Anemia

Anemias are a group of diseases characterized by a decrease in hemoglobin (Hb) or red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood. The WHO defines anemia as:

- ***in men***: Hb less than 13 g/dL (<8.07 mmol/L)
- ***in women***: Hb less than 12 g/dL (<7.45 mmol/L)

Classification:

Anemias can be classified by:

Morphologic classifications

- Macrocytic cells (vitamin B12 deficiency or folic acid deficiency)
- Microcytic cells (iron deficiency)
- Normocytic anemia (blood loss or chronic disease)

Functional classification

Anemias can be:

1. ***Hypoproliferative causes***

- *Due to marrow damage*
- *Iron deficiency anemias*
- *Stimulation, as seen in:*
    - *Renal disease*
    - *Inflammation*
    - *Metabolic disease*

2. ***Maturation disorders***

- *Cytoplasmic defects, such as:*
    - *Thalassemia*
    - *Iron deficiency anemia*
    - *Sideroblastic anemia*
- *Nuclear maturation defect, such as:*
    - *Folate deficiency anemia*
    - *Vit. B12 deficiency anemia*
    - *Refractory anemia*

3. ***Hemorrhage/hemolysis***

As occur in case of:

- *Blood loss*
- *Intravascular hemolysis*
- *Autoimmune disease*
- *Hemoglobinopathy*
- *Metabolic/membrane defect*

Signs and symptoms

Signs and symptoms depend on rate of development and age and cardiovascular status of the patient.

Acute-onset anemia is characterized by cardiorespiratory symptoms such as tachycardia, light-headedness and breathlessness.

Chronic anemia is characterized by weakness, fatigue, headache, symptoms of heart failure, vertigo, faintness, cold sensitivity, pallor and loss of skin tone.

Diagnosis

- In general, rapid diagnosis is essential because anemia is often a sign of underlying pathology.
- Initial evaluation of anemia involves a complete blood cell count (CBC), reticulocyte index, and examination of the stool for occult blood.
- Elderly patients with symptoms of anemia should undergo a CBC with peripheral smear and reticulocyte count and other laboratory studies as needed to determine the etiology of anemia.
- The diagnosis of anemia in pediatric populations requires use of age- and gender adjusted norms for laboratory values.

FYI: Diseases Causing Anemia of Inflammation

<table>
<tr><td colspan="3">➢ Common causes</td></tr>
<tr><td>• Chronic infections
– HIV
– Subacute bacterial endocarditis
– Osteomyelitis
– Chronic UTIs
– TB
– Other chronic lung infections (e.g., lung abscess, bronchiectasis)</td><td>• Chronic inflammation
– RA
– SLE
– IBS
– Inflammatory osteoarthritis
– Gout
– Collagen vascular diseases
– Chronic inflammatory liver diseases</td><td>• Malignancies
– Carcinoma
– Lymphoma
– Leukemia
– Multiple myeloma</td></tr>
<tr><td colspan="3">➢ Less common causes</td></tr>
<tr><td colspan="3">• Alcoholic liver disease
• Congestive heart failure
• Thrombophlebitis
• Chronic obstructive pulmonary disease
• Ischemic heart disease</td></tr>
</table>

Iron-deficiency anemia

Patient is considered suffering iron-deficiency anemia when hemoglobin concentration is less than 9 g/dL (<90 g/L; <5.59 mmol/L).

Iron-deficiency anemia can be caused by blood loss, chronic diseases, inadequate dietary intake, inadequate gastrointestinal absorption and increased iron demand (e.g., pregnancy). It can be a result of pica (compulsive eating of nonfood items) or pagophagia (compulsive eating of ice).

Iron-deficiency anemia is characterized by glossal pain, smooth tongue and reduced salivary flow.

✓ **Diagnosis:**

The earliest and most sensitive laboratory change for iron-deficiency anemia is decreased serum ferritin (storage iron), which should be interpreted in conjunction with decreased transferrin saturation and increased total iron-binding capacity (TIBC).

Hemoglobin, hematocrit (HCT) and RBC indices usually remain normal until later stages of Iron-deficiency anemia.

✓ **Treatment:**

- 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 200 mg elemental iron in two or three divided doses.
- Iron should be taken at least 1 hour before meals because food interferes with absorption, but administration with food may be needed to improve tolerability.
- Parenteral iron may be considered for patients with iron malabsorption, intolerance of oral iron therapy, or noncompliance. Parenteral administration, however, does not hasten the onset of hematologic response.
- Iron dextran, sodium ferric gluconate, ferumoxytol, and iron sucrose are available parenteral iron preparations with similar efficacy but different molecular size, pharmacokinetics, bioavailability and adverse effect profiles.

Ferritin in COVID-19

Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from COVID-19. On this basis, scientists are supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of COVID-19.

Vitamin B12–deficiency anemia

Vitamin B12–deficiency anemia can be caused by inadequate dietary intake, decreased absorption, and inadequate utilization. Deficiency of intrinsic factor causes decreased absorption of vitamin B12 (i.e., pernicious anemia).

Neurologic effects (e.g., numbness and ataxia) of vitamin B12 deficiency may occur in absence of anemia. Psychiatric findings, including irritability, depression, and memory impairment, may also occur with vitamin B12 deficiency.

✓ **Diagnosis:**

It is a macrocytic anemia, mean corpuscular volume is usually elevated to greater than 100 fL.* Vitamin B12 and folate concentrations can be measured to differentiate between the two deficiency anemias. A vitamin B12 value less than 150 pg/mL (<111 pmol/L).**

✓ **Treatment:**

Oral vitamin B12 supplementation (cyanocobalamin) appears to be as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B12 absorption pathway is independent of intrinsic factor.

Parenteral therapy acts more rapidly than oral therapy and is recommended if neurologic symptoms are present.

**Femtoliter (fL) = 10^{-15} liter*

*** Picogram (pg) = 10^{-12}g*

Folic acid–deficiency anemia

Folic acid–deficiency anemia can be caused by can be caused by inadequate dietary intake, decreased absorption, and inadequate utilization.
Also, it can be caused by hyperutilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt.

Drugs can cause anemia by reducing absorption of folate (e.g., phenytoin) or through folate antagonism (e.g., methotrexate).

✓ **Clinical presentation**

Anemia with folate deficiency is not associated with neurologic or psychiatric symptoms.

✓ **Diagnosis:**

It is a macrocytic anemia; mean corpuscular volume is usually elevated to greater than 100 fL. Vitamin B12 and folate concentrations can be measured to differentiate between the two deficiency anemias. A decreased RBC folate concentration (<150 ng/mL [<340 nmol/L]) appears to be a better indicator of folate-deficiency anemia than a decreased serum folate concentration (<3 ng/mL [<7 nmol/L]).

✓ **Treatment:**

Oral folate, 1 mg daily for 4 months, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, a dose of 1 to 5 mg daily may be necessary.

Folinic acid or leucovorin (a reduced folic acid) is used patients using methotrexate which is classified as an antimetabolite due to its antagonistic effect on folic acid metabolism (folate antagonist). Many patients treated with methotrexate experience mucosal, gastrointestinal, hepatic or hematologic side effects. Supplementation with folic or folinic acid during treatment with methotrexate may ameliorate these side effects and minimize its toxicity.

Anemia of inflammation

Anemia of inflammation is a newer term used to describe both anemia of chronic disease and anemia of critical illness. Anemia of inflammation is a hypoproliferative anemia that traditionally has been associated with infectious or inflammatory processes, tissue injury and conditions associated with release of proinflammatory cytokines.

✓ **Diagnosis:**

The diagnosis of anemia of inflammation is usually one of exclusion, with consideration of coexisting iron and folate deficiencies. Serum iron is usually decreased, but, unlike iron-deficiency anemia, serum ferritin is normal or increased, and total iron-binding capacity is decreased. The bone marrow reveals an abundance of iron; the peripheral smear reveals normocytic anemia.

✓ **Treatment:**

Treatment of anemia of inflammation is less specific than that of other anemias and should focus on correcting reversible causes. Iron is not effective when inflammation is present. RBC transfusions are effective but should be limited to episodes of inadequate oxygen transport and Hb of 8 to 10 g/dL (80–100 g/L; 4.97–6.21 mmol/L).

Erythropoiesis-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa, can be considered, but response can be impaired in patients with anemia of inflammation (off-label use). An erythropoiesis-stimulating agent use may result in iron deficiency. Therefore, patient may need oral iron therapy.

Note:

- Potential toxicities of exogenous erythropoiesis-stimulating agent (ESA) administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue.
- Hemoglobin must be monitored during ESA therapy. An increase in hemoglobin 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.
- Erythropoiesis-stimulating agents use in children is controversial because it has not been shown to clearly reduce transfusion requirements.

Sickle cell syndromes

Sickle cell syndromes, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are hereditary conditions characterized by the presence of sickle hemoglobin (HbS) in red blood cells.

Sickle cell trait

Sickle cell trait is the heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene producing HbS (HbAS) gene. Individuals with sickle cell trait are asymptomatic, except for rare painless hematuria.

Sickle cell disease

Sickle cell disease can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia.

Pathophysiology

- Clinical manifestations of sickle cell disease are due to impaired circulation, RBC destruction, and stasis of blood flow. Additional contributing factors include functional asplenia, deficient opsonization and coagulation abnormalities.
- RBCs are sickled upon deoxygenation and unsickled upon oxygenation leading to RBC membrane damage and irreversible sickling and resulting in shortened circulatory survival and chronic hemolysis.
- Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels, leading to local tissue hypoxia that accentuates the pathologic process.

Diagnosis

Sickle cell disease is identified by using isoelectric focusing, high-performance liquid chromatography or electrophoresis.

Laboratory findings include:

- low hemoglobin
- increased reticulocyte, platelet and white blood cell counts;
- sickle forms on the peripheral smear.

Clinical presentation

- Cardinal features of sickle cell disease are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4 to 6 months of age when HbS replaces fetal hemoglobin (HbF).
- Common findings include pain with fever, pneumonia, splenomegaly and swelling of the hands and feet (e.g., dactylitis).
- Usual clinical signs and symptoms of sickle cell disease include chronic anemia, fever, pallor, arthralgia, scleral icterus, abdominal pain, weakness, anorexia, fatigue, hepatomegaly, splenomegaly, cardiomegaly, and hematuria.
- Acute complications of sickle cell disease include fever and infection, stroke, acute chest syndrome, and priapism.
- ***Acute chest syndrome*** is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
- ***Sickle cell crisis*** can be precipitated by infection, dehydration, stresses, and sudden temperature changes. The most common type is ***vaso-occlusive crisis***, which is manifested by pain over the involved areas without change in Hb.
- ***Aplastic crisis*** is characterized by acute decrease in Hb with decreased reticulocyte count manifested as fatigue, dyspnea, pallor and tachycardia.
- ***Splenic sequestration crisis*** is a massive enlargement of the spleen, leading to hypotension, shock, and sudden death in young children. Repeated infarctions lead to ***autosplenectomy***; therefore, incidence declines as adolescence approaches.
- Chronic complications involve many organs and include pulmonary hypertension, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, depression, and hematuria and other renal complications. Children experience delayed growth and sexual maturation.

Treatment

The goals of treatment are to reduce hospitalizations, complications and mortality.

Vaccines	Routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations are recommended.
Antibiotics	Prophylactic antibiotic is recommended until 5 years of age. It Begins at age 2 months or earlier.
Folic acid	Folic acid is recommended in adult patients, pregnant women and patients of all ages with chronic hemolysis.
Hydroxyurea	It is a chemotherapeutic agent. It has many effects on blood cells, including the stimulation of fetal hemoglobin (HbF) production. Increased level of HbF correlates with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent crises and higher mortality.
Decitabine	It can be used in adults who do not respond to hydroxyurea.
Analgesics	Opioid analgesics are used to control acute crisis and chronic pain.
	Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) add to the effects of opioids during painful crisis. This allows use of lower doses of narcotics.
Treatment of pulmonary hypertension	Endothelin receptor antagonist: bosentan
	PDE5 inhibitors: sildenafil and tadalafil
	They are used to treat pulmonary hypertension associated with sickle cell disease.
Blood transfusion	Chronic transfusions are indicated for primary and secondary stroke prevention in children.
	Treatment of aplastic crisis is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia.
Iron chelators	Iron overload is a consequence of the numerous transfusions required and may lead to complications such as heart or liver failure. Iron chelators (deferoxamine, deferasirox, and deferiprone) help maintain hemoglobin levels within the desired range.

New agents

L-glutamine oral powder	In July 2017, the FDA approved L-glutamine oral powder for patients age 5 years and older to reduce severe complications of SCD.
Crizanlizumab	It is a P-selectin inhibitor. It is indicated to reduce frequency of vasoocclusive crises in adults with sickle cell disease. It was approved in November 2019.
Voxelotor	Voxelotor is a HbS polymerization inhibitor. Indicated for treatment of sickle cell disease in adults and adolescents aged 12 years or older. It was approved in November 2019.

Stem cell transplantation

Allogeneic hematopoietic stem cell transplantation is the only curative therapy for sickle cell disease. Risks must be carefully considered and include mortality, graft rejection and secondary malignancies.

Treatment of splenic sequestration

Treatment options for splenic sequestration include:

Observation	Observation alone, especially for adults because they tend to have milder episodes.
Chronic transfusion	Chronic transfusion to delay splenectomy.
Splenectomy	Splenectomy after a life-threatening crisis, after repetitive episodes, or for chronic hypersplenism.

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat and protein metabolism.

Classification:

Previously, diabetes mellitus was divided into:

- Insulin-dependent diabetes mellitus (IDDM)
- Insulin-non-dependent diabetes mellitus (INDDM)

Recently diabetes mellitus is classified as:

- Type-I diabetes mellitus
- Type-II diabetes mellitus
- Others:
  - Gestational diabetes mellitus
  - Drug-induced diabetes mellitus (e.g., glucocorticoids, pentamidine, niacin, α-interferon).
  - Secondary to endocrine disorders (e.g., acromegaly, Cushing syndrome) or other diseases (e.g., pancreatitis)

Clinical presentation

Classic symptoms include polyuria, polydipsia, polyphagia, and weight loss. Other symptoms may include fatigue, nausea, and blurred vision in addition to lower-extremity paresthesias.

Patients with type-II DM are often asymptomatic and may be diagnosed secondary to unrelated blood testing. Lethargy, polyuria, nocturia, and polydipsia can be present. Significant weight loss is less common; more often, patients are overweight or obese.

Diagnosis

Criteria for diagnosis of diabetes mellitus include any one of the following:

1. ***Glycated hemoglobin*** or ***hemoglobin A1c (HbA1c)*** of 6.5% or more
2. ***Fasting plasma glucose*** of 126 mg/dL (7.0 mmol/L) or more. In this test, patient must avoid any caloric intake for at least 8 hours.
3. Two-hour plasma glucose of 200 mg/dL (11.1 mmol/L) or more during an ***oral glucose tolerance test*** (OGTT) using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
4. ***Random plasma glucose*** concentration of 200 mg/dL (11.1 mmol/L) or more with classic symptoms of hyperglycemia or hyperglycemic crisis.

HbA1c testing in diagnosing diabetes

Classification	HbA1c values		Normal random glucose test results
	WHO	*ADA*	*ADA*
Non-diabetic	<6.0%	<5.7	80–140 mg/dl (4.4–7.8 mmol/l)
Prediabetes or Impaired glucose regulation (IGR)	6.0–6.4%	5.7–6.4%	140-200 mg/dl (7.8–11.1 mmol/l)
Type 2 diabetes	6.5% or more		≥ 200 mg/dl (≥11.1 mmol/l)

Screening:

Screening is not recommended for Type-I DM, but it is recommended for Type-II DM for adults over 45 years every 3 years. It is also recommended that children over age 10 years and adolescents who, along with being overweight or obese, have at least one additional diabetes risk factor be screened for prediabetes and type 2 diabetes.

Type-I diabetes mellitus

- Type 1 DM (5–10% of cases) usually develops in childhood or early adulthood.
- It results from autoimmune-mediated destruction of pancreatic β-cells, resulting in absolute deficiency of insulin.
- Individuals are often thin and are prone to develop diabetic ketoacidosis if insulin is withheld or under conditions of severe stress.
- Between 20% and 40% of patients present with diabetic ketoacidosis after several days of polyuria, polydipsia, polyphagia and weight loss.
- A balanced diet is needed to achieve and maintain healthy body weight. The meal plan should be moderate in carbohydrates and low in saturated fat, with a focus on balanced meals.

Treatment:

- All patients with type 1 DM require insulin, but the type and manner of delivery differ among patients and clinicians.
- The average daily ***insulin*** requirement is 0.5 to 0.6 units/kg. Requirements may fall to 0.1 to 0.4 units/kg in the honeymoon phase. Higher doses (0.5–1 unit/kg) are warranted during acute illness or ketosis.
- The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve near-normal blood glucose values throughout the day.

- A ***regimen of two daily injections*** that may roughly approximate physiologic insulin secretion is split-mixed injections of a morning dose of intermediate-duration insulin and regular insulin before breakfast and again before the evening meal
- The ***Honeymoon phase*** (or Honeymoon period) amongst people with type 1 diabetes refers to the period of time shortly following diabetes diagnosis when the pancreas is still able to produce a significant enough amount of insulin to reduce insulin needs and aid blood glucose control. This does not indicate that the diabetes is in remission or can be cured.
- ***Pramlintide*** (an amylinomimetic agent) may be appropriate in some of type 1 DM patients. At initiation of therapy, each dose of prandial insulin should be reduced by 30% to 50% to prevent hypoglycemia.
- ***Dapagliflozin*** is the first oral agent to be approved in the treatment of type 1 DM (*It is approved in UK and EU but rejected by US-FDA*).
- ***Sotagliflozin*** is SGLT1/SGLT2 inhibitor. It is approved in *EU* only.
- These agents are indicated as an adjunct to insulin therapy to in patients who have failed to achieve adequate glycemic control despite optimal insulin therapy.

Type-II diabetes mellitus

- Type 2 DM (90% of cases) is characterized by a combination of some degree of insulin resistance and relative insulin deficiency.
- Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production and decreased skeletal muscle uptake of glucose.
- Patient often requires caloric restriction to promote weight loss.

Treatment:

- Patients with mild cases (HBA1C 7% or less) are usually treated with therapeutic lifestyle measures and an agent that will not cause hypoglycemia.
- Moderate cases could be initially treated with a single oral agent or combination therapy.
- Patients with much higher initial HBA1C values (more than 8.5%) may benefit from initial therapy with two oral agents or even insulin.
- Insulin therapy should be considered if the HBA1C is greater than 8.5% to 9% on multiple therapies. Sulfonylureas are often stopped when insulin is added and insulin sensitizers are continued.
- Patients are often transitioned to insulin by using a bedtime injection of an intermediate or long-acting insulin with oral agents used primarily for glycemic

control during the day. Insulin sensitizers are commonly used with insulin because most patients are insulin resistant.

First line:

Symptomatic patients may initially require insulin or combination oral therapy to reduce glucose toxicity:

In case of HbA1C raised up to 6.5%:

- Standard-release ***metformin*** is used as monotherapy.

In case of HbA1C raised up to 7.5%:

- *Metformin + DPP-4 inhibitor*
- *Metformin + sulfonylurea*.
- *Metformin + SGLT2 inhibitor (Gliflozins)*
- *Metformin + a glitazone*

Then aim is to support patient for an HbA1C level less than 7%.

Metformin is first line agent for ***obese patients.*** Near-normal-weight patients may be better treated with insulin secretagogues, such as a ***sulfonylurea***, although metformin will work in this population.

In case of contraindication of metformin:

- Recently, even metformin is contraindicated, the recent guideline does not recommend sulfonylurea as monotherapy treatment for type 2 DM.
- SGLT2 inhibitor (Gliflozins) may be appropriate if metformin is contraindicated or not tolerated.
- A ***glitazone*** may be used in obese patients intolerant of or having a contraindication to metformin.
- The recommended treatment options are:
    - *a DPP-4 inhibitor and pioglitazone or*
    - *a DPP-4 inhibitor and a sulfonylurea or*
    - *a glitazone and a sulfonylurea.*

When initial therapy is no longer keeping the patient at the goal, multiple oral agents or insulin therapy may be appropriate. Triple therapy often consists of:

- *Metformin, a sulfonylurea, and a glitazone.*
- *Metformin, a sulfonylurea, and a DPP-4 inhibitor.*
- *Metformin, a GLP-1 agonist and a glitazone.*
- *Metformin, a sulfonylurea, and SGLT2 inhibitor (Gliflozins)*
- *Metformin, a glitazone, and SGLT2 inhibitor (Gliflozins)*
- *Insulin bases therapy is another option.*

- If triple therapy is not effective, not tolerated or contraindicated, *Metformin, a sulfonylurea and a GLP-1 mimetic* may be used especially in obese patients with BMI > 35 kg/m^2 or can't use insulin based therapy.
- *GLP-1 mimetics* are used in patients with HbA1C more than 11%.
- *GLP-1 mimetics* can be used in combination with insulin.
- *An SGLT2 inhibitor + insulin* with or without other antidiabetic agent is an option.

Estimating Total Daily Insulin Requirements

These are initial doses only; they must be refined using self-monitoring of blood glucose (SMBG) results. Patients may be particularly resistant to insulin if their blood glucose concentrations are high (glucose toxicity); once glucose concentrations begin to drop, insulin requirements often decrease precipitously.
The weight used is actual body weight. Insulin dose requirements can change dramatically over time depending on circumstances (e.g., a growth spurt, modest weight gain or loss, illness).

Type 1 diabetes	Initial dose	0.3–0.5 unit/kg
	Honeymoon phase	0.2–0.5 unit/kg, *or (0.1 to 0.4 unit/kg)*
	With ketosis, during illness, during growth	1.0–1.5 units/kg
Type 2 diabetes (*doses vary depending on degree of insulin resistance*)		
	With insulin resistance	0.7–1.5 units/kg

When a twice-daily regimen is suggested, 2/3 of total daily dose (TDD) is administered in the morning and 1/3 of TDD in the evening.

Prevention of Type 2 Diabetes Mellitus

The following measures are recommend:

- Weight reduction
- Proper nutrition
- Regular physical activity
- Cardiovascular risk factor reduction
- Aggressive treatment of hypertension and dyslipidemia

- ***Insulins:***

Insulin Type		Onset	Peak	Duration
Ultrashort acting	**Insulin lispro, insulin aspart, insulin glulisine**	12-30 min	0.5-3 hr	3-5 hr
	Insulin analogs that are more rapidly absorbed, peak faster, and have shorter durations of action than regular insulin. Usually taken before a meal to cover the blood glucose elevation from eating. Used with longer-acting insulin			
Short acting	**Regular insulin**	30 min	2.5-5 hr	4-24 hr
	Usually taken about 30 minutes before a meal to cover blood glucose elevation from eating. Used with longer-acting insulin.			
Intermediate acting	**Isophane insulin - Insulin NPH** (*Neutral protamine Hagedorn*)	1-2 hr	4-12 hr	14-24 hr
	Covers the blood glucose elevations when rapid-acting insulins stop working. Often combined with rapid- or short-acting insulin and usually taken twice a day. Variability in absorption, inconsistent preparation by the patient, and inherent pharmacokinetic differences may contribute to a labile glucose response, nocturnal hypoglycemia, and fasting hyperglycemia.			
Long acting **"peakless"**	**Insulin glargine, ultralente insulin, insulin detemir and insulin degludec**	3-4 hr	No defined peak	≥24 hr
	• Result in less nocturnal hypoglycemia than NPH insulin when given at bedtime. • Often combined, when needed, with rapid- or short-acting insulin • Lowers blood glucose levels when rapid-acting insulins stop working • Taken once or twice a day • Insulin glargine is available in combination with lixisenatide, while insulin degludec is available in combination with liraglutide			
Inhaled insulin	*Technosphere insulin*		12-15 min	160 min
	Dry powder of insulin that inhaled and absorbed through pulmonary tissue			
Insulin Pumps	*E.g. Accu-chek Spirit, Dana Diabecare IIS, Omnipod*® System, *OneTouch Ping*®, *MiniMed Paradigm*® *REAL-Time Revel*™			

List of antidiabetic agents

Biguanides	***Metformin*** enhances insulin sensitivity of hepatic and peripheral (muscle) tissues, allowing for increased glucose uptake. It does not induce hypoglycemia when used alone. Metformin is logical in overweight/obese type 2 DM patients. If patients taking metformin have any illness that leads to dehydration or hypoperfusion, the drug should be temporarily discontinued because of a possible increased risk of lactic acidosis.
Sulfonylureas *(Insulin Secretagogues)*	Sulfonylureas exert hypoglycemic action by stimulating pancreatic secretion of insulin. The most common side effect is hypoglycemia. Weight gain is common. ***Examples***: glibenclamide (glyburide), glimepiride, glipizide and gliclazide. *Others: chlorpropamide, tolazamide, and tolbutamide*
Dipeptidyl Peptidase-4 Inhibitors ***DPP-4 Inhibitors***	DPP-4 inhibitors partially reduce the inappropriately elevated glucagon postprandially and stimulate glucose-dependent insulin secretion. Mild hypoglycemia may occur, but DPP-4 inhibitors do not increase risk of hypoglycemia as monotherapy or in combination with medications that have a low incidence of hypoglycemia. ***Examples include***: sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin.
***SGLT2 inhibitor* (*Gliflozins*)**	***Selective Sodium-Glucose Transporter-2 Inhibitors*** Gliflozins inhibit reabsorption of glucose in the kidney and therefore lower blood sugar. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are approved in USA and EU. *Luseogliflozin, ipragliflozin, remogliflozin and tofogliflozin are available worldwide.*
Thiazolidinediones (Glitazones)	***Pioglitazone*** and ***rosiglitazone*** enhance insulin sensitivity in muscle, liver and fat tissues indirectly. Insulin must be present in significant quantities. Glitazones should be used with caution in patients with heart failure or other underlying cardiac disease. They are contraindicated in patients with class III or IV heart failure.

Meglitinides *(Insulin Secretagogues)*	***<u>Short-acting Insulin Secretagogues</u>*** ***Repaglinide*** and ***nateglinide*** lower glucose by stimulating pancreatic insulin secretion, but insulin release is glucose dependent and diminishes at low blood glucose concentrations. Hypoglycemic risk appears to be less with meglitinides than with sulfonylureas.
GLP-1 Agonists (Incretin mimetics)	***<u>Glucagon-like Peptide 1 Agonists</u>*** They enhance insulin secretion and reduce hepatic glucose production. They also increase satiety, slow gastric emptying and promote weight loss. Agents include: *Exenatide, liraglutide*, *lixisenatide, albiglutide, dulaglutide* and *semaglutide*. Liraglutide is marketed under 2 brands: *Victoza* (used as antidiabetic agent) and *Saxenda* (an antiobesity agent).
α-Glucosidase Inhibitors	***Acarbose*** and ***miglitol*** prevent breakdown of sucrose and complex carbohydrates in the small intestine, prolonging carbohydrate absorption.
Amylinomimetic	***Pramlintide*** suppresses inappropriately high postprandial glucagon secretion, decreases prandial glucose excursions, increases satiety, and slows gastric emptying. It has little effect on fasting blood glucose.
Bile Acid Sequestrants	***Colesevelam*** binds bile acid in the intestinal lumen, decreasing the bile acid pool for reabsorption. Its mechanism in lowering plasma glucose levels is unknown.
Dopamine Agonists	This quick-release formulation (*Cycloset*® 0.8mg) is the only ***bromocriptine*** product indicated for type 2 DM. It is indicated as an adjunct to diet and exercise to improve glycemic control. It acts on circadian neuronal activities within the hypothalamus to reset the abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in patients with insulin resistance.

Gestational diabetes mellitus (GDM)

Pregnant women should undergo risk assessment for gestational diabetes mellitus at first prenatal visit and have glucose testing if at high risk (e.g., positive family history, personal history of gestational diabetes mellitus, marked obesity, or member of a high-risk ethnic group).

Treatment:

The efficacy and safety of insulin have made it the standard for treatment of diabetes during pregnancy. Early intervention with insulin or an oral agent is key to achieving a good outcome when diet therapy fails to provide adequate glycemic control.

Nevertheless, the oral agents glibenclamide and metformin are gaining popularity. Glibenclamide should not be used in the first trimester, because its effects, if any, on the embryo are unknown.

Metformin is a biguanide, which functions mainly by decreasing hepatic glucose output. Metformin crosses the placenta, and umbilical cord levels have been shown to be even higher than maternal levels.

Pregnant women with preexisting type 1 or type 2 diabetes are recommended to consider taking a low daily aspirin dose beginning at the end of the first trimester in order to lower their preeclampsia risk.

Management of Hypoglycemia

Hypoglycemia and weight gain are the most common adverse effects of insulin and some oral antidiabetic agents. Hypoglycemia is defined according to the following serum glucose levels:

- < 50 mg/dL in men
- < 45 mg/dL in women
- < 40 mg/dL in infants and children

Treatment of hypoglycemia is as follows:

- Glucose (10–15g) given orally for conscious patients.
- Dextrose IV may be required for unconscious patients.
- Glucagon, 1g intramuscularly, is preferred in unconscious patients when IV access cannot be established.

Management of Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes that mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes. This condition is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis and ketonuria.

Signs and symptoms

The most common early symptoms of DKA are the insidious increase in polydipsia and polyuria. The following are other signs and symptoms of DKA:

- Malaise, generalized weakness and fatigability
- Nausea and vomiting, decreased appetite and anorexia
- Rapid weight loss
- History of failure to comply with insulin therapy or missed insulin injections due to vomiting or psychological reasons or history of mechanical failure of insulin infusion pump
- Decreased perspiration
- Altered consciousness (e.g., mild disorientation, confusion); frank coma is uncommon but may occur when the condition is neglected or with severe dehydration/acidosis.

On examination, general findings may include ill appearance, dry skin, labored respiration, dry mucous membranes, decreased skin turgor, decreased reflexes, characteristic acetone (ketotic) breath odor, tachycardia, hypotension, tachypnea and hypothermia.

Treatment:

Managing diabetic ketoacidosis in an intensive care unit during the first 24-48 hours always is advisable. The following points must be considered:

- Correction of fluid loss with intravenous fluids
- Correction of hyperglycemia with insulin
- Correction of electrolyte disturbances, particularly potassium loss
- Correction of acid-base balance
- Treatment of concurrent infection, if present

Regular and analog human insulins are used for correction of hyperglycemia. Clinical considerations in treating diabetic ketoacidosis include the following:

- Only short-acting insulin is used for correction of hyperglycemia in DKA.
- The optimal rate of glucose decline is 100 mg/dL/h.
- The blood glucose level should not be allowed to fall lower than 200 mg/dL during the first 4-5 hours of treatment.

- Avoid induction of hypoglycemia because it may develop rapidly during correction of ketoacidosis and may not provide sufficient warning time.

Close attention to clinical laboratory data allows for tracking of the underlying acidosis and hyperglycemia, as well as prevention of common potentially lethal complications such as hypoglycemia, hyponatremia and hypokalemia.

Complications

Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease.
Microvascular complications include retinopathy, neuropathy, and nephropathy.

Hypertension

ACE inhibitors and ARBs are recommended as initial therapy. Many patients require multiple agents. Diuretics or calcium channel blockers frequently are useful as second and third agents.
Antiplatelet therapy (aspirin or clopidogrel) for adults with type 2 diabetes without cardiovascular disease is not recommended.

Coronary Heart Disease

- Multiple-risk-factor intervention (treatment of dyslipidemia and hypertension, smoking cessation and antiplatelet therapy) reduces macrovascular events.
- ACE inhibitors and angiotensin receptor blockers are generally recommended for initial therapy.
- Many patients require multiple agents, so diuretics, calcium channel blockers and β-blockers are useful as second and third agents.
- Note: β-blockers mask signs of hypoglycemia except sweatiness.

Nephropathy

- Glucose and BP control are most important for prevention of nephropathy, and BP control is most important for retarding the progression of established nephropathy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have are used in patients with diabetes.
- Diuretics are frequently necessary due to volume-expanded states and are recommended second-line therapy.

Stroke

Drug therapy with ACE inhibitors or ARBs is recommended. Statin therapy, especially in patients with other risk factors; monotherapy with fibrates may also be considered to lower stroke risk.

Peripheral Vascular Disease and Foot Ulcers

Claudication and nonhealing foot ulcers are common in type 2 DM. Smoking cessation, correction of dyslipidemia and antiplatelet therapy are important treatment strategies.

Cilostazol may reduce symptoms in selected patients. Revascularization is successful in some patients.

Local debridement and appropriate footwear and foot care are important in early foot lesions. Topical treatment and other measures may be beneficial in more advanced lesions.

Diabetic Foot Infections

Foot infections are the most common problems in persons with diabetes. These individuals are predisposed to foot infections because of a compromised vascular supply secondary to diabetes. Local trauma and/or pressure (often in association with lack of sensation because of neuropathy), in addition to microvascular disease, may result in various diabetic foot infections that run the spectrum from simple, superficial cellulitis to chronic osteomyelitis.

Diabetic foot infections typically take one of the following forms:

- Cellulitis
- Deep-skin and soft-tissue infections
- Acute osteomyelitis
- Chronic osteomyelitis

Cellulitis is the easiest diabetic foot infection to cure, because it does not pose the same circulatory limitations that the more serious infections do, making it easier for medications to reach the infection site. In contrast, chronic osteomyelitis, which is the most difficult diabetic foot infection to cure, requires surgical debridement before antibiotic therapy can be effective. The patient may participate in activities as tolerated. However, weight bearing may be contraindicated. Glycemic control must be achieved to favorably affect outcome; it is important for microbial eradication and tissue healing.

Neuropathy

- Distal symmetrical peripheral neuropathy is the most common complication in patients with type 2 DM. Paresthesias, numbness, or pain may be 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 empiric, including low-dose tricyclic antidepressants, anticonvulsants (e.g., gabapentin, pregabalin, and

rarely carbamazepine), duloxetine, venlafaxine, topical capsaicin, and various analgesics, including tramadol and NSAIDs.

- ***Gastroparesis*** can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of metoclopramide, domperidone or erythromycin may be helpful.
- Patients with ***orthostatic hypotension*** may require mineralocorticoids or adrenergic agonists.
- ***Diabetic diarrhea*** is commonly nocturnal and frequently responds to a 10 to 14 days' course of an antibiotic such as doxycycline or metronidazole. Octreotide may be useful in unresponsive cases.
- ***Erectile dysfunction*** is common, and initial therapy should include a trial of an oral phosphodiesterase-5 (PDE5) inhibitor (e.g., sildenafil, vardenafil or tadalafil) or prostaglandin E1 (PGE1), which known as alprostadil, intracavernosal injection.

Retinopathy

Patients with established retinopathy should be examined by an ophthalmologist at least every 6 to 12 months. Early background retinopathy may reverse with improved glycemic control and optimized blood pressure control. Laser photocoagulation has markedly improved sight preservation in diabetic patients.

Complications include wet age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME). Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is also highly effective for sight preservation. Bevacizumab (off label use), ranibizumab, aflibercept and brolucizumab are used. Other agents include pegaptanib and verteporfin.

Patients with diabetes also tend to develop senile cataracts sooner than persons without diabetes. However, development of senile cataracts is not related to the degree of glycemic control.

Aldose reductase inhibitors are a group of compounds that are investigated for treatment of diabetic complications including neuropathy and retinopathy. Only epalrestat is commercially available in some countries including China, India and Bangladesh.

Heart failure

Heart failure (HF), often referred to as chronic heart failure (CHF) or congestive cardiac failure (CCF), is a progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body's metabolic needs.
Heart failure can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction).

Classification

Heart failure can be classified by the primary underlying etiology as ischemic or non-ischemic with 70% of heart failure related to ischemia (Coronary artery disease). Non-ischemic etiologies include hypertension, viral illness, thyroid disease. Heart failure manifests most commonly in adults older than 60 years.

1. Systolic failure vs. Diastolic failure

With systolic failure (problem in contraction): there is a decreased ejection of blood from the heart during systole. With diastolic failure (problem in the filling of ventricles), filling of the ventricles during diastole is reduced.

2. Low-output failure vs. High-output failure

- ***Low-output failure*** is a reduced pumping efficiency of the heart (it include systolic failure and diastolic failure). (*Note: The term "heart failure" will refer to low-output HF in this lecture.*)
- ***High-output failure***, the cardiac output is normal or elevated but still cannot meet the metabolic and oxygen need of the tissues. Common causes of high-output failure include hyperthyroidism (hypermetabolism) and anemia.

Causes of heart failure

The leading causes of heart failure are coronary artery disease and hypertension. Also, anemia and kidney diseases are causes.

Causes of systolic dysfunction

- Reduced muscle mass (e.g., myocardial infarction [MI])
- Dilated cardiomyopathies
- Ventricular hypertrophy.

Causes of diastolic dysfunction

- Increased ventricular stiffness
- Ventricular hypertrophy
- Infiltrative myocardial diseases
- Myocardial ischemia and MI, mitral or tricuspid valve stenosis
- Pericardial disease (e.g., pericarditis and pericardial tamponade).

Ventricular hypertrophy can be caused by:

- Pressure overload (e.g., systemic or pulmonary hypertension and aortic or pulmonic valve stenosis)
- Volume overload (e.g., valvular regurgitation, shunts, high-output states).

As cardiac function decreases after myocardial injury, the heart relies on compensatory mechanisms:

1. Tachycardia and increased contractility through sympathetic nervous system activation
2. The Frank–Starling mechanism: whereby increased preload increases stroke volume
3. Vasoconstriction
4. Ventricular hypertrophy and remodeling

The neurohormones and autocrine/paracrine factors for heart failure include:

- Angiotensin II
- Norepinephrine
- Aldosterone
- Natriuretic peptides
- Arginine vasopressin
- Endothelin peptides
- Some circulating biomarkers (e.g., C-reactive protein).

Common precipitating factors from a previously compensated heart failure patient to decompensated heart failure:

- Myocardial ischemia and MI
- Atrial fibrillation
- Pulmonary infections
- Non-adherence with diet or drug therapy
- Inappropriate medication use

Drugs may precipitate or exacerbate heart failure because of their negative inotropic, cardiotoxic, or sodium- and water-retaining properties.

Pathophysiology

When the heart fails, compensatory mechanisms attempt to maintain cardiac output. However, as heart failure progresses, these mechanisms become pathophysiological. These mechanisms involve the following:

A-Activation of the renin-angiotensin-aldosterone system (RAAS).

The decrease in renal perfusion leads to activation of the RAAS which stimulates sodium and water retention in an attempt to increase intravascular volume and hence preload and this will produces greater tension on the ventricular wall and the heart dilates abnormally. Thus, impairs contractile function of the heart and results in a further decrease in cardiac output (CO) .

ACE inhibitors, ARBs, and aldosterone antagonists serve to blunt these deleterious effects].

B- Stimulation of sympathetic nervous system (SNS)

The SNS is activated in heart failure. Activation of the sympathetic nervous system may initially increase cardiac output through increased myocardial contractility and heart rate. Prolonged sympathetic stimulation also causes negative effects, including increase myocardial oxygen demand worsen underlying ischemia death of cardiac cells. Sympathetic stimulation also causes peripheral vasoconstriction. β-Blockers appear to ameliorate the deleterious effects of catecholamines.

C- Cardiac Remodeling

Progression of HF results in a process referred to as
cardiac remodeling. The three primary manifestations of cardiac remodeling are chamber dilatation, LV cardiac muscle hypertrophy, and a resulting spherical shape of the LV chamber. Remodeling worsens HF.

Signs and symptoms

- Patient presentation may range from asymptomatic to cardiogenic shock.
- Primary symptoms are dyspnea (particularly on exertion) and fatigue, which lead to exercise intolerance. Other pulmonary symptoms include orthopnea, paroxysmal nocturnal dyspnea, tachypnea, and cough.
- Fluid overload can result in pulmonary congestion and peripheral edema.

- Nonspecific symptoms may include fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite, mental status changes, and weight gain.
- Physical examination findings may include pulmonary crackles, S3 gallop, cool extremities, Cheyne–Stokes respiration, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness and anxiety, sometimes with coughing and pink, frothy sputum), peripheral edema, jugular venous distention, hepatojugular reflux, and hepatomegaly.

Staging

The American College of Cardiology/American Heart Association (ACC/AHA) staging system is defined by the following 4 stages:

Stage A	High risk of heart failure but no structural heart disease or symptoms of heart failure
Stage B	Structural heart disease but no symptoms of heart failure
Stage C	Structural heart disease and symptoms of heart failure.
Stage D	Refractory heart failure requiring specialized interventions.

Patients with stage C have structural heart disease and previous or current HF symptoms and include both HF with reduced ejection fraction (*HF_rEF*) and HF with preserved ejection fraction (*HFpEF*) while patients with stage D are considered HF with reduced ejection fraction (*HF_rEF*).

While according to New York Heart Association (NYHA) Classification, heart failure is classified into 4 stages:

Stage 1	No symptoms and no limitation in ordinary physical activity. e.g. shortness of breath when walking, climbing stairs etc.
Stage 2	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Stage 3	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m). Comfortable only at rest.
Stage 4	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Diagnosis

- History and physical examination
- ***Laboratory tests*** may include:
    - Complete blood cell count
    - Serum electrolytes (including calcium and magnesium)
    - Renal, hepatic, and thyroid function tests
    - Urinalysis
    - Lipid profile
    - A1C. B-type natriuretic peptide (BNP)
- ***Chest radiograph*** may also show ventricular hypertrophy, pleural effusions and pulmonary edema.
- ***Echocardiogram (ECG)*** can demonstrate ventricular hypertrophy and also identify abnormalities of the pericardium, myocardium, or heart valves and quantify left ventricular ejection fraction (LVEF) to determine if systolic or diastolic dysfunction is present.

Treatment

The therapeutic goals for chronic HF are relieve or reduce symptoms, slow disease progression, and prolong survival.

Nonpharmacologic Interventions

1. ***Dietary modifications*** in HF consist of sodium restriction and sometimes fluid restriction. Patients should routinely practice moderate salt restriction (2–2.5 g sodium or 5–6 g salt per day). Patients should be educated to avoid cooking with salt and to limit intake of foods with high salt content. Fluid restriction may not be necessary in many patients. When applicable, a general recommendation is to limit fluid intake from all sources to less than 2 liters per day.
2. ***Exercise***, while discouraged when the patient is acutely decompensated (Acute heart failure), is recommended when patients are stable. The heart is a muscle that requires activity to prevent atrophy. Regular low intensity, aerobic exercise that includes walking, swimming, or riding a bike is encouraged, while heavy weight training is discouraged.
3. ***Modification of classic risk factors***, such as tobacco and alcohol consumption, is important to minimize the potential for further aggravation of heart function.

Treatment of chronic heart failure

- The first step in the treatment of chronic heart failure is to determine the etiology or precipitating factors. Treatment of underlying disorders (e.g., hyperthyroidism) may obviate the need for treating heart failure.
- Nonpharmacologic interventions include cardiac rehabilitation and restriction of fluid intake and dietary sodium.

- ***Stage A:***

Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended for heart failure prevention in patients with multiple vascular risk factors.

- ***Stage B:***

Treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process.

In addition to treatment measures outlined for stage A, patients with a previous MI should receive both ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) and β-blockers regardless of the ejection fraction.

Patients with reduced ejection fractions should also receive both agents, regardless of whether they have had an MI.

- ***Stage C:***

Most should receive the treatments for stages A and B, as well as initiation and titration of a diuretic (if clinical evidence of fluid retention), ACE inhibitor, and β-blocker (if not already receiving a β-blocker for previous MI, left ventricular [LV] dysfunction, or other indication).

If diuresis is initiated, and symptoms improve once the patient is euvolemic, long-term monitoring can begin.

If symptoms do not improve, an aldosterone receptor antagonist, ARB (in ACE inhibitor–intolerant patients), digoxin, and/or hydralazine/isosorbide dinitrate may be useful with carefully screened patients.

Other general measures include moderate sodium restriction, daily weight measurement, immunization against influenza and pneumococcus, modest physical activity, and avoidance of medications that can exacerbate heart failure.

- ***Stage D:***

These are patients with refractory heart failure (i.e., symptoms at rest despite maximal medical therapy).

They should be considered for specialized therapies, including mechanical circulatory support, continuous IV positive inotropic therapy, cardiac transplantation, or hospice care (when no additional treatments are appropriate).

Drugs summary:

Diuretics

- Diuretic therapy is recommended for all patients with clinical evidence of fluid retention. They are not mandatory for patients without fluid retention.
- ***Thiazide diuretics*** (e.g., hydrochlorothiazide) are relatively weak and are used alone infrequently in heart failure. However, thiazides or the thiazide-like diuretic metolazone can be used in combination with a loop diuretic to promote very effective diuresis.
- Thiazides may be preferred over loop diuretics in patients with only mild fluid retention and elevated blood pressure because of their more persistent antihypertensive effects.
- ***Loop diuretics*** (furosemide, bumetanide, and torsemide) are usually necessary to restore and maintain euvolemia in heart failure. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.

Aldosterone Antagonists

Spironolactone and ***eplerenone*** diuretic effects are minimal. Their therapeutic benefits result from other actions. They reduce mortality.

Low-dose aldosterone antagonists may be appropriate for:

1. Patients with mild to moderately severe systolic heart failure who are receiving standard therapy.
2. Patients with left-ventricular dysfunction and either acute heart failure or diabetes early after MI.

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with heart failure and reduced LVEF (stage C).
- ACE inhibitors should also be used to prevent the development of heart failure in at-risk patients (i.e., stages A and B).

Angiotensin II receptor blockers

ARBs are recommended to be used only in patients with stage A, B, or C heart failure who are intolerant of ACE inhibitors. Only candesartan and valsartan are FDA-approved for the treatment of heart failure. Losartan is approved in EU.

β-Blockers

- β-blockers slow disease progression, decrease hospitalizations, and reduce mortality in patients with systolic heart failure.
- β-blockers are recommended to be used in all stable patients with heart failure and a reduced LVEF in the absence of contraindications or a clear history of β-blocker intolerance. Patients should receive a β-blocker even if symptoms are mild or well controlled with ACE inhibitor and diuretic therapy.
- β-Blockers are also recommended for asymptomatic patients with a reduced LVEF (stage B) to decrease the risk of progression to heart failure.
- β-blockers are to be initiated in stable patients who have no or minimal evidence of fluid overload.
- ***Carvedilol***, ***metoprolol succinate*** (CR/XL), ***nebivolol*** and ***bisoprolol*** are the only β-blockers shown to reduce mortality.

Calcium channel blockers

Non-dihydropyridine calcium channel blockers (diltiazem or verapamil) should be considered for patients with atrial fibrillation warranting ventricular rate control who either are intolerant to or have not responded to a β-blocker. A non-dihydropyridine or dihydropyridine (e.g., amlodipine) CCB can be considered for symptom-limiting angina or hypertension.

Digoxin

- Digoxin has positive inotropic effects. Digoxin does not improve survival in patients with heart failure but does provide symptomatic benefits.
- Digoxin should be considered for patients with chronic systolic heart failure and supraventricular tachyarrhythmias such as atrial fibrillation, to help control ventricular response rate.
- Digoxin should be used for patients in normal sinus rhythm together with standard heart failure therapies (ACE inhibitors, β-blockers, and diuretics) in patients with symptomatic heart failure to reduce hospitalizations.

Nitrates and Hydralazine

- Nitrates (nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) and hydralazine have complementary hemodynamic actions.
- Nitrates are primarily venodilators, producing reductions in preload.

- Hydralazine is a direct arterial vasodilator that reduces systemic vascular resistance and increases stroke volume and cardiac output.
- The combination of nitrates and hydralazine improves the composite endpoint of mortality, hospitalizations for heart failure, and quality of life in some patients.

Anticoagulants

Patients with heart failure and depressed left ventricular (LV) ejection fraction are thought to have an increased risk of thrombus formation due to low cardiac output. Hospitalized patients with heart failure are at a high risk for venous thromboembolism and should receive prophylaxis. Anticoagulants (e.g. warfarin and dabigatran) are indicated in the presence of:

1. an LV thrombus
2. a thromboembolic event with or without evidence of an LV thrombus,
3. paroxysmal or chronic atrial arrhythmias.

New agents:

- The I(f) inhibitor **ivabradine** is used to lower heart rate and has been shown to reduce the risk for hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LVEF ≤35%, who are in sinus rhythm with resting heart rate ≥70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
- **Sacubitril** is an angiotensin receptor-neprilysin inhibitor (ARNI). It is available in combination with valsartan. This combination has been shown to significantly reduce cardiovascular death and hospitalization in patients with chronic heart failure. This combination is approved to reduce the risk of cardiovascular death and hospitalization for HF in patients with NYHA class II–IV HF and reduced LVEF.
- In January 2021, the FDA approved **vericiguat**, soluble guanylate cyclase (sGC) stimulator. Vericiguat stimulates sGC, the intracellular receptor for endogenous nitric oxide (NO), which catalyzes cyclic guanosine monophosphate (cGMP) production. It is indicated to reduce the risk of cardiovascular death and heart failure hospitalization in adults following a hospitalization for HF or need for outpatient IV diuretics, who have symptomatic chronic HF and ejection fraction <45%.

Treatment of acute decompensated heart failure (ADHF)

- Acute decompensated heart failure (ADHF) involves patients with new or worsening signs or symptoms requiring additional medical care, such as emergency department visits and hospitalizations.
- Hospitalization is recommended or should be considered depending on patient presentation. Admission to an intensive care unit (ICU) may be required if the patient experiences hemodynamic instability requiring frequent monitoring, invasive hemodynamic monitoring, or rapid titration of IV medications with close monitoring.
- Correction of causes of decompensation should be done if possible.
- Medications that may aggravate heart failure should be evaluated carefully and discontinued when possible.
- If fluid retention is evident, aggressive diuresis, often with IV diuretics, should be accomplished.
- Standard treatment should be optimized with an ACE inhibitor and β-blocker. β-blockers should generally be continued during hospitalization unless recent dose initiation or up-titration was responsible for decompensation. In such cases, β-blocker therapy may be temporarily withheld or dose-reduced.
- Most patients may continue to receive digoxin at a low dose.
- Appropriate management of ADHF is aided by determination of whether the patient has signs and symptoms of fluid overload ("wet" HF) or low cardiac output ("dry" HF)

Drugs summary:

Diuretics

- IV ***loop diuretics***, including furosemide, bumetanide, and torsemide, are used for acute decompensated heart failure (ADHF), with furosemide being the most widely studied and used agent.
- Diuresis may also be improved by adding a second diuretic with a different mechanism of action (e.g., combining a loop diuretic with a distal tubule blocker (thiazide) such as metolazone or hydrochlorothiazide).
- The loop diuretic–thiazide combination should generally be reserved for inpatients who can be monitored closely for the development of severe sodium, potassium, and volume depletion.

Positive Inotropic Agents

- ***Dobutamine*** has a potent inotropic effect without producing a significant change in heart rate. It increases cardiac index because of inotropic stimulation, arterial vasodilation, and a variable increase in heart rate.
- ***Milrinone*** produces positive inotropic and arterial and venous vasodilating effects. During IV administration, milrinone increases cardiac output with minimal change in heart rate.
- ***Dopamine*** should generally be avoided in acute decompensated heart failure (ADHF), but its pharmacologic actions may be preferable to dobutamine or milrinone in patients with marked systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures, where dopamine may be necessary to raise central aortic pressure.
- ***Noradrenaline*** (norepinephrine), also should be avoided.
- *Dopamine and noradrenaline are sometimes combined with traditional inotropes so each drug can be adjusted independently to achieve the desired hemodynamic response, although little data exist to support that practice.*

Vasodilators

Arterial vasodilators	They reduce afterload and cause a reflex increase in cardiac output.
Venodilators	They reduce preload by increasing venous capacitance, improving symptoms of pulmonary congestion in patients with high cardiac filling pressures.
Mixed vasodilators	Mixed arteriovenous vasodilators act on both arterial resistance and venous capacitance vessels, reducing congestive symptoms while increasing cardiac output

Examples:

Sodium nitroprusside	a mixed arteriovenous vasodilator
IV ***nitroglycerin***	a venodilator and mild arterial vasodilator
Nesiritide	It is a human B-type natriuretic peptides (hBNP). It is a venous and arterial vasodilator.

Vasopressin receptor antagonists

The vasopressin receptor antagonists' (***tolvaptan*** and ***conivaptan***) action results in vasoconstriction, myocyte hypertrophy, coronary vasoconstriction, and positive inotropic effects.

- Tolvaptan facilitates diuresis in acute heart failure. It is used in the treatment of hyponatremia.
- Conivaptan is indicated for hypervolemic and euvolemic hyponatremia due to a variety of causes but is not indicated for patients with HF.

Mechanical circulatory support

- Ultrafiltration and wireless invasive hemodynamic monitoring (W-IHM) may be used to manage congestive symptoms.
- Temporary *mechanical circulatory support* (MCS) with an *intra-aortic balloon pump* (IABP), *ventricular assist device* (VAD), or *extracorporeal membrane oxygenation* (ECMO) may be considered for used in the short-term (days to several weeks) for temporary hemodynamic stabilization until the underlying etiology of cardiac dysfunction resolves or has been corrected ("bridge to recovery") or they can also be used long term (several months to years) until evaluation for definitive therapy (e.g., durable MCS or cardiac transplantation) can be completed ("bridge to decision").

Surgical therapy

Heart transplantation is the best therapeutic option for patients with chronic irreversible class IV heart failure, with a 10-year survival of 50% in well-selected patients.

Hypertension

Hypertension is persistently or chronic medical condition characterized by elevated arterial blood pressure.

Hypertension may be primary, which may develop as a result of environmental or genetic causes, or secondary, which has multiple etiologies, including renal, vascular, and endocrine causes.
Primary or essential hypertension accounts for 90-95% of adult cases, and secondary hypertension accounts for 2-10% of cases.

Classification of Blood Pressure

Classification	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	and	<80
Prehypertensive	120-139	or	80-89
Stage I hypertension	140-159	or	90-99
Stage II hypertension	≥ 160	or	≥ 100

Clinical presentation and diagnosis

- Patients with uncomplicated primary hypertension are usually asymptomatic initially.
- Elevated blood pressure may be the only sign of primary hypertension on physical examination.
- Diagnosis should be based on the average of two or more readings taken at each of two or more clinical encounters.
- Other examinations and laboratory tests are done to investigate any underlying cause of complication.
- Signs of end-organ damage occur primarily in the eye, brain, heart, kidneys, and peripheral blood vessels.

Lifestyle modifications

Lifestyle modifications are considered as the non-pharmacologic approach to treat hypertension. They include:

- Weight loss if overweight
- Adoption of an eating plan
- Dietary sodium restriction
- Regular aerobic physical activity
- Stop alcohol consumption
- Smoking cessation.

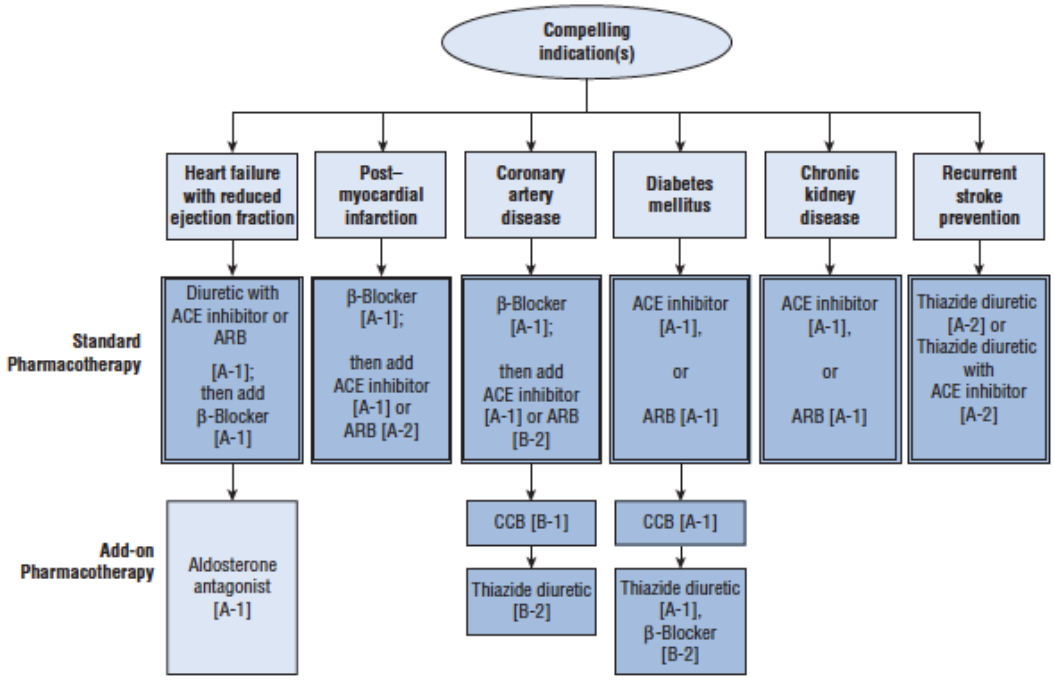
Treatment

- For the first-line treatment of hypertension, a medication from the following drug groups are recommended as an option:
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin II receptor blockers (ARBs)
  - Calcium channel blockers (CCBs),
  - Thiazide diuretics
- Most patients with stage 1 hypertension should be treated initially with a first-line antihypertensive drug or a two-drug combination.
- β-Blockers are used to either treat a specific compelling indication or as combination therapy with a first-line antihypertensive agent for patients without a compelling indication
- Combination therapy is recommended for patients with stage 2 hypertension, preferably with two first-line agents.

Compelling indications for individual drug classes

Other antihypertensive drug classes are alternatives that may be used for select patients after first-line agents:

- α1-blockers
- Direct renin inhibitors
- Central α2-agonists
- Peripheral adrenergic antagonists
- Direct arterial vasodilators



Summary of antihypertensive agents

<table>
<tr><td colspan="3">Angiotensin-Converting Enzyme Inhibitors (ACE-I)</td></tr>
<tr><td colspan="2">• Captopril
• Lisinopril
• Enalapril
• Ramipril
• Perindopril
• etc.</td><td>• ACE inhibitors are a first-line option. If they are not the first agent used, they should be the second agent tried in most patients.
• A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.
• They may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. They are contraindicated in pregnancy.</td></tr>
<tr><td colspan="3">Angiotensin II Receptor Blockers</td></tr>
<tr><td colspan="2">• Losartan
• Telmisartan
• Valsartan
• Olmisartan
• Candesartan
• Eprosartan
• Irbesartan</td><td>• Unlike ACE inhibitors, ARBs do not block bradykinin breakdown.
• All ARBs have similar antihypertensive efficacy and fairly flat dose-response curves.
• Addition of a calcium channel blocker or thiazide diuretic significantly increases antihypertensive efficacy.
• ARBs have a low incidence of side effects. They may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. ARBs are contraindicated in pregnancy.</td></tr>
<tr><td colspan="3">Calcium Channel Blockers (CCBs)</td></tr>
<tr><td>Dihydropyridines</td><td>• Nifedipine
• Amlodipine
• Felodipine
• Nicardipine
• Clevidipine</td><td rowspan="2">• CCBs cause vasodilation and a corresponding reduction in blood pressure.
• They are considered as a first line option.</td></tr>
<tr><td>Non- Dihydropyridines</td><td>• Verapamil
• Diltiazem</td></tr>
<tr><td colspan="3">Diuretics</td></tr>
<tr><td>Thiazide and thiazide-like diuretics</td><td>• Hydrochlorothiazide
• Chlorthalidone
• Indapamide</td><td>They are the preferred type of diuretic for most hypertensive patients.</td></tr>
<tr><td>Loop diuretics</td><td>• Furosemide
• Bumetanide
• Torsemide</td><td>Loop diuretics are more potent for inducing diuresis but are not ideal antihypertensives unless relief of edema is also needed.</td></tr>
</table>

<table>
<tr><td rowspan="2">Potassium-sparing diuretics</td><td>• Amiloride
• Triamterene</td><td>Potassium-sparing diuretics are weak antihypertensives when used alone and provide minimal additive effect when combined with a thiazide or loop diuretic.</td></tr>
<tr><td>Aldosterone antagonists
• Spironolactone
• Eplerenone</td><td>Aldosterone antagonists are also potassium-sparing diuretics but are more potent antihypertensives with a slow onset of action (up to 6 weeks with spironolactone).</td></tr>
<tr><td colspan="3">β-Blockers</td></tr>
<tr><td>• Atenolol
• Bisoprolol
• Metoprolol
• etc.</td><td colspan="2">β-Blockers are only considered appropriate first-line agents to treat specific compelling indications. (e.g. post-MI or coronary artery disease)</td></tr>
<tr><td colspan="3">α1-Receptor Blockers</td></tr>
<tr><td>• Prazosin
• Terazosin
• Doxazosin</td><td colspan="2">• They are selective α1-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation.
• These agents are most effective when given with a diuretic to maintain antihypertensive efficacy and minimize edema.
• They are indicated in the treatment of benign prostatic hyperplasia.</td></tr>
<tr><td colspan="3">Direct Renin Inhibitor (Aliskiren)</td></tr>
<tr><td colspan="3">• Aliskiren blocks the RAAS at its point of activation, resulting in reduced plasma renin activity and blood pressure.
• Aliskiren is approved for monotherapy or in combination with other agents.
• It should not be used in combination with an ACE inhibitor or an ARB.
• Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to aliskiren.
• It is contraindicated in pregnancy.</td></tr>
<tr><td colspan="3">Central α2-Agonists</td></tr>
<tr><td colspan="2">• Clonidine
• Methyldopa</td><td>• They lower blood pressure primarily by stimulating α2-adrenergic receptors in the brain.
• Chronic use results in sodium and fluid retention. Other side effects include depression, orthostatic hypotension, dizziness and anticholinergic effects.</td></tr>
</table>

Reserpine	
• Reserpine has a long half-life that allows for once-daily dosing, but it may take 2 to 6 weeks before the maximal antihypertensive effect is seen. • Reserpine can cause significant sodium and fluid retention, and it should be given with a diuretic (preferably a thiazide).	
Direct Arterial Vasodilators	
• Hydralazine • Minoxidil	• They cause direct arteriolar smooth muscle relaxation. • Hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a sympathetic inhibitor and a diuretic.

Secondary hypertension

Secondary hypertension is usually caused by an underlying condition, such as chronic kidney disease (CKD), a renovascular disease, Cushing syndrome, coarctation of the aorta, obstructive sleep apnea, hyperparathyroidism, pheochromocytoma, primary aldosteronism and hyperthyroidism.

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

Some drugs that may increase blood pressure include corticosteroids, estrogens, NSAIDs, amphetamines, sibutramine, cyclosporine, tacrolimus, erythropoietin, and venlafaxine.

Hypertensive crisis

Hypertensive crisis is a situation in which measured blood pressure values are markedly elevated (BP >180/120 mmHg). Pheochromocytoma, which is a rare neuroendocrine tumor, can cause a hypertensive crisis due to elevated levels of catecholamines.

Resistant hypertension

Resistant hypertension is defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic).

Accelerated hypertension

Accelerated hypertension is defined as a recent significant increase over baseline blood pressure that is associated with target organ damage.

Hypertensive urgency

Hypertensive urgency is severely elevated blood pressure with no evidence of target organ damage.

Hypertensive urgency needs prompt but gradual control of blood pressure using an oral agents. Rapidly acting oral agents are used, such as:

- labetalol, a beta-blocker
- captopril, a short-acting ACE inhibitor which lowers blood pressure within 15 to 30 minutes of oral dosing
- clonidine.

Outpatient follow-up is appropriate, but needs blood pressure assessment at least weekly.

Malignant hypertension

Malignant Hypertension or hypertensive emergency is a condition in which elevated blood pressure results in target organ damage.

Manifestations of acute end organ damage in hypertensive emergency are:

- Hypertensive encephalopathy
- Intracranial hemorrhage
- Unstable angina
- Acute myocardial infarction
- Left ventricular failure with pulmonary edema
- Acute aortic dissection
- Eclampsia

Blood pressure must be brought down rapidly but in a controlled fashion in an intensive care unit (ICU) by administering intravenous antihypertensive medications, which have a rapid effect and are easily titratable such as:
Nicardipine, clevidipine, labetalol, esmolol, hydralazine, nitroglycerin (intravenous), sodium nitroprusside and enalaprilat.

Hypertension in Children and Adolescents

Secondary hypertension is more common in children and adolescents than in adults.

Non-pharmacologic treatment is the cornerstone of therapy of primary hypertension. Medical or surgical management of the underlying disorder usually normalizes blood pressure. ACE inhibitors, ARBs, β-blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.

Hypertension in Pregnancy:

Gestational hypertension

Gestational hypertension is a transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy without the presence of protein in the urine or other signs of preeclampsia.

Treatment of Gestational hypertension

- Methyldopa is considered the drug of choice because of experience with its use.
- Hydralazine, β-Blockers (other than atenolol), labetalol, and Nifedipine (a CCB) are also reasonable alternatives.
- ACE inhibitors, ARBs, and the direct renin inhibitor aliskiren are contraindicated in pregnancy.

Preeclampsia

- Preeclampsia (or Pre-eclampsia) is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4-6 weeks postpartum.
- It is clinically defined by hypertension and proteinuria, with or without pathologic edema.
- The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is a form of severe pre-eclampsia.
- WHO recommends low-dose aspirin for the prevention of preeclampsia in women at high risk and recommends it be started before 20 weeks of pregnancy. In US, low-dose aspirin is to be started before 14 weeks of pregnancy.

Eclampsia

Eclampsia, which is considered a complication of severe preeclampsia, is commonly defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia. It is associated with high mortality rate.

Treatment:

- The agents of choice for blood pressure control during eclampsia are hydralazine and/or labetalol.
- Convulsions are prevented and treated using magnesium sulfate. Calcium gluconate injection is used for the management of magnesium toxicity.
- Diazepam is suitable alternative. Phenobarbital also can be use.
- If seizure does not resolved by medical intervention, termination of pregnancy is recommended.

Osteoporosis

Osteoporosis is a bone disorder characterized by:

- Low bone density
- Impaired bone architecture
- Compromised bone strength predisposing to fracture.

Pathophysiology

Bone loss occurs when resorption exceeds formation, usually from high bone turnover when number and/or depth of bone resorption sites greatly exceed ability of osteoblasts to form new bone.

Bone mineral density (BMD) is reduced and bone structural integrity is impaired due to increased immature bone that is not yet adequately mineralized.

Estrogen deficiency during menopause increases osteoclast activity, increasing bone resorption more than formation.

Secondary causes and aging are the most common contributing factors to male osteoporosis.

Age-related osteoporosis results from hormone, calcium and vitamin D deficiencies leading to accelerated bone turnover and reduced osteoblast formation.

Drug-induced osteoporosis may result from many drugs, for example:

- Systemic corticosteroids including depot medroxyprogesterone acetate
- Thyroid hormone replacement
- Antiepileptic drugs (e.g., phenytoin and phenobarbital)

Clinical presentation

- Many patients are unaware that they have osteoporosis and only present after fracture.
- Fractures can occur after bending, lifting or falling or independent of any activity.
- The most important complication of osteoporosis is fracture of the hip.
- Other most common fractures involve vertebrae, proximal femur and distal radius (wrist or Colles fracture).
- Physical examination findings: bone pain, postural changes (i.e., kyphosis) and loss of height (>3.8 cm).

Imaging:

Measurement of central (hip and spine) BMD with dual-energy x-ray absorpiometry (DXA).

BMD measurement

BMD measurement is recommended in the following patients:

- Women age 65 years and older and men age 70 years and older, regardless of clinical risk factors.
- Younger postmenopausal women and women in menopausal transition with clinical risk factors for fracture.
- Men age 50-69 years and other adults with clinical risk factors for fracture (e.g., low body weight, prior fracture, high-risk medication use, disease or condition associated with bone loss).
- BMD is to be monitored in high-risk individuals with a low BMD every 1 to 3 years.

Scoring tools:

Fracture Risk Assessment Tool (**FRAX score**) is used to estimate the probability of a fracture within the next 10 years. The output is a percentage, and higher values indicate a greater risk of fracture. The formula of FRAX score uses factors such as:

- Age and gender
- weight and height
- smoking history and alcohol use
- fracture history including patient's previous fracture and parent fractured hip
- Medical history and health issues such as using glucocorticoid use, rheumatoid arthritis or secondary osteoporosis, in addition to bone mineral density (BMD)

The ***T-score*** on your bone density report shows how much your bone mass differs from the bone mass of an average healthy 30 year old adult. A T-score is the score of bone density (BMD or DXA) test is measured as a standard deviation from the mean. The manufacturers of the DXA machines have programmed them to use a formula to compute these values.

Laboratory testing:

- CBC
- Creatinine
- Blood urea nitrogen
- Calcium, phosphorus
- Alkaline phosphatase
- Albumin
- Thyroid-stimulating hormone
- Free testosterone
- 25-hydroxyvitamin D
- 24-hour urine concentrations of calcium and phosphorus

Treatment

✓ Non-pharmacologic therapy

- Balanced diet with adequate intake of calcium and vitamin D.
- Stop alcohol consumption
- Caffeine intake should be limited
- Smoking cessation (especially before menopause)
- Aerobics and exercises

✓ Pharmacologic therapy

All therapies should be given with adequate calcium and vitamin D intakes. Guidelines include the following recommendations for choosing drugs to treat osteoporosis:

First-line agents	Alendronate, risedronate, zoledronic acid, denosumab • Generic alendronate is usually first-line treatment because of its broad spectrum of anti-fracture efficacy and low cost. • Other agents may be appropriate therapy if alendronate is contraindicated or poorly tolerated
Second-line agents	Ibandronate, raloxifene
third-line agent	Raloxifene (if not used as 2nd line agent)
Last-line agent	Calcitonin

- Teriparatide is considered as treatment option for patients with very high fracture risk or in whom bisphosphonate therapy has failed.
- Combination therapy with two or more agents has not been shown to have a greater effect on fracture reduction than single therapy.

Specific indications:

Indications	Options
Lower risk for vertebral fracture (and for hip fracture in some cases)	Bisphosphonates, denosumab, parathyroid hormone peptides, raloxifene, and strontium ranelate
Postmenopausal women	Calcitriol, etidronate, and hormone replacement therapy
Men at increased fracture risk	Alendronate, risedronate, zoledronic acid, and teriparatide
Risk for fracture with glucocorticoid therapy	Alendronate or other bone-protective treatment
Prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women	Alendronate, etidronate, and risedronate; treatment options for both genders are teriparatide and zoledronic acid
Prevention and treatment of glucocorticoid-induced osteoporosis in men	Teriparatide and zoledronic acid
Very high risk, especially for vertebral fractures	Parathyroid hormone peptides

Medications Summary:

Calcium Supplementation

Calcium intake is essential in the prevention and treatment of osteoporosis as it increases BMD. There are many forms of calcium. These following calcium salts are example for the available forms.

Calcium carbonate	Less expensive, most efficiently when taken with food.
Calcium citrate	taken with or without food.
Tricalcium phosphate	Not a good option for people with kidney disease.

Recently, some studies mentioned that calcium effects are less than those of other therapies as calcium supplementation on its own also does not reduce fracture incidence and is no longer recommended for treatment of osteoporosis.

Vitamin D Supplementation

"Calcium and vitamin D" supplementation is widely recommended for older persons who are housebound or live in residential or nursing homes and is often recommended as an adjunct to other treatments for osteoporosis.

Recent evidence indicates that it is inappropriate to use vitamin D for osteoporosis prevention in community-dwelling adults who do not have specific risk factors for vitamin D deficiency.

- Calcitriol (1,25-dihydroxyvitamin D) is the active metabolite of vitamin D.
- Alfacalcidol is a synthetic analogue of calcitriol.

These two agents reduce bone loss by maximizing intestinal calcium absorption and BMD and have been shown to reduce vertebral fractures and other fractures, but not consistently, as well as falls.
Serum calcium should be monitored regularly in patients receiving these drugs.

Calcium Metabolism Modifiers – Bisphosphonates (*or* ***Biphosphonates)***

- Bisphosphonates inhibit bone resorption and become incorporated into the bones, giving them long biologic half-lives of up to 10 years.
- Bisphosphonates provide some of the higher BMD increases and fracture risk reductions.
- Osteonecrosis of the jaw can occur very rarely with bisphosphonate therapy
- Withdrawal of bisphosphonate treatment is associated with decreases in BMD and bone turnover after 2-3 years for alendronate and 1-2 years for ibandronate and risedronate
- If bisphosphonates are discontinued, fracture risk should be reevaluated after every new fracture, or after 2 years if no new fracture occurs.

Examples	***indications***
Alendronate	• Treatment of osteoporosis in men and steroid-induced osteoporosis. • Prevention in postmenopausal women
Ibandronate	• In USA: Indicated for treatment and prevention of osteoporosis in postmenopausal women • In UK: only for treatment, but not the prevention, of postmenopausal osteoporosis
Risedronate	• Treatment of osteoporosis in men • Treatment of steroid-induced osteoporosis. • Treatment and prevention of postmenopausal osteoporosis • Prevention of steroid-induced osteoporosis.
Zoledronate	
Etidronate	Recently, less commonly used
Clodronate	less effective

Calcium Metabolism Modifiers - Calcitonin

- Calcitonin is an endogenous hormone released from the thyroid gland when serum calcium is elevated. Salmon calcitonin is used clinically because it is more potent and longer lasting than the mammalian form.
- Calcitonin inhibits osteoclasts and decreases the rate of bone resorption, reduces bone blood low and may have central analgesic actions.
- It is indicated for osteoporosis treatment for women at least 5 years past menopause but it is effective in all age groups in preventing vertebral bone loss.
- Calcitonin-salmon injection should be reserved for patients who refuse or cannot tolerate bisphosphonates or in whom bisphosphonates are contraindicated. Use of calcitonin-salmon injection is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass.
- Calcitonin is useful in treating acute pain associated with osteoporotic vertebral fractures but is no longer recommended for treatment of osteoporosis because it is associated with malignancy with long-term use.
- It has to be given parenterally or intranasally. Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy.

Denosumab

- Denosumab is a RANK ligand inhibitor that acts as an antiresorptive agent by inhibiting osteoclast formation and increases osteoclast apoptosis.
- It is indicated for treatment of osteoporosis in postmenopausal women and in patients at high risk for fracture.
- It is also approved to increase bone mass in men receiving androgen-deprivation therapy for
- Non-metastatic prostate cancer and in women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.
- Atypical femoral fractures and osteonecrosis of the jaw have both been associated with denosumab.
- Severe hypocalcemia has been reported, usually in the first week of treatment with denosumab, especially in patients with renal impairment.
- Patients should be instructed to take 1000 mg of calcium daily and at least 400 IU of vitamin D daily.

- *RANK = receptor activator of nuclear factor-kappa B*

Romosozumab

Romosozumab is a monoclonal antibody (IgG2) that binds sclerostin, a regulatory factor in bone metabolism. Sclerostin inhibition increases bone formation and, to a lesser extent, decreases bone resorption.

It is indicated for osteoporosis treatment in postmenopausal women at high risk for fracture, also indicated for patients in whom other available osteoporosis therapy has failed or who are intolerant of other available osteoporosis therapy.

Mixed Estrogen Agonists/Antagonists

- **Raloxifene** is an oral selective estrogen receptor modulator (SERM) that it is estrogen agonist in bone but it is antagonist in breast and uterine tissue. So, It protects against breast cancer. Raloxifene decreases vertebral fractures and increases spine and hip BMD.
- It is approved for prevention and treatment of postmenopausal osteoporosis.
- After discontinuation, the beneficial effect is lost, and bone loss returns to age- or disease-related rates.
- ***Bazedoxifene*** is available in combination with conjugated estrogens for prevention of postmenopausal osteoporosis in non-hysterectomized women.
- Other available SERMs are used in the treatment of breast cancer such as tamoxifen and toremifene. They are not indicated in osteoporosis.

Estrogen Therapy and its combinations

- Estrogen derivatives are approved for the prevention of osteoporosis and relief of menopause-associated vasomotor symptoms and vulvovaginal atrophy.
- Estrogens increase bone formation and reduce bone resorption. They also increase calcium absorption and decrease renal calcium loss.
- Estrogens are no longer indicated as a first-line approach for the treatment of osteoporosis in postmenopausal women as estrogen therapy increases risk of breast cancer, stroke, venous thromboembolism, and coronary disease. They are indicated for prevention of osteoporosis in women at significant risk and for whom other osteoporosis medications cannot be used.
- Hormone therapy (estrogen with or without a progestogen) significantly decreases fracture risk.

- Hormone replacement therapy (HRT), if started soon after menopause, is effective in preventing vertebral fractures but has to be continued lifelong if protection against fractures is to be maintained.
- Examples:

Estrogens	• Conjugated estrogens (Premarin) • Estradiol • Estropipate
Estrogens/Progestins	• Ethinyl estradiol with norethindrone • Estradiol with norethindrone acetate
Estrogens/Progestins-HRT	• Conjugated estrogens and medroxyprogesterone • Estradiol and norgestimate • Estradiol and levonorgestrel

Anabolic therapies - Parathyroid hormone peptides:

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. These agents are very expensive. They include:

Teriparatide (*recombinant portion of human parathyroid hormone*)

- Teriparatide increases bone formation, bone remodeling rate and osteoblast number and activity.
- It reduces vertebral and non-vertebral fractures in postmenopausal women. It does not reduce hip fractures.
- Teriparatide is indicated for the following indications:
    - treatment of postmenopausal women at high risk for fracture
    - men with idiopathic or hypogonadal osteoporosis at high fracture risk
    - men or women intolerant to other osteoporosis medications
    - patients with glucocorticoid-induced osteoporosis.

Abaloparatide

It is indicated for the treatment of:

- postmenopausal women with osteoporosis at high risk for fracture
- patients who have failed or are intolerant to other osteoporosis therapies.

Recombinant parathyroid hormone peptide (*Preotact*®, Natpara®)

Preotact® can also be used. It has similar efficacy as teriparatide. It is indicated to control hypocalcemia in patients with hypoparathyroidism.

Strontium ranelate

- Strontium ranelate, which both increases bone formation and reduces bone resorption, reduces vertebral and non-vertebral (including hip) fractures in postmenopausal women with osteoporosis.
- It is well tolerated, but it is restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments including patients who are unable to tolerate bisphosphonates.
- It should be avoided in patients with severe renal disease (creatinine clearance less than 30 mL/min).
- It has been reported to cause severe *drug rash with eosinophilia and systemic symptoms* (DRESS).

Testosterone

Testosterone is not indicated for osteoporosis, but the male osteoporosis guideline recommends testosterone alone for men with testosterone concentrations of less than 200 ng/dL [6.9 nmol/L] if low fracture risk and in combination with an osteoporosis medication if high fracture risk.

Gout

Gout is the most common inflammatory joint disease in men and the most common inflammatory arthritis in older women. It is caused by deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricemia.

Chronic hyperuricemia is associated with disorders of purine metabolism due to under excretion or over production of uric acid, the final metabolite of endogenous and dietary purine metabolism.

Gout usually presents as a monoarthritis in the first metatarsophalangeal joint (big toe) of the foot and is often referred to as podagra. Subsequent attacks may be polyarticular. Other commonly affected joints include the mid-foot, ankle, knee, wrist and finger joints.

Uric acid

Uric acid is the end product of purine degradation. An increased urate pool in individuals with gout may result from overproduction or underexcretion. Overproduction of uric acid may result from abnormalities in enzyme systems that regulate purine metabolism. Uric acid may be overproduced because of increased breakdown of tissue nucleic acids.

Cytotoxic drugs can result in overproduction of uric acid due to lysis and the breakdown of cellular matter.
Dietary purines are insignificant in generation of hyperuricemia without some derangement in purine metabolism or elimination. Two thirds of uric acid produced daily is excreted in urine. The remainder is eliminated through gastrointestinal tract.
Drugs that decrease renal uric acid clearance include loop and thiazide diuretics, nicotinic acid, salicylates, ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, ribavirin, interferon, ritonavir, teriparatide and cytotoxic drugs.
Aspirin has a bimodal effect; low doses inhibit uric acid excretion and increase urate levels, while doses greater than 3 g/day are uricosuric.

Complication:

- ***Uric acid nephrolithiasis*** occurs in 10% to 25% of patients with gout.
- In ***acute uric acid nephropathy***, ***acute renal failure*** 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.

Tophus

Tophi are a late complication of hyperuricemia. Most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists and hands.

Clinical presentation:

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). Other affected joints are the insteps, ankles, heels, knees, wrists, fingers and elbows. Attacks commonly begin at night. Affected joints are erythematous, warm and swollen. Fever and leukocytosis are common.

- ***Factors*** of acute attacks include stress, trauma, alcohol ingestion, infection, surgery, drugs, renal disease and genetic factors.

Diagnosis

Aspiration of synovial fluid from the affected joint and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.

Treatment

Goals of treatment are to:

- Terminate the acute attack
- Prevent recurrent attacks
- Prevent complications associated with chronic deposition of urate crystals in tissues.

Treatment of Acute gouty arthritis

- ***Non-pharmacologic Therapy***

Local ice application is the most effective adjunctive treatment.

- ***Pharmacologic Therapy***

Most patients may be treated successfully with NSAIDs, corticosteroids or colchicine.

- ***NSAIDs*** have excellent efficacy and minimal toxicity with short-term use. Indomethacin, naproxen and sulindac are suggested. Others are likely to be effective.
- ***Aspirin*** or other salicylates **must be avoided** in gout as they can increase plasma uric acid levels and increase the risk of gout.

- ***Corticosteroid*** efficacy is equivalent to NSAIDs; they can be used systemically or by intra-articular (IA) injection. Systemic therapy is necessary if an attack is polyarticular. Examples include methylprednisolone, prednisone and prednisolone.
- ***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. It is to be used only within 36 hours of attack onset because the likelihood of success decreases substantially if treatment is delayed.
- Some references suggest using ***interleukin-1 (IL-1) inhibitors*** in the management of acute flares, in patients with refractory disease who have responded inadequately to standard therapies.
    - such as canakinumab, anakinra and rilonacept

Treatment of Hyperuricemia

Nonpharmacologic Therapy

- lifestyle/dietary modification:
    - limiting consumption of high-fructose corn syrup and purine-rich foods
    - Stop alcohol intake
- Maintenance of a high level of hydration with water
- weight loss through caloric restriction and exercise

Pharmacologic Therapy

The goal of urate-lowering therapy is to achieve and maintain serum uric acid less than 6 mg/dL (357 μmol/L), and preferably less than 5 mg/dL (297 μmol/L) if signs and symptoms of gout persist.

- ***Xanthine oxidase inhibitors*** reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. They are effective in both overproducers and underexcretors of uric acid.
    - Examples include Allopurinol and Febuxostat.
- ***Uricosurics*** are the agent that increase renal clearance of uric acid. Patients with a history of urolithiasis should not receive uricosurics.
    - Probenecid increases renal clearance of uric acid by inhibiting the postsecretory renal proximal tubular reabsorption of uric acid. It can be used as monotherapy, but it is less effective than other agents.
        - A combination of probenecid/colchicine is available.
    - Lesinurad is the first ***selective uric acid reabsorption inhibitor*** (**SURI**). It is indicated in combination with a xanthine oxidase inhibitor for hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.
        - A combination of lesinurad/allopurinol is available.

  - Others uricosurics: benzbromarone and sulinpyrazone
- The use of these recombinant ***uricolytics*** (***uricases***) is usually restricted to severe, refractory cases of gout because of the high cost, the need for intravenous administration and the development of neutralizing antibodies with subsequent hypersensitivity reactions.
  - ***Pegloticase*** is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble. It is indicated for antihyperuricemic therapy in adults refractory to conventional therapy.
  - ***Rasburicase*** is licensed to treat hyperuricemia caused by tumor lysis (i.e. tumor lysis syndrome).
- Adrenocorticotropic hormone (***corticotropin***) stimulates the production and release of endogenous steroids. It is an effective treatment of acute crystal-induced arthritis in postoperative patients and in other patients who cannot take oral medications. Also, it is indicated in screening of adrenocortical insufficiency.
  - *Adrenocorticotropic hormone that is made synthetically is tetracosactide (INN), also known as tetracosactrin (BAN) and cosyntropin (USAN)*
  - *and the acetate ester, tetracosactide acetate (JAN), also known as tetracosactrin acetate (BAN).*

Prophylaxis therapy

- 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.
- ***Prophylactic anti-inflammatory therapy*** should be used to prevent such gout attacks. Low-dose oral ***colchicine*** (0.6 mg twice daily) and low-dose ***NSAIDs*** as first-line prophylactic therapies are recommended. For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.
- Low-dose ***corticosteroid*** therapy (e.g., prednisolone ≤10 mg/day) is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy.

Pseudogout

Pseudogout is caused by calcium pyrophosphate crystals and is more accurately termed calcium pyrophosphate disease (CPPD) or calcium pyrophosphate dihydrate crystal deposition disease, also known as pyrophosphate arthropathy.
Treatment of the acute phase of pseudogout is identical to that of acute gout. In patients with idiopathic pseudogout, a deterrent regimen of colchicine may be used. If an underlying metabolic problem is responsible for pseudogout, the arthritis may be cured when the underlying problem is addressed.

University of Anbar - College of Pharmacy
Clinical Pharmacy II - Osteoarthritis

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

Classification:

- Primary (idiopathic) osteoarthritis, the most common type, has no known cause.
- Secondary osteoarthritis is associated with a known cause, such as trauma, metabolic or endocrine disorders and congenital factors.

Pathophysiology:

- Osteoarthritis usually begins with damage to articular cartilage through injury, excessive joint loading from obesity or other reasons, or joint instability or injury.
- Damage to cartilage increases activity of chondrocytes in attempt to repair damage, leading to increased synthesis of matrix constituents with cartilage swelling.
- Cartilage loss causes joint space narrowing and painful, deformed joints. Remaining cartilage softens and develops fibrillations, followed by further cartilage loss and exposure of underlying bone. New bone formations (osteophytes) at joint margins distant from cartilage destruction are thought to help stabilize affected joints.
- Inflammatory changes can occur in the joint capsule and synovium. Interleukin-1, prostaglandin E2, tumor necrosis factor-α (TNF-α), and nitric oxide in synovial fluid may also play a role.
- Pain may result from distention of the synovial capsule by increased joint fluid; microfracture; periosteal irritation or damage to ligaments, synovium, or the meniscus.

Clinical presentation

- Risk factors include increasing age, obesity, repetitive use through work or leisure activities, joint trauma, and genetic predisposition.
- Symptoms include deep, aching pain in affected joints. Pain accompanies joint activity and decreases with rest.
- 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.

- Limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report weakness or instability.
- Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion.
- Presence of warm, red, and tender joints suggests inflammatory synovitis.

Diagnosis

- 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 is made through patient history, physician examination, radiologic findings and laboratory testing.
- Criteria for classification of osteoarthritis 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

Non-pharmacologic therapy

Nonpharmacologic interventions, which are the cornerstones of osteoarthritis therapy, include the following:

- Exercise and physical therapy (including heat and cold application)
- Overweight patients who have early signs of osteoarthritis or who are at high risk should be encouraged to lose weight
- Occupational therapy and assistive and orthotic devices (canes, walkers, braces, heel cups, insoles).
- Surgical procedures (e.g., osteotomy, arthroplasty, joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy.

Pharmacologic therapy

Treatment is to be started with Paracetamol for mild or moderate osteoarthritic pain without apparent inflammation. If the clinical response to paracetamol is not satisfactory or if the clinical presentation of osteoarthritis is inflammatory, an NSAID is considered. The lowest effective dose is to be used or intermittent dosing if symptoms are intermittent, then full doses can be tried if the patient's response is insufficient.

Paracetamol	Paracetamol is a preferred first-line treatment; it may be less effective than oral NSAIDs.
NSAIDs	Nonselective NSAIDs (ibuprofen, naproxen, diclofenac, ketoprofen, etc…) or cyclooxygenase-2 (COX-2) selective inhibitors (e.g., celecoxib) are recommended. Oral NSAIDs are an alternative first-line treatment for patients with hand osteoarthritis. For knee osteoarthritis, **topical** NSAIDs are recommended. Topical NSAIDs are a first-line option for hand osteoarthritis.
	Topical capsaicin is an alternative first-line treatment for hand osteoarthritis. It is a reasonable option for patients unable to take oral NSAIDs.
Corticosteroid	Intra-articular corticosteroid injections (e.g., triamcinolone, betamethasone, methylprednisolone) are recommended for both hip and knee osteoarthritis. Injections can be given with concomitant oral analgesics for additional pain control.
Tramadol	Tramadol is recommended for hand, hip and knee osteoarthritis in patients who have failed scheduled full-dose paracetamol and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive intra-articular corticosteroids.
Opioids	Opioids (e.g. codeine) should be considered in patients not responding adequately to non-pharmacologic and first-line pharmacologic therapies.
Duloxetine	Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI). It can be used as adjunctive treatment in patients with partial response to first-line analgesics.
Hyaluronic acid	Intra-articular hyaluronic acid is not routinely recommended for knee osteoarthritis pain. It supports the lubricating and shock-absorbing properties of articular cartilage. It is used to treat patients with osteoarthritic knee pain that is unresponsive to conservative nonpharmacologic therapy and simple analgesics.
Glucosamine / chondroitin and rubefacients	Oral Glucosamine and/or chondroitin and topical rubefacients (e.g., methyl salicylate, trolamine salicylate) lack uniform efficacy for hip and knee pain and are not preferred treatment options.
Skeletal muscle relaxants	The use of certain skeletal muscle relaxants has been shown to be helpful in osteoarthritis. Example: carisoprodol, dantrolene and baclofen.

Other modalities:

Platelet-rich plasma (PRP)
Concerns have been raised regarding PRP clinical efficacy.

Prolotherapy
In prolotherapy, small volumes of an irritant solution are injected at ligament and tendon insertions and in adjacent joint spaces over several treatment sessions. Prolotherapy use can lead to improvement in pain, function, and stiffness.

Arthroscopy
Arthroscopy is indicated for removal of meniscal tears and loose bodies; less predictable arthroscopic procedures include debridement of loose articular cartilage with a microfracture technique and cartilaginous implants in areas of eburnated subchondral bone.

Osteotomy
Osteotomy is used in active patients younger than 60 years who have a malaligned hip or knee joint and want to continue with reasonable physical activity.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetric joint involvement and systemic manifestations.

Pathophysiology

- Rheumatoid arthritis results from dysregulation of humoral and cell-mediated immunity. Most patients produce antibodies called ***rheumatoid factors*** (RF); these seropositive patients tend to have a more aggressive course than seronegative patients.
- Factors and mediators participate in the inflammatory mechanism include:
  - Immunoglobulins (Ig) which activate the complement system,
  - Proinflammatory cytokines, such as: tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-1 (IL-6).
  - Activated T cells, which produce the cytotoxins and cytokines.
  - Activated B cells produce plasma cells, which form antibodies.
  - Signaling molecules such as Janus kinase (JAK). Janus kinase is a tyrosine kinase and has effects on production of cytokines and immunoglobulins.
  - Vasoactive substances (histamine, kinins, prostaglandins)
- Chronic inflammation of synovial tissue lining the joint capsule results in tissue proliferation (pannus formation). Pannus invades cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to joint destruction. End results may be loss of joint space and joint motion, bony fusion (ankylosis), joint subluxation, tendon contractures, and chronic deformity.

Clinical presentation

- Nonspecific prodromal symptoms developing over weeks to months include fatigue, weakness, low-grade fever, anorexia and joint pain. Stiffness and myalgias may precede development of synovitis.
- Joint involvement tends to be symmetric and affect small joints of the hands, wrists, and feet; elbows, shoulders, hips, knees, and ankles may also be affected.
- Joint stiffness typically is worse in the morning, usually exceeds 30 minutes, and may persist all day.
- On examination, joint swelling may be visible or apparent only by palpation. Tissue is soft, spongy, warm, and may be erythematous.
- Joint deformities may involve subluxations of wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan neck deformity, boutonnière deformity, and ulnar deviation).
- **Extra-articular involvement** may include rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, ocular manifestations, pericarditis,

cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.

Diagnosis

- The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010. These criteria are intended for patients early in their disease and emphasize early manifestations. The ACR/EULAR classification system uses a scoring system incorporates the following 4 factors:
    - Joint involvement
    - Serology test results
    - Acute-phase reactant test results
    - Patient self-reporting of the duration of signs and symptoms
- Patient with a combined score of 6 or more out of 10 indicating that the patient has definite RA.

- Laboratory abnormalities include:
    - Normocytic, normochromic anemia
    - Thrombocytosis or thrombocytopenia
    - Leukopenia
    - Elevated erythrocyte sedimentation rate (ESR)
    - C-reactive protein
- Differential diagnosis includes positive results for the following tests:
    - Rheumatoid factor (60%–70% of patients)
    - Anticitrullinated protein antibody (ACPA) (50%–85% of patients)
    - Antinuclear antibodies (25% of patients).
- ***Aspirated synovial fluid*** may reveal turbidity, leukocytosis, reduced viscosity, and normal or low glucose relative to serum concentrations.
- Early ***radiologic findings*** include soft tissue swelling and osteoporosis near the joint (periarticular osteoporosis).

Treatment

Nonpharmacologic therapy

- Rest, weight reduction if obese, occupational therapy, physical therapy and use of assistive devices.
- Patients with severe disease may benefit from surgical procedure and joint replacements.

Pharmacologic therapy

Disease-modifying antirheumatic drugs (DMARDs) should be started as soon as possible. They slow RA disease progression.

Nonbiologic DMARDs:

- Common nonbiologic DMARDs include methotrexate (MTX), sulfasalazine, hydroxychloroquine and leflunomide.
- The order of selection is not clearly defined, but MTX is often chosen initially because long-term data suggest superior outcomes compared with other DMARDs and lower cost than biologic agents.
- Combination therapy with two or more nonbiologic DMARDs may be effective when single-DMARD treatment is unsuccessful.
  - ✓ Recommended combinations include:
    1. MTX + hydroxychloroquine
    2. MTX + leflunomide
    3. MTX + sulfasalazine
    4. MTX + hydroxychloroquine + sulfasalazine.
- Less frequently used include azathioprine, penicillamine, gold salts (gold thiomalate, auranofin), minocycline, cyclosporine, and cyclophosphamide. These agents have either less efficacy or higher toxicity, or both.
- Tofacitinib, baricitinib and upadacitinib are nonbiologic JAK inhibitor indicated for patients with moderate to severe RA who have failed or have intolerance to MTX. They are used as monotherapy or in combination with other nonbiologic DMARDs.

Biologic DMARDs

- Biologic DMARDs have proven effective for patients failing treatment with nonbiologic DMARDs. They include:

Anti-TNF agents	Etanercept, infliximab, adalimumab, golimumab and certolizumab pegol
IL-6 receptor antagonist	tocilizumab and sarilumab
Anti-CD20	Rituximab (It depletes peripheral B cells)
Co-stimulation modulator (Anti-CD80/CD86 on T cells)	Abatacept
IL-1 receptor antagonist	anakinra

- Anti-TNF biologics may also be used in patients with early disease of high activity and poor prognostic factors, regardless of previous DMARD use.
- Anti-TNF biologics are used in combination with other DMARDs. Etanercept and adalimumab can be used as monotherapy.

- Rituximab is used in combination with MTX. Other non-TNF inhibitor biologics can be used in combination with MTX or as monotherapy.
- The use of biologics in combination with MTX or other DMARD is more effective than biologic monotherapy.

Non-steroidal anti-inflammatory drugs:

- Non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids may be used for symptomatic relief if needed. They provide relatively rapid improvement compared with DMARDs, which may take weeks to months before benefit is seen. However, NSAIDs have no impact on disease progression, and corticosteroids have potential for long-term complications.
- 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.
- Commonly used NSAIDs include ibuprofen, naproxen, ketoprofen, celecoxib and diclofenac.

Corticosteroids

- Corticosteroids have anti-inflammatory and immunosuppressive properties.
- Oral corticosteroids (e.g., prednisolone and methylprednisolone) can be used to control pain and synovitis while DMARDs are taking effect. Low-dose, long-term corticosteroid therapy may be used to control symptoms in patients with difficult-to-control disease.
- ***High-dose oral or IV*** bursts may be used for several days to suppress disease flares. After symptoms are controlled, taper the drug to the lowest effective dose.
- The ***intramuscular*** route is preferable in nonadherent patients. Depot forms are available. (e.g. triamcinolone and methylprednisolone)
- ***Intra-articular injections*** of depot forms may be useful when only a few joints are involved.

Other treatments:

- ***Paracetamol*** is used for analgesia in patients with documented hypersensitivity to aspirin or NSAIDs, those with upper GI disease, and those who are taking oral anticoagulants. This agent does not have anti-inflammatory properties.
- ***Tramadol*** has been used to reduce pain in patients with RA. However, this agent only provides analgesic effects and does not have anti-inflammatory properties.
- ***Topical agents*** such as diclofenac can provide analgesia for patients with RA. This agent is commonly used in patients who experience acute pain.

Juvenile idiopathic arthritis

Juvenile rheumatoid arthritis (JRA) or juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases of childhood.

The etiology is unknown, and the genetic component is complex, making clear distinctions between the various subtypes difficult.

Signs and symptoms

History findings in children with juvenile idiopathic arthritis may include the following:

- Arthritis present for at least 6 weeks before diagnosis
- Either insidious or abrupt disease onset, often with morning stiffness or gelling phenomenon and arthralgia during the day
- Complaints of joint pain or abnormal joint use
- Limited ability to participate in physical education classes
- Spiking fevers occurring once or twice each day at about the same time of day
- Evanescent rash on the trunk and extremities
- Psoriasis or more subtle dermatologic manifestations

Some types of juvenile idiopathic arthritis

- Systemic-onset juvenile idiopathic arthritis
- Oligoarticular juvenile idiopathic arthritis
- Polyarticular juvenile idiopathic arthritis
- Psoriatic arthritis
- Enthesitis-related arthritis
- Undifferentiated arthritis

Treatment

<table>
<tr><td rowspan="3">DMARDs</td><td>Non-biologic DMARDs</td><td colspan="2">methotrexate, sulfasalazine</td></tr>
<tr><td rowspan="2">Biologic DMARDs</td><td>TNF-alpha inhibitors</td><td>etanercept, adalimumab</td></tr>
<tr><td>Others</td><td>abatacept, tocilizumab, canakinumab, anakinra</td></tr>
<tr><td>NSAIDs</td><td colspan="3">• Commonly used NSAIDs include ibuprofen, naproxen, ketoprofen, piroxicam, and diclofenac.
• Indomethacin is particularly effective for fever and pericarditis and is usually preferred for children with active systemic JIA.</td></tr>
</table>

Corticosteroids	• Corticosteroids are potent anti-inflammatory drugs used in patients with JIA to bridge the time until DMARDs are effective. • Adverse events associated with long-term steroid use make dose reductions and cessation important in due course. • Example: Methylprednisolone and prednisolone.

Notes regarding NSAIDs:

- Aspirin is no longer the drug of first choice because of the increased frequency of gastric toxicity and hepatotoxicity when compared to other NSAID medications.
- COX-2 inhibitor (celecoxib) may have a role in treatment when a bleeding diathesis is a potential problem.

Asthma

Asthma is a chronic inflammatory disorder of the airways causing airflow obstruction and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The airflow obstruction is often reversible, either spontaneously or with treatment.

Epidemiology and Etiology:

- Current estimates suggest that asthma affects 300 million people worldwide, with a predicted additional 100 million people affected by 2025.
- The socio-economic impact is enormous, as poor control leads to days lost from school or work, unscheduled health-care visits and hospital admissions.
- Asthma results from a complex interaction of genetic and environmental factors, but the underlying cause is not well understood. The onset of asthma occurs early in life for most patients.
- There appears to be an inherited component because the presence of asthma in a parent is a strong risk factor for development of asthma in a child. This risk increases when a family history of atopy is also present.
- ***Atopy*** is an exaggerated IgE-mediated immune response. The ***atopic triad*** or ***atopy triad*** is a set of comorbid conditions – atopic dermatitis (eczema), asthma, and allergic rhinitis.

Predisposing factors:

- Inhaled allergens
- Respiratory viral infection
- Cold dry air
- Smoke
- Pollutants.

Pathophysiology:

- Asthma is characterized by inflammation, airway hyperresponsiveness (AHR), and airway obstruction.
- Asthma is caused by a complex interaction between inflammatory cells and mediators. Mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells are of central importance.

- After exposure to an asthma-precipitating factors, inflammatory mediators (such as histamine, leukotrienes, prostaglandins, etc…) are released from the inflammatory cells that cause airway injury, including mucus hypersecretion, airway edema, increased reactivity of smooth muscle and airway smooth muscle constriction resulting in airway obstruction.
- Airway hyperresponsiveness (AHR) refers to the tendency of airways to narrow excessively in response to triggers that have little or no effect in normal individuals.

Clinical Manifestations:

A-Chronic asthma:

- Signs and Symptoms include episodes of dyspnea, chest tightness, dry, hacking cough (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.
- Severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. There is a wide spectrum of disease severity, ranging from patients with occasional, mild bouts of breathlessness (that require no medications or only occasional short-acting inhaled β2-agonists) to patients who wheeze daily despite continuous high dosages of medication.

B-Acute severe asthma:

- Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm result in profound airway narrowing that is poorly responsive to bronchodilator therapy.
- 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. Patients may be anxious and agitated. Symptoms are unresponsive to usual measures [inhaled short-acting β-agonists (SABA).
- Signs include expiratory and inspiratory wheezing on auscultation; dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis; and hyperinflated chest with intercostal and supraclavicular retractions.

Diagnosis:

1. The diagnosis of asthma is predominantly clinical and based on a characteristic history:
   a. History of recurrent episodes of coughing, wheezing, chest tightness, or shortness of breath.
   b. Patients may have family history of allergy or asthma or symptoms of allergic rhinitis.
2. Supportive evidence is provided by the demonstration of variable airflow obstruction, preferably by using spirometry to measure forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]. The FEV1 is a measure of the FEV in the first second of exhalation. The forced vital capacity (FVC) is the maximum volume of air exhaled with maximum effort after maximum inspiration.
3. Pulse oximetry is a noninvasive means of assessing the degree of hypoxemia during an acute exacerbation. The oximeter measures oxygen saturation in arterial blood (SaO_2) and pulse.
4. Peak expiratory flow rate (PEFR), obtained through the patient forcefully breathing out into a peak flow meter can be used to monitor control of asthma.
   a. It gives slightly less reproducible results than the spirometer but has the advantage that the patient can do regular tests at home with a hand-held meter.
   b. The peak flow meter measures peak expiratory flow (PEF) rate, the maximum flow rate that can be forced during expiration.
   c. The PEF can be used to assess the improvement or deterioration in the disease as well as the effectiveness of treatment.
5. Arterial blood gases (ABGs) (to measure arterial partial pressure of oxygen [PaO_2], arterial partial pressure of carbon dioxide [$PaCO_2$], and pH) should be obtained for patients in severe asthma.
6. In patients with acute severe asthma:
   a. Peak expiratory flow (PEF) and FEV1 are less than 40% of normal predicted values.
   b. Pulse oximetry reveals decreased arterial oxygen and O_2 saturations.
   c. Arterial blood gases may reveal metabolic acidosis and low partial pressure of oxygen (PaO_2).

Management:

Desired Outcomes:

A. Chronic Asthma: Asthma is a chronic condition but may be controlled with appropriate treatment in the majority of patients. The goal of treatment should be to obtain and maintain complete control using the least amount of medications and minimizing adverse effects.
B. Acute Asthma: Acute or worsening asthma can be life-threatening.The goals of therapy are to correct significant hypoxemia, and reverse airflow obstruction rapidly.

Nonpharmacologic therapy:

1. Patient education is very important. Some components of asthma education involve asthma trigger avoidance, proper administration of inhaled medications, and asthma self management.
2. Trigger Avoidance: Avoidance of known allergenic triggers can improve symptoms and reduce medication use.
   a. Major triggers that may worsen asthma control include pollen, dust mites, air pollution, cold air, exercise, strong odors, emotions, tobacco smoke, certain medications (e.g., β-blockers), sulfite-containing foods and beverages, and comorbid conditions (e.g., allergic rhinitis, sinusitis, upper respiratory infections, gastroesophageal reflux disease, obesity, etc.).
   b. Exercise is one of the most common precipitants of asthma symptoms (exercise-induced asthma). Pretreatment with a SABA 5 minutes prior to exercise is the treatment of choice and will protect against bronchospasm for 2 to 3 hours. Regular treatment with an inhaled corticosteroid (ICS) also prevents bronchospasm associated with exercise.
   c. A yearly influenza vaccine is recommended for patients 6 months and older with asthma to decrease the risk of complications from influenza.
   d. Patients with aspirin-sensitive asthma are usually adults and often present with the triad of rhinitis, nasal polyps, and asthma. In these patients, acute asthma may occur within minutes of receiving aspirin or NSAIDs. These patients are counseled against using NSAIDs. Although acetaminophen is generally safe, doses larger than 1 g may cause acute asthmatic reactions in some patients.
3. Patients with acute severe asthma should receive oxygen to maintain PaO_2 greater than 90% (>95% in pregnancy and heart disease).

Pharmacologic Therapy:

Treatment of chronic asthma involves avoidance of triggers known to precipitate or worsen asthma and use of long-term control and quick-relief medications. There are two types of asthma medications: quick-relief medications and long-term control medications.

A. Long-term control medications include ICS, inhaled long-acting β2-agonists (LABAs), oral theophylline, oral leukotriene receptor antagonists (LTRAs), and biological agents. In patients with severe asthma, systemic corticosteroids may be used as a long-term control medication.
B. Quick-relief medications include SABAs, anticholinergics, and short bursts of systemic corticosteroids.

Drug Delivery Devices:

A. Direct airway administration of asthma medications through inhalation is the most efficient route and minimizes systemic adverse effects.
B. Inhaled asthma medications are available in metered-dose inhalers (MDIs), dry powder inhalers (DPIs) (more easy to use than MDI), and nebulized solutions.
C. Poor inhaler technique results in increased oropharyngeal deposition of the drug, leading to decreased efficacy and increased adverse effects.
D. Because MDIs are challenging to use correctly, use of valved-holding chambers (VHCs) (Spacer device) is recommended with MDIs to decrease the need for coordination of actuation with inhalation, decrease oropharyngeal deposition, and increase pulmonary drug delivery.

Stepwise approach for managing asthma in adults

The main principle of asthma pharmacologic step therapy is to add therapy in steps until control is achieved (step up) and decrease therapy in reverse steps (step down) to established the lowest effective dose necessary to maintain control.

Step 1: Occasional use of inhaled bronchodilators:

For patients with mild intermittent asthma, it is usually sufficient to prescribe an inhaled SABA, such as salbutamol or terbutaline, to be used as required. Recent guideline recommends *as-needed* low dose ICS (budesonide) + formoterol as preferred agent.

Step 2: Introduction of regular preventer therapy:

For patients who are not controlled on ***Step 1***, regular anti-inflammatory therapy (preferably ICS, such as beclometasone, budesonide, or fluticasone) should be started.

Step 3: Add-on therapy:

1. If a patient remains poorly controlled, despite regular use of ICS; a thorough review should be undertaken of adherence, inhaler technique and ongoing exposure to modifiable aggravating factors. A further increase in the dose of ICS may benefit some patients but, in general, add-on therapy should be considered.
2. LABAs, represent the first choice of add-on therapy. Fixed combination inhalers of ICS and LABAs are more convenient, and increase compliance.

Step 4: Poor control on moderate dose of inhaled steroid and add-on therapy: Addition of a fourth drug:

In adults, the dose of ICS may be increased. Oral therapy with leukotriene receptor antagonists, high dose ICS or tiotropium may be considered.

Step 5: Continuous or frequent use of oral steroids:

At this stage, a further increase in the dose of ICS. Treatment should be done under supervision of a pulmonologist. Oral corticosteroid (such as prednisolone - usually administered as a single daily dose in the morning), tiotropium or a biological agent may be added to control symptoms.

GINA Strategy

The ***preferred reliever*** is *as-needed* low dose ICS (budesonide) + formoterol. SABA (salbutamol) is considered as another option.

Steps	Symptoms frequency	Controller therapy
Step 1	• < twice a month	• *as-needed* low dose ICS (budesonide) + formoterol. • *other option:* ICS is taken whenever SABA is taken.
Step 2	• ≥ twice a month but less than daily	• Daily low dose ICS, or • *as-needed* low dose ICS + formoterol • *other option:* o daily LTRA o ICS is taken whenever SABA is taken.
Step 3	• Most days • Waking with asthma once a week or more	• low dose ICS + LABA • *other option:* o medium dose ICS o low dose ICS + LTRA
Step 4	• Most days • Waking with asthma once a week or more • Low lung function	• medium dose ICS + LABA • *other option:* o high dose ICS o add-on tiotropium o add-on LTRA
Step 5	Cases need specialist intervention	• high dose ICS + LABA • add-on therapy: o tiotropium o biological agents • *other option: oral corticosteroid* (OCS)

Step-down therapy

Once asthma control is established, the dose of inhaled (or oral) corticosteroid should be titrated to the lowest dose at which effective control of asthma is maintained.

Medications review

A-Corticosteroids

Corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma and are available in inhaled, oral, and injectable dosage forms.

Inhaled Corticosteroids:

- ICSs (budesonide, fluticasone, beclomethasone, flunisolide, mometasone, etc.) are the preferred therapy for all forms of persistent asthma in all age groups.
- Although some beneficial effect is seen within 12 hours of administration of an ICS, 2 weeks of therapy is necessary to see significant clinical effects.
- Local adverse effects of ICS include oral candidiasis, cough, and dysphonia. The incidence of local adverse effects can be reduced by using a spacer or valved-holding chamber (VHC) attached to the inhaler and by having the patient rinse the mouth with water and expectorate after using the ICS.

Systemic Corticosteroids

- Prednisone, prednisolone, and methylprednisolone are systemic corticosteroids used in asthma treatment. These medications are the cornerstone of treatment for acute asthma not responding to an inhaled SABA.
- Because of serious potential adverse effects, systemic corticosteroids are avoided as long-term controller medication for asthma, if possible. Systemic corticosteroids are only used in patients who have failed other therapies.

B-Inhaled Short-Acting β2-Agonists (SABA):

e.g.: salbutamol (= albuterol), terbutaline and levosalbutamol.
Inhaled SABAs are the most effective agents for reversing acute airway obstruction caused by bronchoconstriction and are the drugs of choice for treating acute asthma and symptoms of chronic asthma as well as preventing exercise-induced bronchospasm.

C-Inhaled Long-Acting β2-Agonists (LABA):

- Salmeterol and formoterol are LABAs that provide up to 12 hours of bronchodilation after a single dose.

- Indacaterol, olodaterol and vilanterol are ultra-LABAs. They are indicated in the treatment of COPD.
- Formoterol has an onset of action similar to that of salbutamol. It is recently approved for the treatment of acute bronchospasm. Combination of formoterol with an ICS is considered as the preferred choice to relief acute asthmatic attacks.
- LABAs are indicated for chronic treatment of asthma as add-on therapy for patients not controlled on low to medium doses of ICS.

D-Anticholinergics:

Two anticholinergic medications are available:

- Inhaled ***ipratropium bromide*** is short-acting muscarinic antagonists (SAMA). It is only indicated as adjunctive therapy in severe acute asthma not completely responsive to β2-agonists alone.
- ***Tiotropium bromide*** is a long-acting inhaled muscarinic antagonists (LAMA) available in a DPI. There is increasing evidence supporting its use as a long-term controller medication in patients with uncontrolled asthma already taking an ICS.
- Other LAMAs include glycopyrronium (Glycopyrrolate), aclidinium and umeclidinium. They are only indicated in the treatment of COPD.

E- Leukotriene Modifiers:

- The available leukotriene receptor antagonists (LTRAs) are montelukast and zafirlukast.
- Although these agents offer the convenience of oral administration, they are significantly less effective than low ICS doses.
- They are not used to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods.
- Zileuton is a 5-lipoxygenase inhibitor.

F-Methylxanthines:

- Methylxanthines are ineffective by aerosol and must be taken systemically (orally or IV). Sustained-release theophylline is the preferred oral preparation, whereas aminophylline is the preferred parenteral product due to increased solubility.

- Theophylline use is limited because of lower efficacy as a long-term controller medication compared with ICS, a narrow therapeutic index with potentially life threatening toxicity, and multiple clinically important drug interactions.

G-Mast Cell Stabilizers:

Cromolyn sodium is available inhalation powder and as a nebulizer solution. It is indicated for prophylaxis of mild persistent asthma in children and adults.

H-Biological agents

- ***IgE inhibitors***

Omalizumab is an anti-IgE monoclonal antibody. It is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high dose inhaled corticosteroid together with a long-acting $beta_2$ agonist.

- ***IL-5 inhibitors***

Mepolizumab and ***benralizumab*** are approved for patients ≥12 years old with severe asthma and are administered SC, while ***reslizumab*** is approved for severe asthma in patients ≥18 years old and is administered IV. Mepolizumab and reslizumab are dosed every 4 weeks; benralizumab is dosed every 4 weeks for 3 months then every 8 weeks.

- ***IL-4 inhibitors***

Dupilumab targets the IL-4α receptor, thus blocking signaling of IL4 and IL-13, which are cytokines that promote IgE synthesis and inflammatory cell recruitment. Dupilumab is approved for patients with moderate-to-severe asthma age ≥12 years old with an eosinophilic phenotype and is administered SC every 2 weeks.

I- Magnesium sulfate

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.

A single 2 g of IV magnesium sulfate infusion is used for patients with severe asthma exacerbations.

Treatment of Acute Asthma

Treatment includes the following measures:

Oxygen	High concentrations (humidified if possible) should be administered to maintain the oxygen saturation above 92% in adults.
High doses of inhaled bronchodilators	Short-acting β2-agonists are the agent of choice. In hospital, they are most conveniently given via a nebuliser driven by oxygen. Ipratropium bromide provides further bronchodilator therapy and should be added to salbutamol in acute severe or life-threatening attacks.
Systemic corticosteroids	These reduce the inflammatory response and hasten the resolution of an exacerbation. They should be administered to all patients with an acute severe attack. They can usually be administered orally as prednisolone, but I.V hydrocortisone may be used in patients who are vomiting or unable to swallow.

Asthma in Pregnancy

- Because uncontrolled asthma is a greater risk to the fetus than asthma medication use, it is safer for pregnant women to have asthma treated with medications than to experience worsening asthma. Consequently, asthma exacerbations should be managed aggressively with pharmacotherapy. The stepwise approach to asthma therapy in pregnancy is similar to that for the general population.
- Budesonide has the most safety data in humans and is the preferred ICS; it is the only ICS classified as pregnancy category B. However, there are no data indicating that other ICS contribute to increased risk to the mother or fetus.
- Salbutamol is the drug of choice for the treatment of asthma symptoms and exacerbations in pregnancy.

Chronic Obstructive Pulmonary Disease

COPD is characterized by progressive airflow limitation that is not fully reversible. Two principal conditions (referred to as phenotypes) include:

- **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.
- **Emphysema:** Abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, without fibrosis.

Clinical presentation

Initial symptoms include chronic cough and sputum production; patients may experience cough for several years before dyspnea develops. Dyspnea is worse with exercise and progressive over time, with decreased exercise tolerance or decline in physical activity. Chest tightness or wheezing may be present.
Physical examination may be normal in milder stages. When airflow limitation progresses, patients may have shallow breathing, increased resting respiratory rate, “barrel chest” due to lung hyperinflation, pursed lips during expiration, use of accessory respiratory muscles, and cyanosis of mucosal membranes.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest a four-grade classification of airflow limitation:

1. mild
2. moderate
3. severe
4. very severe

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.

No COPD medication has been conclusively shown to slow lung function decline or prolong survival. The GOLD guidelines recommend that a combined "ABCD" classification system based on symptom severity and risk of future exacerbations be used as a stepwise approach to pharmacotherapy.

Bronchodilators are the mainstay of drug therapy; classes include

- SABA
- LABA
- SAMA
- LAMA
- Methylxanthines

Short-acting inhaled bronchodilators (SABAs and SAMAs) relieve symptoms (e.g., dyspnea) and increase exercise tolerance. Long-acting inhaled bronchodilators (LABAs and LAMAs) relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status. Bronchodilators do not significantly improve measurements of expiratory airflow such as FEV1.

Patient Category		**Initial Therapy**
A	less symptoms less exacerbation risk	• short- or long-acting bronchodilator, depending on symptoms
B	more symptoms Less exacerbation risk	• LAMA or LABA for symptom control
C	less symptoms More exacerbation risk	• long-acting bronchodilator for exacerbation prevention; LAMA is preferred over LABA for initial therapy
D	more symptoms more exacerbation risk	• long-acting bronchodilator for exacerbation prevention • LAMA is preferred over LABA for initial therapy • If highly symptomatic (ie, CAT >20), consider dual long-acting bronchodilators (LAMA/LABA) • If blood eosinophil count ≥300/μL (0.3 × 109/L), consider starting ICS/LABA instead of LAMA/LABA

Other therapies:

Roflumilast

Roflumilast is a phosphodiesterase 4 (PDE4) inhibitor that relaxes airway smooth muscle and decreases activity of inflammatory cells and mediators such as TNF-α and IL-8. Roflumilast is recommended for patients with recurrent exacerbations despite treatment with triple inhalation therapy (LAMA/LABA/ICS). It may also be considered as escalation therapy for patients with recurrent exacerbations on dual long-acting bronchodilators (LAMA/LABA) who are not candidates for ICS, such as those with low blood eosinophil count or who are at higher risk of adverse effects associated with ICS. Because theophylline and roflumilast have similar mechanisms of action, they should not be used together.

Azithromycin

Chronic azithromycin was associated with a lower rate of COPD exacerbation and improved quality-of-life scores in one study.

Based on limited evidence supporting long-term treatment (beyond 1 year), current guidelines recommend to consider adding chronic azithromycin only for patients with recurrent exacerbations despite optimal therapy and who are not active smokers.

α1-Antitrypsin Replacement Therapy

The protective antiprotease α1-antitrypsin (AAT) inhibits protease enzymes, including neutrophil elastase. AAT deficiency increases risk for premature emphysema.

For patients with inherited AAT deficiency-associated emphysema, treatment focuses on reduction of risk factors such as smoking, symptomatic treatment with bronchodilators, and augmentation therapy with replacement AAT.

Several proprietary alpha1-proteinase inhibitors are available: Glassia, Prolastin-C, Aralast, Aralast-NP, and Zemaira.

Pneumonia

Pneumonia is an inflammatory condition of the lung affecting primarily the alveoli. Typical signs and symptoms include a varying severity and combination of productive or dry cough, chest pain, fever, and trouble breathing, depending on the underlying cause.

Upper Respiratory Tract Infections

- *Pharyngitis*
- *Otitis media*
- *Acute bacterial rhinosinusitis*
- *etc…*

Lower Respiratory Tract Infections

- *Acute bronchitis*
- *Chronic bronchitis*
- *Bronchiolitis*
- *Pneumonia*
- *Tuberculosis*
- *etc…*

Community-acquired pneumonia

The vast majority of pneumonia cases acquired in the community by otherwise healthy adults are due to *S. pneumoniae* (including drug-resistant). Other common bacterial causes are *M. pneumoniae*, *Legionella species*, *Chlamydophila pneumoniae*, M. catarrhalis, and *H. influenza* and a variety of viruses.

Healthcare-associated pneumonia

Healthcare-associated pneumonia (HCAP), also called hospital-acquired pneumonia or nosocomial pneumonia, is a classification used to distinguish non-hospitalized patients at risk for multi drug-resistant (MDR) pathogens (e.g., *P. aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus* [MRSA]) from those with community-acquired pneumonia.

Ventilator-associated pneumonia

Ventilator-associated pneumonia is a type of lung infection that occurs in people who are on mechanical ventilation breathing machines in hospitals. As such, ventilator-associated pneumonia typically affects critically ill persons that are in an intensive care unit (ICU). Ventilator-associated pneumonia is a major source of increased illness and death. Persons with ventilator-associated pneumonia have increased lengths of ICU hospitalization and have up to a 20-30% death rate.

Clinical presentation

Clinical presentation differs from patient to patient according to the type of microorganism and severity of infection. Pneumonia can be classified into:

- Gram-Positive and Gram-Negative Bacterial Pneumonia

- Anaerobic Pneumonia
- Mycoplasma pneumoniae
- Viral Pneumonia

The types differ in signs and symptoms, clinical presentation on physical examination and radiography.

Signs and symptoms of pneumonia include:

- Abrupt onset of fever, chills, dyspnea, and productive cough
- Rust-colored sputum or hemoptysis
- Pleuritic chest pain

On physical examination, the following findings may present:

- Tachypnea and tachycardia
- Dullness to percussion
- Increased tactile fremitus, whispered pectoriloquy, and egophony
- Chest wall retractions and grunting respirations
- Diminished breath sounds over the affected area
- Inspiratory crackles during lung expansion

Chest radiography may show dense lobar or segmental infiltrate.

Laboratory examination may reveal leukocytosis with a predominance of polymorphonuclear cells. Also, low oxygen saturation on arterial blood gas or pulse oximetry may present.

Treatment

- The first priority on assessing the patient with pneumonia is to evaluate the adequacy of respiratory function.
- The supportive care of the patient with pneumonia includes the use of humidified oxygen for hypoxemia, fluid resuscitation, administration of bronchodilators when bronchospasm is present, and chest physiotherapy with postural drainage if there is evidence of retained secretions.
- The treatment of bacterial pneumonia initially involves the empiric use of relatively broad-spectrum antibiotics.

University of Anbar - College of Pharmacy
Clinical Pharmacy II – Pneumonia treatment options

Outpatient/Community-acquired Pneumonia

Clinical Setting and/or Patient Characteristics	*Empirical Therapy*
• No at-risk comorbidity (diabetes, heart/lung/liver/renal disease, alcoholism, malignancy, asplenia) • no antimicrobial use in past 3 months	• Macrolide • Doxycycline
• At-risk comorbidity (diabetes, heart/lung/liver/renal disease, alcoholism, malignancy, aspelnia) • Immunosuppressive condition /drugs • antimicrobial use in past 3 months	• Antipneumococcal fluoroquinolone • β-lactam + *either* macrolide *or* doxycycline
• Regions with more than 25% rate of macrolide-resistant *S. pneumoniae*	

Inpatient/Community-acquired Pneumonia

Clinical Setting and/or Patient Characteristics	*Usual Pathogens*	*Empirical Therapy*
Non-ICU	*Common pathogens*	• Antipneumococcal fluoroquinolone • β-lactam + *either* macrolide *or* doxycycline
ICU	*Common pathogens*	• Antipneumococcal fluoroquinolone • β-lactam + *either* macrolide *or* doxycycline
	If MRSA suspected	Add vancomycin or linezolid to above regimen
	If P. aeruginosa suspected	• Antipseudomonal • antipneumococcal β-lactam + *either*: o ciprofloxacin OR o levofloxacin OR o aminoglycoside + azithromycin OR o aminoglycoside + moxifloxacin
	If influenza suspected	Add oral oseltamivir or intravenous peramivir (when oral medications not possible)

Hospital-acquired pneumonia

Clinical Setting and/or Patient Characteristics	*Empirical Therapy*
• Low mortality risk • No MDR HAP risk factors • Local MRSA prevalence <20%	• Piperacillin–tazobactam • Cefepime • Levofloxacin • Imipenem • Meropenem
• Low mortality risk • MDR HAP risk factors • Local MRSA ≥20% OR unknown	• Piperacillin–tazobactam • Cefepime • Levofloxacin • Ciprofloxacin • Imipenem • Meropenem • Aztreonam + vancomycin • Linezolid
• High mortality risk • MDR risk factor(s)	Double cover P. aeruginosa with two of the following, avoiding two from the same class: • Piperacillin–tazobactam • Cefepime • Levofloxacin • Ciprofloxacin • Imipenem • Meropenem • Aztreonam • Gentamicin • Tobramycin • Amikacin + vancomycin • Linezolid

Ventilator-associated pneumonia

Clinical Setting and/or Patient Characteristics	*Empirical Therapy*
• No MDR VAP risk factors • Local MRSA and gram-negative bacilli-resistance both <10%	• Piperacillin–tazobactam • Cefepime • Levofloxacin • Imipenem • Meropenem
• No MDR VAP risk factors • Local MRSA ≥10% or unknown • gram-negative bacilli-resistance <10%	• Piperacillin–tazobactam • Cefepime • Levofloxacin • Ciprofloxacin • Imipenem • Meropenem • Aztreonam + vancomycin • Linezolid
• MDR VAP risk factor(s) • local MRSA and gram-negative bacilli-resistance >10% or unknown	Double cover P. aeruginosa with two of the following, avoiding two from the same class: • Piperacillin–tazobactam • Cefepime • Levofloxacin • Ciprofloxacin • Imipenem • Meropenem • Aztreonam • Gentamicin • Tobramycin • Amikacin + vancomycin • Linezolid

Aspiration pneumonia

Clinical Setting and/or Patient Characteristics	*Empirical Therapy*
• Community-acquired • Hospital-acquired	• Treat as above for CAP • Treat as above for HAP • Treat as above for CAP/HAP using antibiotic with anaerobic coverage or add clindamycin or metronidazole

Tuberculosis

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

Epidemiology

- Globally, 2 billion people are infected and roughly 2 million people die from TB each year.
- *M. tuberculosis* is transmitted from person to person by coughing or sneezing. Close contacts of TB patients are most likely to become infected.
- Human immunodeficiency virus (HIV) is the most important risk factor for active TB, especially among people 25 to 44 years of age. An HIV-infected individual with TB infection is over 100-fold more likely to develop active disease than an HIV-seronegative patient.
- Approximately 90% of patients who experience primary disease have no further clinical manifestations other than a positive skin test either alone or in combination with radiographic evidence of stable granulomas. Tissue necrosis and calcification of the originally infected site and regional lymph nodes may occur, resulting in the formation of a radiodense area referred to as a ***Ghon complex***.
- Approximately 5% of patients (usually children, the elderly, or the immunocompromised) experience progressive primary disease at the site of the primary infection (usually the lower lobes) and frequently by dissemination, leading to meningitis and often to involvement of the upper lobes of the lung as well.
- Approximately 10% of patients develop reactivation disease, which arises subsequent to the hematogenous spread of the organism. Most cases of TB are believed to result from reactivation.
- Occasionally, a massive inoculum of organisms may be introduced into the bloodstream, causing widely disseminated disease and granuloma formation known as ***miliary tuberculosis***.

Clinical presentation

The classic presentation of pulmonary TB is nonspecific, indicative only of a slowly evolving infectious process. The onset of TB may be gradual. Physical examination is nonspecific but suggestive of progressive pulmonary disease.

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

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

TB in the elderly is easily confused with other respiratory diseases. It is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis. TB in children may present as typical bacterial pneumonia and is called progressive primary TB.

Diagnosis

- The most widely used screening method for tuberculous infection is the ***tuberculin skin test***, which uses ***purified protein derivative*** (PPD).
- The ***Mantoux method*** of purified protein derivative administration consists of the intracutaneous injection of purified protein derivative containing five tuberculin units. The test is read 48 to 72 hours after injection by measuring the diameter of the zone of induration.
- Some patients may exhibit a positive test 1 week after an initial negative test; this is referred to as a booster effect.
- Confirmatory diagnosis of a clinical suspicion of TB must be made via chest ***radiograph*** and ***microbiologic examination*** of sputum or other infected material to rule out active disease.
- Attempts should be made to isolate *M. tuberculosis* from the infected site.
- ***Interferon-gamma release assays*** (IGRA) is a tests used to measure release of interferon-γ in the patient's blood in response to TB antigens. It may provide quick and specific results for identifying *M. tuberculosis*.

Treatment

- A minimum of two drugs, and generally three or four drugs, must be used simultaneously.
- Drug treatment is continued for at least 6 months and up to 2 to 3 years for some cases of multidrug-resistant TB (MDR-TB).
- Patients with active disease should be isolated to prevent spread of the disease.
- Surgery may be needed to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

Latent Infection

- Chemoprophylaxis should be initiated in patients to reduce the risk of progression to active disease.
- ***Isoniazid*** is the preferred treatment for latent TB, generally given for 9 months.
- ***Rifampicin***, for 4 months, can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.
- ***Rifabutin*** may be substituted for rifampicin for patients at high risk of drug interactions.
- A 12-week ***isoniazid/Rifampicin*** regimen as an equal alternative to 9 months of daily isoniazid for treating latent tuberculosis infection (LTBI).
- Pregnant women, alcoholics, and patients with poor diets who are treated with isoniazid should receive ***pyridoxine***, 10 to 50 mg daily, to reduce the incidence of central nervous system (CNS) effects or peripheral neuropathies.

First-line drugs		***Second-line drugs***	
• *Isoniazid*	• *Rifampicin*	• *Cycloserine*	• *kanamycin*
• *Pyrazinamide*	• *Rifabutin*	• *Streptomycin*	• *Capreomycin*
• *Ethambutol*	• *Rifapentine*	• *Ethionamide*	• *p-Amino-salicylic acid (PAS)*
		• *Amikacin*	• *Moxifloxacin*

Active Disease

- The standard treatment regimen is ***isoniazid, rifampicin, pyrazinamide, and ethambutol*** for ***2 months***, followed by ***isoniazid and rifampicin*** for ***4 months***.
- 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.

- ***HIV***-positive patients should be treated for an additional 3 months and at least 6 months from the time that they convert to smear and culture negativity.
- When isoniazid and rifampicin cannot be used, treatment duration becomes ***2 years*** or more, regardless of immune status.
- Patients who are slow to respond, those who remain culture positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and HIV-positive patients should be treated for 9 months and for at least 6 months from the time they convert to smear and culture negativity.

Drug Resistance

There are varying degrees of drug resistance that are encountered:

- mono-resistance: resistance to one anti-TB drug;
- MDR-TB: resistance to at least isoniazid and rifampicin;
- XDR-TB: resistance to any fluoroquinolone, and at least one injectable second-line drug (capreomycin, kanamycin or amikacin), in addition to multidrug resistance.

Drug resistance should be suspected in the following patients:

- who have received prior therapy for TB
- from geographic areas with a high prevalence of resistance
- who are homeless, institutionalized, IV drug abusers, and/or infected with HIV
- who still have acid-fast bacilli–positive sputum smears after 2 months of therapy
- who still have positive cultures after 2 to 4 months of therapy
- who fail therapy or relapse after retreatment
- known to be exposed to MDR-TB cases

(What are the suggested treatments for MDR-TB?)

Renal Failure

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

Hepatotoxicity

Rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic, and liver function tests (LFTs) should be checked before commencing treatment. If transaminases rise greater than five times the upper limit of normal, or greater than three times normal with symptomatic liver disease, all potentially hepatotoxic drugs (i.e. rifampicin, isoniazid and pyrazinamide) should be stopped immediately. If the patient is well and sputum smear negative (i.e. non-infectious), no treatment is required until after LFTs return to normal.

However, if the patient is unwell or sputum smear positive, TB treatment must continue using two anti-TB drugs with low risk of hepatotoxicity, such as streptomycin and ethambutol, with or without a fluoroquinolone (levoloxacin or moxiloxacin).

Once liver function has returned to normal, the first-line anti-TB drugs can be reintroduced sequentially at full dose over a period of no more than 10 days, usually in the order of ethambutol, isoniazid, rifampicin, then pyrazinamide.

Some guidelines advise against reintroducing pyrazinamide if the hepatotoxic reaction was particularly severe and prolonged, but continuing with ethambutol, rifampicin and isoniazid initially and extending the course duration to 9 months.

Pediatric Tuberculosis

The treatment of TB in children is similar to that of adults, requiring a 2-month intensive phase of four drugs followed by a 4-month continuation phase of two drugs (extended to 12 months for TB affecting the CNS).

Old recommendations suggested a 6-month course of isoniazid and rifampin, supplemented during the first 2 months with pyrazinamide.

Streptomycin may be used in children too young to be monitored for visual acuity as ethambutol can cause ocular toxicity.

Congenital tuberculosis is acquired from maternal extrapulmonary sites at birth, same first line regimen can be used in neonates.

Pregnant Women

- The first-line anti-TB drugs ***isoniazid, rifampicin, pyrazinamide*** and ***ethambutol*** are all considered compatible with use in pregnancy, and any risks of harm from these drugs are outweighed by the risks of untreated active TB.
- The usual treatment of pregnant women is for 9 months.
- Women with TB should be cautioned against becoming pregnant, as the disease poses a risk to the fetus as well as to the mother.
- Supplementation with B vitamins is particularly important during pregnancy.
- ***Rifampicin*** has been rarely associated with birth defects, but those seen are occasionally severe, including limb reduction and CNS lesions.
- Many second-line drugs are not compatible with use in pregnancy, in particular the aminoglycosides.
- ***Ethionamide*** may be associated with premature delivery, congenital deformities, and Down syndrome when used during pregnancy, so it cannot be recommended in pregnancy.
- ***Cycloserine*** is not recommended during pregnancy.
- ***Fluoroquinolones*** should be avoided in pregnancy and during nursing.

Nursing Women

Breastfeeding is considered safe whilst taking anti-TB drugs, and all mothers should take supplemental pyridoxine 10–50 mg daily whilst taking isoniazid.

Tuberculous Meningitis and Extrapulmonary Disease

In general, isoniazid, pyrazinamide, ethionamide, and cycloserine penetrate the cerebrospinal fluid readily. Patients with ***CNS TB*** are often treated for longer periods (9–12 months).

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.

Comparison of WHO classification of anti-tuberculosis drugs between 2014 and 2016 guidelines (للاطلاع)

WHO 2014		WHO 2016		
Group	**Drugs**	**Group**		**Drugs**
Group 1	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin, rifapentine			
Group 2	Streptomycin Kanamycin Amikacin Capreomycin	Group A*		Levofloxacin Moxifloxacin Gatifloxacin
Group 3	Levofloxacin Moxifloxacin Gatifloxacin	Group B		Amikacin Capreomycin Kanamycin (streptomycin)†
Group 4	Ethionamide Prothionamide Cycloserine Terizidonee *p*-Aminosalicylic acid	Group C*		Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
Group 5	Bedaquiline Delamanid Linezolid Clofazimine Amoxicillin/clavulanate Imipenem/cilastatin Meropenem‡ High-dose isoniazid Thioacetazone Clarithromycin	Group D	D1	Pyrazinamide Ethambutol High-dose isoniazid
			D2	Bedaquiline Delamanid
			D3	*p*-Aminosalicylic acid Imipenem-cilastatin‡ Meropenem‡ Amoxicillin-clavulonate‡ (thioacetazone)

* Medicines in groups A and C are shown by decreasing order of usual preference for use.

† Streptomycin may substitute other injectable agents when the other three cannot be used.

‡ Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

Meningitis

Meningitis is a groups of CNS infections that may be caused by a variety of bacteria, fungi, viruses, and parasites.

Common causative agents

Bacterial meningitis	*Streptococcus pneumoniae, group B Streptococcus, Neisseria meningitidis, Haemophilus influenzae, Escherichia coli* and *Listeria monocytogenes*
Fungal meningitis	*Cryptococcus neoformans*
Viral meningitis	*Enteroviruses* and Herpes simplex virus types 1 and 2

Predisposing Factors:

1. Head trauma
2. Immunosuppression
3. Central nervous system shunts
4. Neurosurgical patients
5. Local infections (Sinusitis, Otitis media, Pharyngitis, etc...).

Bacterial meningitis:

- The critical first step in the acquisition of acute bacterial meningitis is nasopharyngeal colonization of the host by the bacterial pathogen. The bacteria first attach themselves to nasopharyngeal epithelial cells and are then phagocytized into the host's bloodstream.
- A common characteristic of most CNS bacterial pathogens (e.g., *H. influenzae, E. coli* and *N. meningitidis*) is the presence of an extensive polysaccharide capsule that is resistant to neutrophil phagocytosis and complement opsonization.

Clinical presentation

- Patients may receive antibiotics before a diagnosis of meningitis is made, delaying presentation to the hospital. Prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose.
- Classic signs and symptoms include fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia and severe headache.

- **Kernig sign** (resistance to extension of the leg when the hip is flexed) and **Brudziński sign** (reflex flexion of the hips and knees produced on flexion of the neck when lying in the recumbent position) may be present but are poorly sensitive and frequently absent in children.
- Purpuric and petechial skin lesions typically indicate meningococcal involvement, although the lesions may be present with *H. influenzae* meningitis. Rashes rarely occur with pneumococcal meningitis.
- Clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash and convulsions, in addition to those just mentioned.

Neurologic sequelae

- The neurologic sequelae of meningitis occur due to the activation of host inflammatory pathways.
- Bacterial cell death causes the release of cell wall components such as lipopolysaccharide, lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan, depending on whether the pathogen is gram-positive or gram-negative. These cell wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1, tumor necrosis factor and other inflammatory mediators).
- These lead to cerebral edema, elevated intracranial pressure, cerebrospinal fluid pleocytosis, decreased cerebral blood flow, cerebral ischemia and death.

Laboratory tests

- An elevated CSF protein (50 mg/dL or more) and a CSF glucose concentration less than 50% of the simultaneously obtained peripheral value suggest bacterial meningitis.
- The values for CSF glucose, protein, and WBC concentrations found with bacterial meningitis overlap significantly with those for viral, tuberculous, and fungal meningitis and cannot always distinguish the different etiologies of meningitis.
- Gram stain and culture of the CSF are the most important laboratory tests performed for bacterial meningitis. When performed before antibiotic therapy is initiated, Gram stain is both rapid and sensitive and can confirm the diagnosis of bacterial meningitis in 75% to 90% of cases.

- ***Polymerase chain reaction*** (PCR) techniques can be used to diagnose meningitis caused by *N. meningitidis*, *S. pneumoniae*, and *H. influenzae type b*.
- ***Latex fixation, latex coagglutination*** and ***enzyme immunoassay tests*** provide for the rapid identification of several bacterial causes of meningitis, including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae type b*.
- The ***rapid antigen tests*** should be used in situations in which the Gram stain is negative.
- Diagnosis of ***tuberculosis meningitis*** employs acid-fast staining, culture, and PCR of the CSF.

Bacterial Meningitis Score

Bacterial Meningitis Score is a validated clinical decision tool aimed to identify children older than 2 months with CSF pleocytosis who are at low risk of bacterial meningitis. This tool incorporates clinical features such as positive CSF Gram stain, presence of seizure, serum absolute neutrophil count of 10,000 cells/mm 3 or more (≥10 × 109/L), CSF protein ≥80 mg/dL (≥800 mg/L), and CSF neutrophil count ≥1000 cells/mm3 (≥1 × 109/L). Treatment is recommended when one or more criteria are present.

Treatment

- The administration of fluids, electrolytes, antipyretics, analgesia, and other supportive measures are particularly important for patients presenting with acute bacterial meningitis.
- Empiric antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism.
- Antimicrobial therapy should last at least 48 to 72 hours or until the diagnosis of bacterial meningitis can be ruled out.
- With increased meningeal inflammation, there will be greater antibiotic penetration.
- In general, therapy of meningitis requires the use of high dosages of antimicrobials administered by the IV route. The antibiotics selected must penetrate adequately into the CSF.

Antibiotic penetration to the CSF:

Very Good	Penetrate CSF well regardless of meningeal inflammation. • Chloramphenicol, metronidazole, TMP-SMX, linezolid
Good	Adequate CSF penetration achieved when the meninges are inflamed. • Penicillins: Penicillin G, ampicillin, nafcillin, piperacillin, ticarcillin • Cephalosporins: cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime • Carbapenems: imipenem, meropenem, • Other β-lactams: aztreonam, clavulanic acid, sulbactam • Fluoroquinolones: ciprofloxacin • Other agents: rifampin
Fair to Poor	Penetration often inadequate even when the meninges are inflamed • Aminoglycosides: amikacin, gentamicin, tobramycin • Macrolides: azithromycin, clarithromycin, erythromycin. • Other agents: clindamycin, vancomycin, daptomycin

Dexamethasone

- In addition to antibiotics, dexamethasone is a commonly used as an adjunctive therapy for the treatment of pediatric meningitis.
- Current recommendations call for the use of adjunctive dexamethasone in infants and children with *H. influenzae* meningitis, initiated 10 to 20 minutes prior to or concomitant with the first dose of antimicrobials. Clinical outcome is unlikely to improve if dexamethasone is given after the first dose of antimicrobial and should therefore be avoided.

Neisseria Meningitidis

- Penicillin G or ampicillin is used for treatment of meningococcal meningitis, Cefotaxime or ceftriaxone are alternative therapies. The recommended duration of therapy is 7 days.
- In case of penicillin resistance, cefotaxime or ceftriaxone are used. Meropenem or moxifloxacin are alternative therapies.
- In general, rifampin, ceftriaxone, ciprofloxacin or azithromycin is given for prophylaxis.

Streptococcus Pneumoniae

- *S. pneumoniae* is the leading cause of meningitis in patients 2 months of age or older.
- Neurologic complications, such as coma and seizures, are common.
- The treatment of choice until susceptibility of the organism is known is the combination of vancomycin plus ceftriaxone. Penicillin may be used for drug-susceptible isolates. The recommended duration of therapy is 10-14 days.
- A vaccine is available for use in infants between 2 months and 9 years of age. Other types of vaccine are available for different ages.

Haemophilus Influenzae

- A third-generation cephalosporin (cefotaxime or ceftriaxone) is the initial antimicrobial therapy.
- Once bacterial susceptibilities are available, ampicillin may be used if the isolate proves ampicillin sensitive. Cefepime and fluoroquinolones are suitable alternatives regardless of β-lactamase activity. The recommended duration of therapy is 7 days.
- Vaccination is usually begun in children at 2 months. The vaccine should be considered in patients older than 5 years with sickle cell disease, asplenia or immunocompromising diseases.

Listeria Monocytogenes

- *L. monocytogenes* is a gram-positive is responsible for 10% of all reported cases of meningitis in those older than 65 years.
- The combination of penicillin G or ampicillin with an aminoglycoside results in a bactericidal effect. Patients should be treated a minimum of 3 weeks. Combination therapy is given for at least 10 days with the remainder completed with penicillin G or ampicillin alone.
- Trimethoprim–sulfamethoxazole with meropenem is an effective alternative.

Gram-Negative Bacillary Meningitis

- Elderly patients are at an increased risk of gram-negative meningitis but typically lack the classic signs and symptoms of the disease.

- Meningitis caused by ***Pseudomonas aeruginosa*** is initially treated with an extended-spectrum β-lactam such as ceftazidime or cefepime, or alternatively aztreonam, ciprofloxacin, or meropenem. The addition of an aminoglycoside—usually tobramycin—to one of the above agents should also be considered.
- If the pseudomonad is suspected to be antibiotic resistant or becomes resistant during therapy, an intraventricular aminoglycoside (preservative-free) should be considered along with IV aminoglycoside.
- Gram-negative organisms, other than *P. aeruginosa*, that cause meningitis can be treated with a third- or fourth-generation cephalosporin such as cefotaxime, ceftriaxone, ceftazidime or cefepime
- Therapy for gram-negative meningitis is continued for a minimum of 21 days. CSF cultures may remain positive for several days or more on a regimen that will eventually be curative.

Chemoprophylaxis:

- People in close contact with patients with meningitis caused by *N. meningitidis* or *H. influenzae* are at an increased risk of contracting the disease. Other types of bacterial meningitis, including cases caused by *S. pneumoniae*, are considered to be less transmissible between people.
- Recommended prophylactic regimens, for adults include one of the following options:
    - rifampin (600 mg orally every 12 hours for 2 days)
    - ciprofloxacin (500 mg orally for one dose)
    - ceftriaxone (250 mg intramuscularly for one dose). It is the recommended agent for pregnant women.

Mycobacterium tuberculosis:

- Treatment regimen for TB meningitis is four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for the first 2 months generally followed by isoniazid plus rifampicin for the duration of therapy (Patients with TB meningitis should be treated for a duration of 9 months or longer and patients with rifampicin-resistant strains should receive 18 to 24 months of therapy).
- The use of glucocorticoids for TB meningitis remains controversial. The administration of steroids such as oral prednisone or IV dexamethasone, improves neurologic sequelae and survival in adults and children.

Fungal meningitis

Cryptococcal meningitis is the most common form of fungal meningitis and is a major cause of morbidity and mortality in immunosuppressed patients.

Amphotericin B is the drug of choice for treatment of acute *C. neoformans* meningitis. Amphotericin combined with flucytosine, is more effective than amphotericin alone.

Viral Encephalitis

The most common viral pathogens are *enteroviruses*, which cause approximately 85% of cases of viral CNS infections. Most cases of enteroviral meningitis or encephalitis are self-limiting with supportive treatment.

Both herpes simplex virus types 1 and 2 have been associated with infections of the CNS. Acyclovir is the drug of choice for herpes simplex encephalitis. Acyclovir is usually administered intravenously for 2 to 3 weeks. The alternative treatment for acyclovir-resistant herpes simplex virus is Foscarnet.

Peptic Ulcer Disease

Peptic ulcer disease refers to a group of ulcerative disorders of the upper gastrointestinal tract that require acid and pepsin for their formation.

Pathogenesis and risk factors

- Pathogenesis of duodenal and gastric ulcers involves pathophysiologic abnormalities and environmental and genetic factors.
- Most peptic ulcers occur in presence of acid and pepsin when *Helicobacter pylori*, NSAIDs or other factors disrupt normal mucosal defense and healing mechanisms. Increased gastric acid secretion may occur with duodenal ulcers, but patients with gastric ulcers usually have normal or reduced rates of acid secretion.
- *H. pylori* infection causes gastric mucosal inflammation in all infected individuals, but only a minority develop an ulcer or gastric cancer.
- Nonselective NSAIDs (including aspirin) cause gastric mucosal damage by two mechanisms:
    - Direct or topical irritation of the gastric epithelium,
    - Systemic inhibition of endogenous mucosal prostaglandin synthesis.
- Use of corticosteroids alone does not increase risk of ulcer or complications, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.
- Epidemiologic evidence links cigarette smoking to peptic ulcer disease, impaired ulcer healing, and ulcer-related gastrointestinal complications. Risk is proportional to amount smoked per day.
- Coffee, tea, cola beverages, beer, milk and spices may cause dyspepsia but do not increase peptic ulcer disease risk.

Clinical presentation

- ***Abdominal pain*** is the most frequent peptic ulcer disease symptom. Pain is often ***epigastric*** and described as burning but can present as vague discomfort, abdominal fullness, or cramping. ***Nocturnal pain*** may awaken patients from sleep, especially between 12 am and 3 am.
- Pain from duodenal ulcers often occurs 1 to 3 hours after meals and is usually relieved by food, whereas food may precipitate or accentuate ulcer pain in gastric ulcers.
- Other symptoms include heartburn, belching, bloating, nausea, vomiting, and anorexia.

Complications

Ulcer complications include:

- Upper GI ***Bleeding*** may be occult or present as melena or hematemesis.

- ***Perforation*** into the peritoneal cavity is associated with sudden, sharp and severe pain.
- Penetration into an adjacent structure (e.g., pancreas, biliary tract or liver)
- Symptoms of ***gastric outlet obstruction*** typically occur over several months and include early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

Diagnosis

- Physical examination may reveal epigastric tenderness between the umbilicus and the xiphoid process that less commonly radiates to the back.
- Routine laboratory tests are not helpful in establishing a diagnosis of peptic ulcer disease. Hematocrit, hemoglobin, and stool guaiac tests are used to detect bleeding.
- Diagnosis of *H. pylori* infection can be made using endoscopic or nonendoscopic tests:

Non-endoscopic tests	
Urea breath test	It is the preferred non-endoscopic method to verify *H. pylori* eradication.
Serologic antibody	This test is reasonable non-endoscopic test to determine *H. pylori* status.
Stool antigen	It is another non-endoscopic test to determine *H. pylori* status.
IgG	Antibodies (immunoglobulin G [IgG]) to *H.* pylori can be measured in serum, plasma, or whole blood.
Endoscopic tests	
Endoscopy	Endoscopy has largely replaced gastrointestinal radiography because it provides a more accurate diagnosis and permits direct visualization of the ulcer.

Exclusion of Zollinger-Ellison syndrome may be required by testing serum gastrin level or secretin stimulation test.

Treatment

- Elimination or reduction of psychological stress and cigarette smoking,
- Avoidance of NSAIDs (including aspirin) or using the lowest effective dose of an NSAID and switching to less toxic NSAIDs. If possible, alternative agents such as paracetamol should be used for pain relief.
- Patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms.
- Emergency surgery may be required for bleeding, perforation or obstruction.

Pharmacological treatment

- ***Antacids*** provide rapid pain relief in most ulcer patients. They contains aluminum, magnesium and/or calcium salts. Sodium based antacid are available as effervescent powder. They are rapid in action but with short duration of action and more side effects (edema and increased blood pressure).
- Antacids available in oral tablets and suspensions. They may be formulated with other active ingredients such as ***simethicone*** to control gas or ***alginic acid*** (as in *Gaviscon*) to act as a physical barrier to acid.
- ***Bismuth subsalicylate*** displays anti-inflammatory and bactericidal action. It also acts as an antacid and used in *H. pylori* eradication regimen.
- Maintenance therapy with a ***proton pump inhibitors*** (PPIs) or an ***H2 receptor antagonist*** to high-risk patients with ulcer complications, patients who fail *H. pylori* eradication and those with *H. pylori* -negative ulcers.
- Continuous PPI treatment is often necessary to maintain healing. Patients with refractory gastric ulcer may require surgery because of the possibility of malignancy.

Ulcer healing drugs *(some agents are not available in Iraqi market)*

<table>
<tr>
<td rowspan="2">Proton pump inhibitors (PPIs)
• Omeprazole
• Lansoprazole
• Rabeprazole
• Pantoprazole
• Esomeprazole
• Dexlansoprazole
• Ilaprazole</td>
<td rowspan="2">H2-receptor antagonists
• Cimetidine
• Famotidine
• Ranitidine
• Nizatidine</td>
<td>Prostaglandin analogue:
• Misoprostol
• Enprostil</td>
</tr>
<tr>
<td>Mucosal protectant
Sucralfate</td>
</tr>
</table>

Other agents:

Potassium-competitive acid blockers or acid pump antagonists are considered as a new class of PPIs.

Vonoprazan is approved in Japan while revaprazan is approved for use in Korea.

Treatment of H. pylori infection

- Empirical antimicrobial therapy is not recommended
- ***First-line therapy*** to eradicate *H. pylori* infection is usually initiated with a proton pump inhibitor–based, three-drug regimen for 10 to 14 days. Amoxicillin, clarithromycin and a nitroimidazole (metronidazole and tinidazole) are the most widely used antibiotics. Tetracycline and fluoroquinolones (e.g. levofloxacin) are also suggested.

- If a ***second treatment*** course is required, the regimen should contain different antibiotics, or a four-drug regimen with a bismuth salt, a nitroimidazole, tetracycline, and a PPI should be used. Rifabutin triple regimen is also suggested.
- If initial treatment fails to eradicate *H. pylori*, second-line (***salvage***) treatment should:
    - Use antibiotics that were not included in the initial regimen
    - Use antibiotics that are not associated with resistance
    - Use a drug that has a topical effect (e.g., bismuth)
    - Extend the treatment duration to 14 days. A 14-day course of the PPI-based quadruple regimen is the most commonly used second-line therapy after failure of a PPI–amoxicillin–clarithromycin regimen.

A combination of bismuth subcitrate, metronidazole and tetracycline (*trade name Pylera*) is available in Iraqi market. Other combinations may be available in Iraqi market.

NSAID-induced ulcers

Patients with NSAID-induced ulcers should be tested to determine *H. pylori* status. If *H. pylori* positive, a treatment with a PPI-based three-drug regimen is recommended. If *H. pylori* negative, discontinue the NSAID and treat with either a PPI, histamine2 receptor antagonist or sucralfate.

If the NSAID must be continued despite ulceration, a treatment with a PPI (if *H. pylori* negative) or a PPI-based three-drug regimen (if *H. pylori* positive) may be initiated. Co-therapy with a PPI or misoprostol or switching to a selective cyclooxygenase-2 (COX-2) inhibitor is recommended for patients at risk of developing an ulcer-related complication.