia and weight gain**.

4-They may be a good option for patients **with erratic meal schedules**. However, **multiple daily dosing may decrease adherence**.

5-Meglitinides should be taken by mouth **with each meal**.

Bile Acid Sequestrants

Colesevelam. Its mechanism in lowering plasma glucose levels is unknown, and its role in therapy is unclear.

Dopamine Agonists

1-**Bromocriptine mesylate** is FDA approved for treatment of type 2 DM. The mechanisms by which it improves glycemic control are unknown .

2-Its role in the treatment of type 2 DM is unclear.

Amylin Analogs

1-**Pramlintide** is a synthetic amylin analog that reduces glucagon secretion, slows gastric emptying, and increases satiety. **It was the first noninsulin agent approved for patients with type 1 DM.**

2-It is used **primarily in type 1 DM as adjunctive therapy** for patients who are not achieving **PPG goals** despite maximizing mealtime insulin doses.

3-It can also **decrease weight** and may allow for lower mealtime insulin doses.

Treatment of Type 2 Diabetes

1-Upon diagnosis, **set a patient-specific A1C target**. **Implement comprehensive lifestyle modifications** .

2-**Initiate with metformin [**or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals] **(Unless there is a comorbidity in which other agents are preferred). Recommendations based on patient-specific comorbidities** include:

- ✔**High risk or established ASCVD**: SGLT2 inhibitor or GLP1RA.
- ✔**Heart Failure (HF)**: SGLT2 inhibitor. Avoid TZDs in patients with HF.
- ✔**CKD (with or without ASCVD):** SGLT2 inhibitor.

3-If the initial A1C is close to goal (eg, ≤7.5%) **consider initial treatment with lifestyle modifications alone** if the patient is motivated.

4-Consider **starting two medications** (e.g. metformin plus a second agent) if the initial A1C is >**1.5% higher than the target A1C.**

5-**Consider early introduction of basal insulin in patients with** very high A1C levels (>10%), or symptoms of hyperglycemia.

6-**See patients at least every 3 months if they are not meeting their goals and at least every 6 months if they are meeting goals.** Add additional therapy if glucose targets have not been met.

7-Most patients eventually require combination therapy.

8-If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug(s), **then triple therapy is warranted**, adding a drug from another class.

9-People with type 2 DM can often be managed with **oral medications for years before injectable medications are needed.**

10-Insulin is recommended for extreme (A1C >10%) or symptomatic hyperglycemia. Otherwise, **GLP-1 RAs are preferred over basal insulin** because they have equal or superior A1C lowering efficacy and lead to weight loss instead of weight gain with a low risk of hypoglycemia.

11-**Basal insulin can be initiated** if additional glucose lowering is needed after the GLP-1 RA dose has been maximized.

12-**If the A1C target is not reached by maximally titrating basal insulin**, PPG levels are likely elevated and **a GLP1-RA or SGLT-2 inhibitor should be considered** if the patient is not already taking one.

13-**Prandial insulin is also an option**. Titrate the dose over time to achieve target PPG levels <180 mg/dL. **A second or third injection can be added** to the other meals if needed.

Treatment of Hyperglycemia in Type 1 Diabetes

1-All patients with type 1 DM require exogenous insulin. Achieving adequate glycemic control usually requires **intensive insulin regimens designed to provide insulin in a manner that mimics normal physiologic insulin secretion**, with consistent secretion of

insulin throughout the day to manage glucose levels overnight and in between meals (ie, basal insulin), and bursts of insulin in response to glucose rises after ingestion of carbohydrates (ie, prandial insulin).

2-**Intensive insulin regimens** can be given with either **multiple daily injections** (MDI) or use of **continuous subcutaneous insulin infusion** (CSII) via an **insulin pump.**

3-A common MDI approach is **one injection of long-acting insulin** (eg, insulin glargine) for the basal component and **three injections** of rapid acting insulin (eg, insulin lispro) for the prandial component.

4-**A less expensive option consists of two injections of intermediate-acting insulin (eg, NPH insulin) and two injections of short-acting insulin (eg, regular insulin).** However, the ADA Standards of Care recommend that most patients should **use rapid-acting insulins** rather than regular insulin to reduce the risk of hypoglycemia.

5-**Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs** . The pump infuses a basal rate constantly throughout the day and allows **the patient to give bolus doses using a bolus dose calculator** based on current glucose levels, carbohydrate intake, and insulin on board.

6-**The total daily insulin dose is divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals).** The insulin doses would then be adjusted based on self-monitoring of blood glucose (**SMBG**) data. Ideally, patients should learn to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake.

7-Patients should also **SMBG before each meal or use continuous glucose monitoring (CGM) to evaluate the insulin regimen and make treatment decisions**. Bolus insulin doses can be better individualized by using carbohydrate-to-insulin ratios (C:I ratios) and correction factors (CF).

8-**Pramlintide is indicated as adjunctive treatment** in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin.

9-Assess patients every 3 months if uncontrolled and every 6 months if controlled. Patients on intensive insulin therapy should SMBG at least four times daily, before meals and at bedtime.

10-**Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur**. SMBG is crucial during times of intercurrent illness or stresses for early detection and prevention of DKA.

11-Current guidelines recommend **CGM in patients with type 1 DM who are not meeting glycemic goals.** They are also recommended in patients with **hypoglycemia unawareness** to better detect and prevent hypoglycemic events.

Common insulin regimens.

(A) Multiple-component insulin regimen consisting of **one injection of long-acting** insulin (detemir, glargine degludec) to provide basal glycemic coverage and **three injections of rapid-acting insulin** (aspart, lispro, glulisine) to provide glycemic coverage for each meal.

(B) Insulin regimen consisting of **two injections of intermediate-acting insulin** (NPH) and rapid-acting insulin (aspart, lispro, glulisine), or short-acting regular insulin.

(C) **Insulin administration by insulin infusion device**. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump.

Hypoglycemia

1-**Hypoglycemia is a common complication** of some diabetes medications.

2-The severity of hypoglycemia is classified as follows:

- **Level 1** (hypoglycemia alert value; ≤70 mg/dL: May not cause symptoms but should be treated **with a fast-acting carbohydrate** and may need medication dose adjustment.
- **Level 2** (clinically significant hypoglycemia; <54 mg/dL: Serious, clinically important hypoglycemia
- **Level 3** (severe hypoglycemia): Associated with cognitive impairment requiring external assistance for recovery and can be life threatening.

3-**Initial autonomic symptoms include** tachycardia, palpitations, sweating, tremors, and hunger. **Neuroglycopenic symptoms** often occur with BG <60 mg/dL and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness.

4-Some patients have **hypoglycemia unawareness** and are unable to detect the early warning symptoms of hypoglycemia; they are at increased risk for the serious sequelae associated with severe hypoglycemia.

5-**SMBG and CGM can be useful in preventing hypoglycemia**. Patients must be educated to understand situations that increase risk of hypoglycemia (eg, delaying meals, during or after exercising, or fasting).

6-**Treatment of hypoglycemia** requires ingestion of carbohydrates, preferably glucose. Patients should carry a source of fast-acting glucose with them at all times and use the **"rule of 15" f**or proper treatment:

- First use SMBG to confirm BG <70 mg/dL and then **ingest 15 g** of fast-acting carbohydrates such as 1/2 cup (4 oz or 125 mL) of milk, juice, or soda; 1 tablespoon of honey; hard candy; jelly beans; or glucose tablets.
- **Repeat SMBG in 15 minutes**; if the BG is <70 mg/dL, **repeat the process.**
- **Once the BG is normalized**, **eat a snack or meal that includes complex carbohydrates** and protein to prevent further hypoglycemic episodes.

7-If the patient is unc**o**nscious, **give IV glucose or glucagon injection**. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV glucose cannot be rapidly administered.

8-**A glucagon kit should be prescribed and readily available to all patients on insulin who have a history of or high risk for severe hypoglycemia**. It can take 10–15 minutes before glucose levels start to rise, and patients often **vomit**.

9-**Position the patient on the side with the head tilted slightly downward to avoid aspiration.**

10-Clinicians **should monitor hypoglycemia at every visit**.

11-**Reevaluate the treatment regimen** of patients with frequent or severe hypoglycemia to minimize future episodes.

Complications and Comorbidities

Macrovascular Complications

1-Macrovascular complications (eg, CHD, stroke) **are the leading causes of death in people with diabetes.**

2-The ADA recommends **low-dose aspirin therapy** (75–162 mg daily) **in all patients with established ASCVD.** Clopidogrel may be used in patients allergic to aspirin.

3-The role of antiplatelet therapy for primary CV prevention is unclear because the benefits may be offset by a higher risk of bleeding; **some practice guidelines recommend aspirin if the 10-year risk of a CV event is >20%.**

4-In patients with **established ASCVD**, use of a **GLP1-RA or an SGLT-2 inhibitor should be strongly considered.**

5-For all patients whose **BP exceeds 120/80 mm Hg,** the ADA recommends dietary changes, physical activity, and weight loss in overweight or obese patients.

6-Drug therapy using agents proven to reduce CV events should be started **for BP >140/90 mm Hg.** A combination of **two medications should be used for BP >160/100 mm Hg**.

7-Initiate **high-intensity statin** therapy in all patients with diabetes and preexisting ASCVD regardless of baseline lipid levels. In the absence of ASCVD, prescribe a **moderate-intensity statin t**o all patients with type 1 or type 2 DM over the age of 40.

8-In patients <40 years of age, a **moderate intensity statin** may be appropriate for patients with multiple CV risk factors.

9-A **fibrate** (e.g., fenofibrate), **omega-3 fatty acid**, or **niacin** can be added for patients with marked **hypertriglyceridemia**.

10-**Peripheral arterial disease** can lead to claudication, nonhealing foot ulcers, and limb amputation. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies. **Cilostazol** may be useful in select patients to reduce symptoms. **Revascularization** surgery can be considered in some situations.

Microvascular Complications

Efforts to improve glucose control significantly reduce the risk of developing microvascular complications and slow their progression.

Nephropathy:

1-**Albuminuria is a marker of renal damage**. The ADA recommends screening for albuminuria upon diagnosis and annually thereafter in persons with type 2 DM.

2-Screening **with type 1 DM** should begin with puberty **and after 5-years'** disease duration.

3-**Glucose and BP control** are important for preventing and slowing progression of nephropathy.

4-**The SGLT2 inhibitors** empagliflozin, canagliflozin, and dapagliflozin significantly **reduce the decline in kidney function in patients with CKD, with or without diabetes**.

5-**ACE** inhibitors and **ARBs** can slow the progression of renal disease in patients with diabetes.

6-**Diuretics** are often necessary due to volume expanded states and are recommended **second-line therapy**.

7-The ADA recommends a **BP goal <140/90 mm Hg in patients with nephropathy** but a **lower target** (e.g., <130/80 mm Hg) **if it can be achieved without undue burden or side effects**. **Three or more antihypertensives are often needed to reach goal BP.**

Retinopathy:

1-Patients with diabetes should have **routine eye examinations to fully evaluate the retina.**

2-**Early retinopathy may reverse with improved glycemic control and optimal BP control**. More advanced retinopathy will not fully regress with improved glycemia.

3-**Laser photocoagulation** has markedly improved sight preservation. **Intravitreal antivascular endothelial growth factor (VEGF) therapy** is also highly effective for sight preservation.

4-**Bevacizumab** (used off-label) and **ranibizumab** are **anti-VEGF monoclonal antibodies**, and **aflibercept** is a VEGF **decoy receptor**.

Neuropathy:

- **Peripheral neuropathy** is the most common complication in patients with type 2 DM. **Paresthesias, numbness**, or **pain** are **the predominant symptoms**. The feet are involved far more often than the hands. **Improved glycemic control is the primary treatment and may alleviate some symptoms.** Pharmacologic therapy is symptomatic and includes low-**dose tricyclic antidepressants** (nortriptyline or desipramine), **duloxetine**, **gabapentin**, **pregabalin**, **venlafaxine**, **topical capsaicin**, and **tramadol**.

- **Gastroparesis**. Improved glycemic control and use of **metoclopramide** or **low-dose erythromycin** may be helpful.

- **Diabetic diarrhea** is often **nocturnal** and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.

- **Orthostatic hypotension** may require mineralocorticoids (eg, **fludrocortisone**) or adrenergic agonists (**midodrine**).

- **Erectile dysfunction** is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil**, **vardenafil**, or **tadalafil**).

Evaluation of therapeutic outcomes

1-**Measure A1C every 3–6 months to follow long-term glycemic control for the previous 2–3 months**.

2-For patients with type 1 DM, **SMBG is typically performed 4–6 times per day**—prior to food intake and physical activity and at bedtime.

3-The optimal **frequency of SMBG in patients with type 2 DM on oral agents is controversial**.

4-**At each visit**, ask patients with type 1 DM **about the frequency and severity of hypoglycemia**.

5-Screen for complications (**eye exams**, assess **BP, examine the feet, screen for albuminuria, check fasting lipid panel)**

6-Administer an **annual influenza vaccine** and assess for administration of the **pneumococcal vaccine and hepatitis B vaccine** series along with management of other CV risk factors (e.g., smoking).

Reference: Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.