Cardiovascular and Metabolic Diseases

Hypertension

What is high blood pressure?

High blood pressure (HBP or hypertension) is when the blood pressure, the force of the blood flowing through blood vessels, is consistently too high.

The best way to know if you have high blood pressure it is to have your blood pressure checked.

Blood pressure numbers and what they mean

- Systolic blood pressure (the upper number) — indicates how much pressure your blood is exerting against your artery walls when the heart beats.
- Diastolic blood pressure (the lower number) — indicates how much pressure your blood is exerting against your artery walls while the heart is resting between beats.

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Prehypertension	120 – 139	or	80 – 89
High Blood Pressure (Hypertension) Stage 1	140 – 159	or	90 – 99
High Blood Pressure (Hypertension) Stage 2	160 or higher	or	100 or higher
Hypertensive Crisis (Emergency care needed)	Higher than 180	or	Higher than 110

Blood pressure categories

The five blood pressure ranges as recognized by the American Heart Association are:

- Normal blood pressure

  Blood pressure numbers that are within the normal (optimal) range of less than 120/80 mm Hg.

- Prehypertension (early stage high blood pressure)

  Prehypertension is when blood pressure is consistently ranging from 120-139/80-89 mm Hg. People with prehypertension are likely to develop high blood pressure unless steps are taken to control it.

- Hypertension Stage 1

  Hypertension Stage 1 is when blood pressure is consistently ranging from 140-159/90-99 mm Hg. At this stage of high blood pressure, doctors are likely to prescribe lifestyle changes and may consider adding blood pressure medication.

- Hypertension Stage 2

  Hypertension Stage 2 is when blood pressure is consistently ranging at levels greater than 160/100 mm Hg. At this stage of high blood pressure, doctors are likely to prescribe a combination of blood pressure medications along with lifestyle changes.

- Hypertensive crisis

  This is when high blood pressure requires emergency medical attention. If the blood pressure is higher than 180/110 mm Hg and there are NO symptoms such as chest pain, shortness of breath, back pain, numbness/weakness, changes in vision or difficulty speaking, wait about five minutes and take it again. If the reading is still at or above that level, you should get help immediately.

Which number is more important?

Typically, more attention is given to systolic blood pressure (the top number) as a major risk factor for cardiovascular disease for people over 50. In most people, systolic blood pressure rises steadily with age due to the increasing stiffness of large arteries, long-term build-up of plaque and an increased incidence of cardiac and vascular disease.

However, elevated systolic or diastolic blood pressure alone may be used to make a diagnosis of high blood pressure. And, according to recent studies, the risk of death from ischemic heart disease and stroke doubles with every 20 mm Hg systolic or 10 mm Hg diastolic increase among people from age 40 to 89.

High blood pressure is a “silent killer”

- Most of the time there are no obvious symptoms.
- Certain physical traits and lifestyle choices can put you at a greater risk for developing high blood pressure.
- When left untreated, the damage that high blood pressure does to your circulatory system is a significant contributing factor to heart attack, stroke and other health threats.

How the blood pressure and circulatory system work

In order to survive and function properly, your tissues and organs need the oxygenated blood that your circulatory system carries throughout the body.

When the heart beats, it creates pressure that pushes blood through a network of tube-shaped blood vessels, which include arteries, veins and capillaries. This pressure — blood pressure — is the result of two forces: The first force (systolic pressure) occurs as blood pumps out of the heart and into the arteries that are part of the circulatory system. The second force (diastolic pressure) is created as the heart rests between heart beats. (These two forces are each represented by numbers in a blood pressure reading.)

Left uncontrolled or undetected, high blood pressure can lead to:

- Heart attack — High blood pressure damages arteries that can become blocked and prevent blood from flowing to tissues in the heart muscle.
- Stroke — High blood pressure can cause blood vessels in the brain to burst or clog more easily.
- Heart failure — The increased workload from high blood pressure can cause the heart to enlarge and fail to supply blood to the body.
- Kidney disease or failure — High blood pressure can damage the arteries around the kidneys and interfere with their ability to effectively filter blood.
- Vision loss — High blood pressure can strain or damage blood vessels in the eyes.
- Sexual dysfunction — This can be erectile dysfunction in men or lower libido in women.
- Angina — Over time, high blood pressure can lead to heart disease or microvascular disease. Angina, or chest pain, is a common symptom.
- Peripheral artery disease (PAD) — Artherosclerosis caused by high blood pressure can cause a narrowing of arteries in the legs, arms, stomach and head, causing pain or fatigue.

Warning Signs of a Heart Attack

Chest discomfort. Most heart attacks involve discomfort in the center of the chest that lasts more than a few minutes, or that goes away and comes back. It can feel like uncomfortable pressure, squeezing, fullness or pain.

Discomfort in other areas of the upper body. Symptoms can include pain or discomfort in one or both arms, the back, neck, jaw or stomach.

Shortness of breath with or without chest discomfort.

Other signs may include breaking out in a cold sweat, nausea or lightheadedness.

How High Blood Pressure Can Lead to Stroke

A stroke occurs when a blood vessel to the brain is either blocked by a clot (ischemic stroke) or bursts (hemorrhagic stroke). When that happens, part of the brain is no longer getting the blood and oxygen it needs, so it starts to die.

The brain controls our movement and thoughts, so a stroke doesn't only hurt our brain — it can threaten our ability to think, move and function. Strokes can affect language, memory and vision.

Severe strokes may even cause paralysis or death.

How High Blood Pressure Can Lead to Kidney Damage or Failure

The kidneys are a pair of regulatory organs located on either side in the back. Their main function is to act as a filter system that removes waste products and excess fluid from the body.

Our kidneys and circulatory system depend on each other for good health. The nephrons in the kidneys are supplied with a dense network of blood vessels, and high volumes of blood flow through them. The kidneys help filter wastes and extra fluids from blood. When the blood vessels become damaged, the nephrons that filter the blood don’t receive the oxygen and nutrients they need to function well. This is why high blood pressure is the second leading cause of kidney failure.

Over time, uncontrolled high blood pressure can cause arteries around the kidneys to narrow, weaken or harden. These damaged arteries are not able to deliver enough blood to the kidney

tissue, the nephrons do not receive the essential oxygen and nutrients — and the kidneys lose their ability to filter blood and regulate the fluid, hormones, acids and salts in the body.

Damaged kidneys fail to regulate blood pressure. Healthy kidneys produce a hormone called aldosterone to help the body regulate blood pressure. Kidney damage and uncontrolled high blood pressure each contribute to a negative spiral. As more arteries become blocked and stop functioning, the kidneys eventually fail.

How High Blood Pressure Can Lead to Vision Loss

The eyes contain many tiny blood vessels. When subjected to the long-term effects of high blood pressure, the following conditions can develop:

- Blood vessel damage (retinopathy)

  A lack of blood flow to the retina leads to blurred vision or the complete loss of sight. People with diabetes and high blood pressure are at an even greater risk for developing this condition. Managing blood pressure is also the only way to treat hypertensive retinopathy.

- Fluid buildup under the retina (choroidopathy)

  This buildup of fluid under the retina, the light-sensitive layer of tissue at the back of the eyeball, results in distorted vision or, in some cases, scarring that impairs vision.

- Nerve damage (optic neuropathy)

  The result of blocked blood flow that damages the optic nerve, it can kill nerve cells in your eyes, which may cause temporary or permanent vision loss.

- High blood pressure can lead to stroke which can also cause vision loss

  In addition to threatening the anatomy of the eye, high blood pressure is also a cause of stroke, which can impair the optic nerve or damage the area of the brain responsible for processing images.

The damage starts in the arteries and the heart

The primary way that high blood pressure causes harm is by increasing the workload of the heart and blood vessels — making them work harder and less efficiently.

Over time, the force and friction of high blood pressure damages the delicate tissues inside the arteries. In turn, LDL (bad) cholesterol forms plaque along tiny tears in the artery walls, signifying the start of atherosclerosis.

The more the plaque and damage increases, the narrower (smaller) the insides of the arteries become — raising blood pressure and starting a vicious circle that further harms your arteries, heart and the rest of your body. This can ultimately lead to other conditions ranging from arrhythmia to heart attack and stroke.

High blood pressure and metabolic syndrome (insulin resistance syndrome)

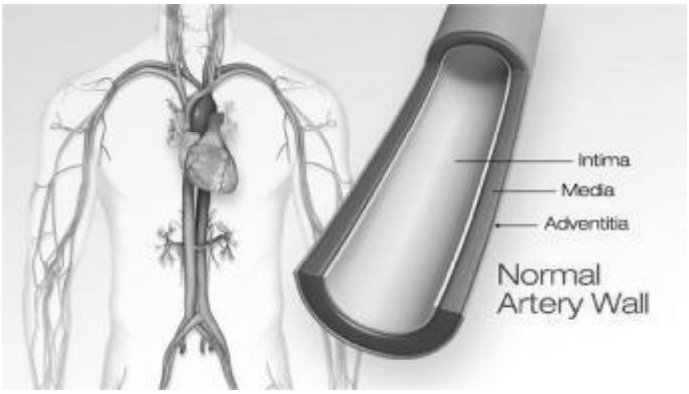
Metabolic syndrome is a group of risk factors, including high blood pressure, that raises risk of heart disease, diabetes, stroke and other health problems. It is diagnosed when any three of these risk factors are present:

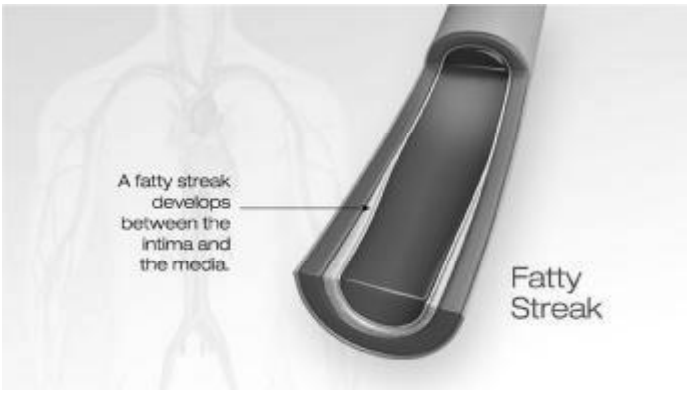
- High blood glucose
- Low levels of HDL (“good”) cholesterol in the blood
- High levels of triglycerides in the blood
- Large waist circumference or “apple-shaped” body
- High blood pressure

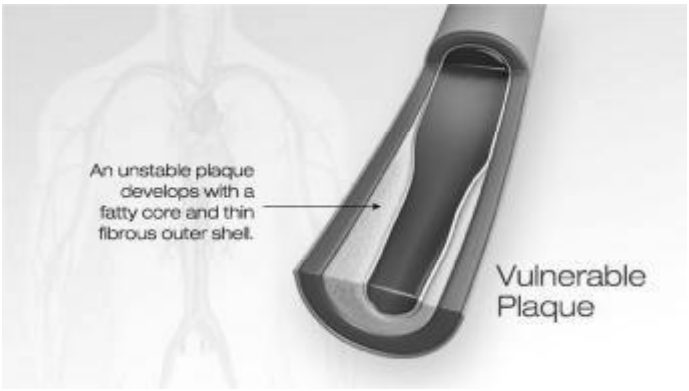
Atherosclerosis

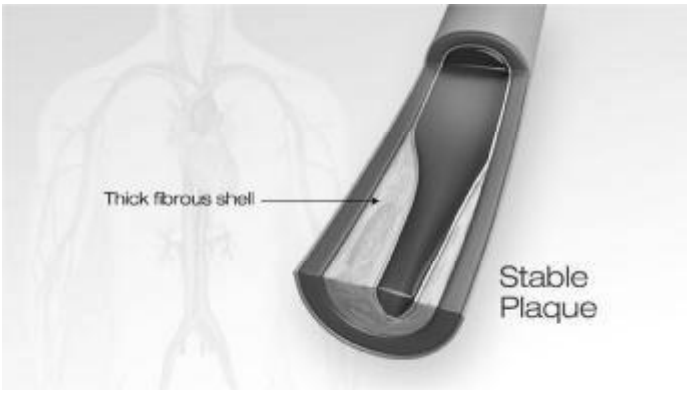
The normal aging process can cause the big elastic arteries to become stiff over time. This is known as arteriosclerosis. This can increase blood pressure, as the ventricles must pump harder to force blood out of the heart and into the arteries.

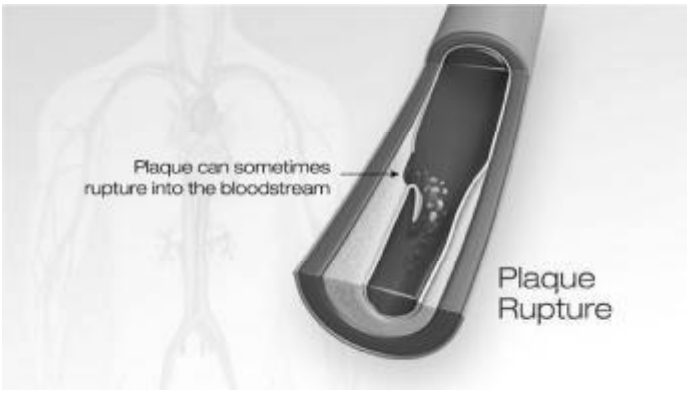
Atherosclerosis is a type of arteriosclerosis. Atherosclerosis causes arteries to narrow, weaken and be less flexible. It's the term for the process of fatty buildup in the inner lining of an artery. The buildup that results is called plaque and reduces the amount of blood and oxygen that is delivered to vital organs.

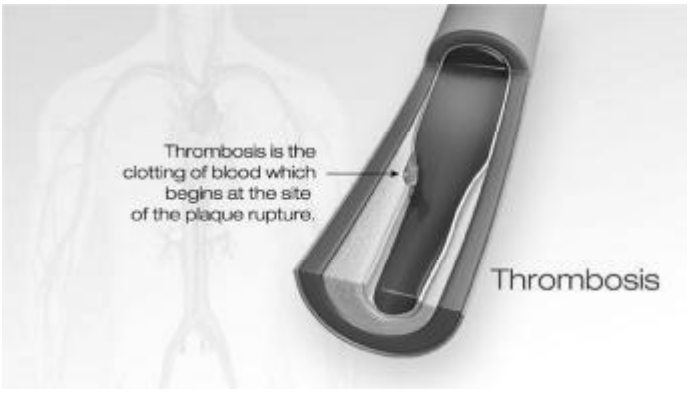


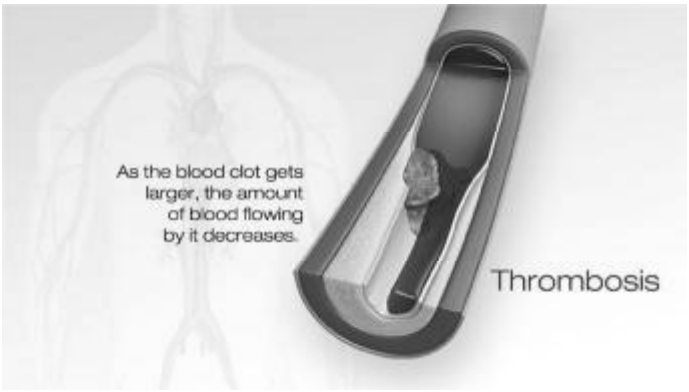


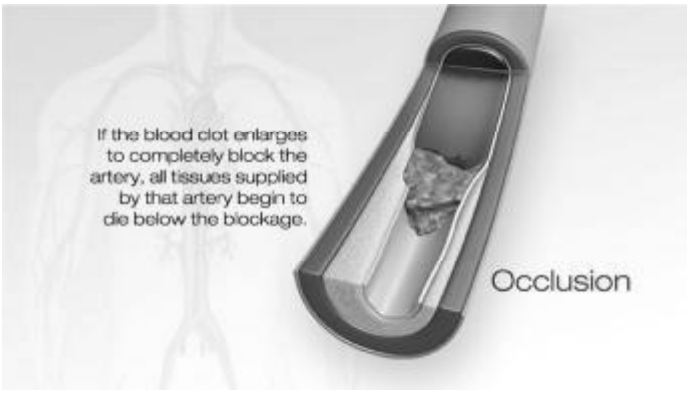






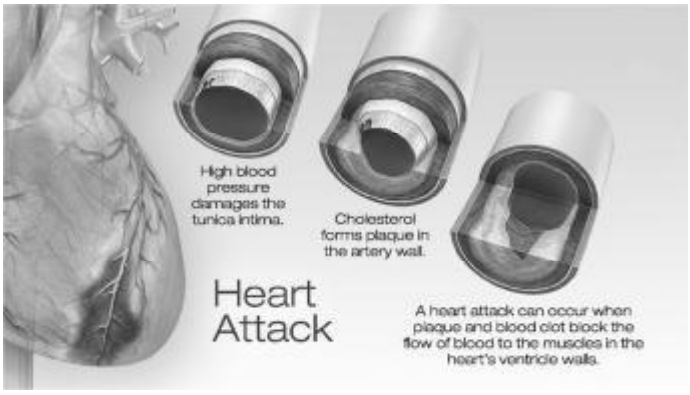






When atherosclerosis is not stopped, it can lead to blocked coronary arteries and a possible heart attack, stroke, or peripheral vascular disease.

HBP can also cause the muscular walls of the ventricles to become thick and stiff. This can lead to heart failure.



Risk Factors for High Blood Pressure

Common hereditary and physical risk factors for high blood pressure include:

- Family history

  If the parents or other close blood relatives have high blood pressure, there's an increased chance that you'll get it, too.

- Age

  The older you are, the more likely you are to get high blood pressure. As we age, our blood vessels gradually lose some of their elastic quality, which can contribute to increased blood pressure. However, children can also develop high blood pressure.

- Gender

  Until age 45, men are more likely to get high blood pressure than women are. From age 45 to 64, men and women get high blood pressure at similar rates. And at 65 and older, women are more likely to get high blood pressure.

Risk factors related to lifestyle

Unlike the traits you are born with, the risk factors related to how you live are things you can change to help prevent and manage high blood pressure, including:

- Lack of physical activity

  Not getting enough physical activity as part of your lifestyle increases your risk of getting high blood pressure. Physical activity is great for your heart and circulatory system in general, and blood pressure is no exception.

- An unhealthy diet, especially one high in sodium

  Good nutrition from a variety of sources is critical for your health. A diet that is too high in salt consumption, as well as calories, saturated fat and sugar, carries an additional risk of high blood pressure. On the other hand, making healthy food choices can actually help lower blood pressure.

- Being overweight or obese

  Carrying too much weight puts an extra strain on your heart and circulatory system that can cause serious health problems. It also increases your risk of cardiovascular disease, diabetes and high blood pressure.

- Drinking too much alcohol

  Regular, heavy use of alcohol can cause many health problems, including heart failure, stroke and an irregular heartbeat (arrhythmia). It can cause your blood pressure to increase dramatically and can also increase your risk of cancer, obesity, alcoholism, suicide and accidents.

Potential contributing risk factors

In addition to the known risk factors, there are others that may contribute to high blood pressure, although how is still uncertain. These potential contributing risk factors include:

- Smoking and tobacco use

  Using tobacco can cause your blood pressure to temporarily increase and can contribute to damaged arteries. Secondhand smoke, exposure to other people's smoke, also increases the risk of heart disease for nonsmokers.

- Stress

  Stress is not necessarily a bad thing in and of itself. But too much stress may contribute to increased blood pressure. Also, too much stress can encourage behaviors that increase blood pressure, such as poor diet, physical inactivity, and using tobacco or drinking alcohol more than usual.

Secondary hypertension

A majority of people with high blood pressure have Primary hypertension, high blood pressure that has no identifiable cause.

A small number of high blood pressure cases are secondary hypertension — high blood pressure that's caused by another medical condition that was present first.

Examples include pregnancy-induced hypertension (PIH), certain heart defects, kidney disorders, and sleep apnea. Most often, if the condition causing the high blood pressure can be

resolved, the individual's blood pressure will normalize as well.

Treatment of Hypertension

There are many drugs with different modes of action that are available for treating patients with hypertension.

1. Diuretics

   Diuretics are medications that act on kidneys to help the body eliminate sodium and water, reducing blood volume.

   Diuretics are often the first, but not the only, choice in high blood pressure medications. Diuretics include hydrochlorothiazide, chlorthalidone, frusemide etc.

   A common side effect of diuretics is increased urination.

2. Beta blockers

   These medications cause the heart to beat slower and with less force thereby reducing the workload on the heart.

   Beta blockers include propranolol, atenolol etc.

3. Angiotensin-converting enzyme (ACE) inhibitors

   These medications — such as lisinopril, ramipril, captopril and others — help relax blood vessels by blocking the formation of angiotensin II that constricts blood vessels.

   People with chronic kidney disease may benefit from having an ACE inhibitor as one of their medications.

4. Angiotensin II receptor blockers (ARBs)

   These medications help relax blood vessels by blocking the action, not the formation, of angiotensin II that narrows blood vessels.

   ARBs include , irbesartan, candesartan, losartan etc.

   People with chronic kidney disease may benefit also by having an ARB as one of their medications.

5. Calcium channel blockers

   These medications — including nifedipine, amlodipine, diltiazem etc.— help relax the muscles of blood vessels. Some may slow the heart rate.

   Calcium channel blockers may work better for older people than do ACE inhibitors alone.

6. Alpha blockers

   These medications reduce nerve impulses to blood vessels thereby reducing the effects of natural chemicals e.g. norepinephrine that narrow blood vessels. Alpha blockers include doxazosin, prazosin etc.

7. Alpha-beta blockers

   In addition to reducing nerve impulses to blood vessels, alpha-beta blockers slow the heart rate to reduce the amount of blood that must be pumped through the vessels. Alpha-beta blockers include carvedilol and labetalol.

8. Central-acting agents

   These medications prevent the brain from signaling nervous system pathways to increase the heart rate and constrict blood vessels.

   Examples include clonidine and methyldopa.

9. Vasodilators

   These medications, including hydralazine and minoxidil, work directly on the muscles in the walls of the arteries, preventing the muscles from contracting and arteries from narrowing.

These lifestyle changes can improve the 'Quality of Life' in hypertension:

- Quit smoking.
- Follow a healthy diet. Eat a variety of fruits, vegetables, and whole grains, plus lean meat, poultry, fish and low-fat/fat-free milk. Diet should be low in fat, cholesterol, sodium and sugar.
- Watch your weight.

- Stay active. Incorporate physical activity such as walking into your lifestyle. Avoid straining or lifting heavy weights. Rest when you need to.
- Get support for the anxiety and stress of living with hypertension. Talk with your healthcare team, or ask for a referral to a counselor.

Managing Blood Pressure with a Heart-Healthy Diet

Eating a heart-healthy diet is important for managing your blood pressure and reducing your risk of heart attack, stroke and other health threats.

Aim to eat a diet that's rich in:

- Fruits
- Vegetables
- Whole-grains
- Low-fat dairy products
- Skinless poultry and fish
- Nuts and legumes

Limit:

- Saturated and trans fats
- Sodium
- Red meat (if you do eat red meat, compare labels and select the leanest cuts available)
- Sweets and sugar-sweetened beverages

Lipid disorders: Understanding the Pathophysiology and Principles of Management

Introduction

Fats are an important constituent of our diet. The use of fats by the body for energy is as important as the use of carbohydrates for this purpose. Besides being a rich source of calories (9 kcal/g), fats provide us with vitamins like vitamins A, D, E and K and also maintain the normalcy of cell membranes & nervous tissue.

Lipid transport in the blood circulation:

Lipoproteins are complexes that carry lipids, particularly, cholesterol and triglycerides in the plasma.

Lipoproteins are complexes made up of hundreds of lipid and protein molecules. The major lipids in the lipoproteins are cholesterol, triglycerides and phospholipids. The proteins, called apolipoproteins, occupy the surface of lipoproteins and play crucial roles in lipid transport and lipoprotein metabolism. The major classes of lipoproteins based on their densities are

1. Chylomicrons
2. Very low density lipoproteins (VLDL)
3. Intermediate density lipoproteins (IDL)
4. Low density lipoproteins (LDL)
5. High density lipoproteins (HDL)

Coronary heart disease is attributable to a large extent to abnormalities in the levels and metabolism of these different plasma lipids and lipoproteins.

A number of studies have shown that lifestyle changes and drug treatment to lower cholesterol (LDL Cholesterol) reduce fatal and nonfatal heart attacks.

Metabolic Fate of Dietary Lipids

As you know, the dietary triglycerides are broken down into fatty acids and monoglycerides during digestion. Then, while passing through the intestinal mucosal cells, they are

resynthesized into new molecules of triglycerides that form minute droplets called chylomicrons.

The dietary triglycerides and cholesterol form the core of these newly synthesized chylomicrons. The triglycerides account for 80 to 95% of the composition of the chylomicrons. The chylomicrons ultimately reach the systemic circulation.

In the plasma, the apolipoprotein C II (apo C II) is transferred from HDL to chylomicrons. Apo C II activates the enzyme lipoprotein lipase (LPL) in fat and muscle tissue leading to the hydrolysis of triglycerides and formation of free fatty acids. Once the triglyceride core of chylomicron has been hydrolyzed, the apo C proteins return back to HDL.

The remaining portion of chylomicron (containing cholesterol) binds to the LDL receptors in the liver.

Thus, dietary triglyceride is made available to the cells of fatty (adipose) tissue & muscle tissue and dietary cholesterol is taken up by the liver, where it can serve various purposes, such as -

- Formation of bile acids.
- Incorporation into cell membranes
- Resecretion of lipoprotein cholesterol back into the blood circulation.
- Excretion in the bile.

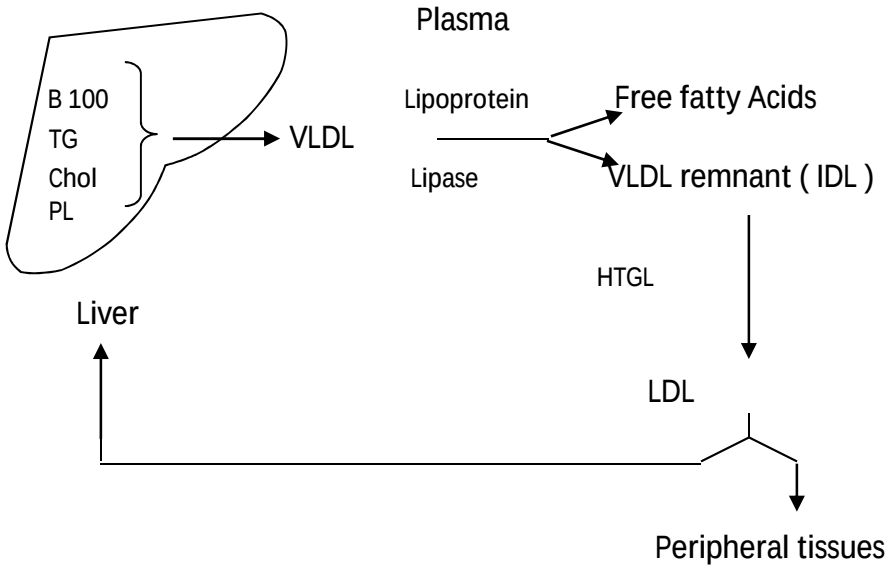
Transport of Endogenous Lipids

The endogenous lipid transport systems carry the lipids from the liver to peripheral tissues and from peripheral tissues back to liver.

The Apolipoprotein B 100 system is involved in the transport of VLDL, IDL and LDL.

In the liver, triglycerides and cholesterol are packaged together with apo B 100 and phospholipids into VLDL and secreted into plasma. In the plasma, VLDL particles are converted to IDL due to the breakdown of triglycerides by the enzyme lipoprotein lipase.

IDL can give rise to LDL under the influence of another enzyme called hepatic triglyceride lipase.



Note : TG – triglycerides
Chol – cholesterol
PL – phospholipids
HTGL – hepatic triglyceride lipase

Apolipoprotein B 100 system

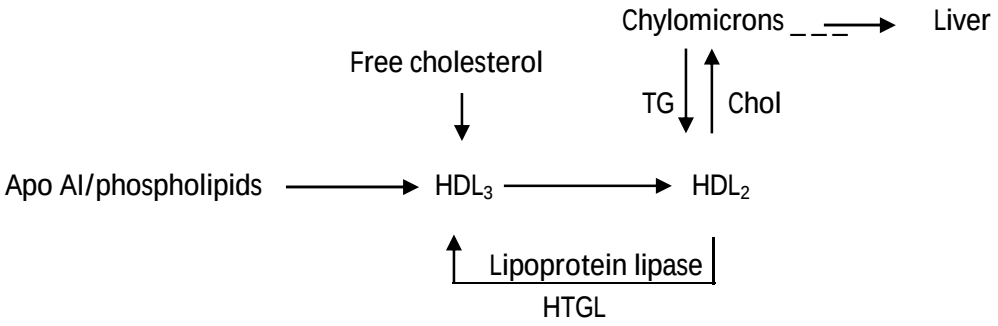
The LDL in plasma is taken up by the LDL receptors in cells in liver as well as peripheral tissues like adrenal glands and gonads (testes or ovaries), the latter utilizing it for synthesis of steroid hormones.

The apolipoprotein A I system is involved in HDL cholesterol metabolism. HDL particles are formed in the plasma by coming together of various apo A proteins and phospholipids.

The small, cholesterol-poor HDL particles are referred to as HDL_3. Free cholesterol is transferred from cell membranes to HDL_3 resulting in formation of HDL_2.

The HDL_2 particles can then exchange the cholesterol for triglycerides from chylomicrons and VLDL.

Thus, cholesterol is picked up from peripheral tissues and brought back to liver. The triglycerides that are transferred to HDL are broken down by lipoprotein lipase and/or hepatic triglyceride lipase. As a result, HDL_2 is converted back into HDL_3.



Apolipoprotein A I system

Disorders related to Dyslipidaemias (abnormal plasma lipid levels)

A. Role Of Lipoproteins In Atherosclerosis.

Abnormal transport and metabolism of chylomicrons may lead to atherosclerosis. The higher the levels and the slower the removal of chylomicrons (or their remnants) in plasma, greater is their migration into vessel wall. The macrophage cells in the vessel wall get transformed into 'foam cells' – the earliest change in the development of atherosclerotic plaque.

Increased plasma levels of LDL cholesterol are an important risk factor for atherosclerosis. In addition to inducing foam cell formation, LDL stimulates secretion of growth factors by endothelial cells, macrophages and smooth muscle cells in the blood vessel. It also leads to proliferation of smooth-muscle cells and increased secretion of collagen.

The fibrous plaque consists of numerous proliferated smooth muscle cells together with macrophages and variable numbers of lymphocytes. The dense connective tissue matrix covers a deeper collection of smooth muscle cells and macrophages, both of which may contain numerous lipid droplets and take the form of 'foam cells'.

On the other hand, HDL-mediated transport of cholesterol from periphery to liver is thought to be the primary mechanism by which HDL protects against atherosclerosis. Other effects of HDL could be removal of cholesterol from the foam cells in atherosclerotic patch or protecting LDL against oxidative changes.

The exact role of VLDL and IDL in atherogenesis is less clear.

B. Hyperlipoproteinemias

The plasma levels of cholesterol or triglycerides or both could be elevated leading to hyperlipoproteinaemia.

- Hypercholesterolemia

  Elevated levels of plasma total cholesterol (> 275 mg/dL) with normal levels of triglycerides are almost always due to an increase in LDL cholesterol concentrations in plasma. [Marked elevation of HDL cholesterol resulting in hypercholesterolemia is rare].

  Elevated LDL cholesterol levels can be caused by genetic defects such as mutation in gene for LDL receptor (Familial hypercholesterolemia) or reduced affinity (attraction) of LDL for LDL receptor (Familial defective Apo B 100). These patients develop xanthomas - yellowish deposits of cholesterol on elbows or buttocks or xanthelasma – deposits of cholesterol on the eyelids. Most patients develop severe atherosclerosis and coronary heart disease [CHD] by early or middle age.

  In polygenic hypercholesterolemia interaction of multiple genetic and environmental factors contribute to hypercholesterolemia. Both overproduction and reduced breakdown of LDL are important in this condition, which is also affected by consumption of saturated fats and cholesterol, age, and physical activity. These patients are at increased risk of atherosclerosis. Xanthomas are not usually present.

- Hypertriglyceridemia

  Several studies have confirmed that plasma triglyceride levels are predictors of coronary heart disease.

  Elevations in plasma triglycerides are usually associated with increased secretion of VLDL triglycerides and low HDL cholesterol levels.

  Obesity, excessive consumption of sugars and saturated fats, lack of physical activity, alcohol consumption, and insulin resistance are commonly associated with hypertriglyceridaemia.

- Hypercholesterolaemia with Hypertriglyceridemia

  Concomitant hypercholesterolaemia with hypertriglyceridemia occurs in two disorders – familial combined hyperlipidemia (FCHL) and dysbetalipoproteinaemia.

  Familial combined hyperlipidaemia – FCHL is associated with increased secretion of VLDL and variations in the genes that regulate the metabolism of VLDL. FCHL is reported to be the most common familial lipid disorder in survivors of myocardial infarction. There is an increased risk of atherosclerosis in patients with FCHL; however, they do not have xanthomas or xanthelasma.

  Dysbetalipoproteinaemia is a rare disorder in which the levels of VLDL triglycerides and VLDL cholesterol are elevated, while the LDL and HDL cholesterol levels are low. These patients have xanthomas and deposits of cholesterol in the palmar creases, which appear as yellow – orange lines. The risk for atherosclerosis and its complications is increased, with onset in the 4^{th} and 5^{th} decade of life.

C. Special situations.

1. Diabetes mellitus – Diabetes can affect lipid and lipoprotein metabolism through several mechanisms.

   In type II Diabetes mellitus, insulin resistance and obesity combine to cause mild to moderate hypertriglyceridaemia and low HDL cholesterol levels. This pattern of abnormal lipid levels is due to overproduction of VLDL.

   Unlike in Type I diabetes, treatment of type II diabetes and weight reduction do not completely correct the lipid abnormalities. It is recommended that these patients should receive therapy with lipid-lowering drugs [see below] to achieve a treatment goal of reduction in LDL levels below 100 mg/dL. Drug therapy for hyperlipidaemia should not be delayed in patients with type II diabetes as they are at increased risk for coronary heart Disease.

2. Hypothyroidism – Hypothyroidism is second only to diabetes mellitus as a cause of secondary hyperlipidaemia. The levels of LDL cholesterol can be elevated and hypertriglyceridaemia can occur if obesity is present. However, correction of hypothyroidism reverses the lipid abnormalities.

3. Other – kidney and liver disease as well as alcohol consumption can cause abnormal lipid levels such as hypertriglyceridaemia and elevated LDL and/or VLDL levels.

Diagnosis of Dyslipidaemias

The lipoprotein analysis should assess VLDL, LDL and HDL levels. The relationship between these lipids is explained by the following equation

LDL Cholesterol = Total Cholesterol – (HDL + triglycerides / 5)

where VLDL cholesterol is estimated as triglycerides / 5 . (This equation cannot be used if triglyceride levels are > 400mg./dL or in patients with dysbetalipoproteinaemia where the ratio of triglycerides to cholesterol in VLDL is much less than 5).

Because plasma triglyceride levels rise & both HDL and LDL cholesterol levels fall modestly after a fat-containing meal, it is preferable to measure plasma lipids after a 12-hour fast.

Some experts advocate the use of total cholesterol / HDL ratios as a better assessment of individual risk.

Management of Dyslipidaemia :

The principles of management of dyslipidaemia involve both dietary changes and drug therapy.

- Hypercholesterolaemia

  The aim of treating hypercholesterolaemia is to reduce the risk of atherosclerosis and its complications. [the term 'Primary prevention' is used to differentiate from 'Secondary prevention' where the drug therapy is started after complications of atherosclerosis have occurred].

  A starting point for treatment involves counseling the patient to modify diet, exercise, smoking and other factors that increase the risk of coronary heart disease such as:-

  1. Family history of CHD
  2. Hypertension
  3. Cigarette Smoking
  4. Diabetes mellitus
  5. Low HDL levels and
  6. Age

Diet:

Individuals with hyperlipidaemia should be encouraged to eat a diet lower in cholesterol and saturated fats.

In general, whole milk dairy products, egg yolks, meats, palm oil and coconut oil should be replaced with fresh fruits and vegetables, complex carbohydrates (whole-grain products), and low-fat dairy products.

Drug therapy is instituted when the LDL cholesterol level is > 200 mg/dL in patients without CHD / risk factors or > 139 mg/dL in patients with CHD.

a) HMG-CoA reductase inhibitors ('statins') – They include lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin. These drugs inhibit the conversion of HMG-CoA to mevalonate – a step in biosynthesis of cholesterol in liver. This causes an increase in LDL receptor levels in hepatocytes (liver cells) leading to increased clearance of LDL-cholesterol from blood circulation.

   At usual doses, HMG-CoA reductase inhibitors reduce total cholesterol by 20 to 30%, LDL-cholesterol by 25 to 40% and triglycerides by 10 to 20% HDL cholesterol levels rise by 5 to 10%.

b) Niacin – The mechanism of action of niacin not fully understood, but it appears to inhibit the secretion of lipoproteins (containing apo B 100) from the liver. Niacin decreases both total and LDL cholesterol by about 25 to 25% reduces VLDL levels by 25 to 35% and raises HDL cholesterol levels by as much as 15 to 25%.

c) Bile acid – binding resins – Cholestyramine (and colestipol) have been in use as lipid – lowering agents for more than 2 decades. These drugs interfere with reabsorption of bile acids in the intestine. This leads to an increase in bile acid synthesis as well as increase in LDL receptors in hepatocytes.

   These agents reduce total cholesterol by about 15 to 25% and LDL cholesterol by 20 to 35%.

   (A limitation of bile acid – binding resins is their tendency to raise triglyceride levels; they should not be given to patients with hypertriglyceridaemia.)

Combination therapy with reductase inhibitors ('statins') and bile acid binding resins or niacin and bile acid binding resins are useful for the treatment of severe elevations of LDL cholesterol and for patients with CHD. The former combination is also useful in patients with combined hypercholesterolaemia and hypertriglyceridaemia.

d) Fibric acids – drugs like Gemfibrozil and Fenofibrate stimulate Lipoprotein lipase activity and increase the production of apolipoprotein. A1. Further, these drugs LPL – induced lipolysis and reduce triglyceride levels in plasma.

Treatment with fibrates leads to 25 to 40% reduction in plasma triglyceride levels and 5 to 15% increase in HDL levels.

- Hypertriglyceridaemia.

The evidence to show that treatment to reduce plasma triglyceride levels leads to long-term benefits is not as strong as that for treatment of hypercholesterolemia.

In patients with isolated elevations of triglyceride levels lifestyle modification is recommended. Weight reduction is important if obesity is present. Replacing some of the saturated fat in diet with monounsaturated fat (which does not increase LDL cholesterol) is also useful.

Drug therapy for hypertriglyceridaemia is indicated when plasma triglycerides rise above 500mg/dL or in patients with risk factors (see above) for coronary heart disease when triglyceride levels rise are > 200mg/dl.

Niacin, Fibrates and Fish oils (which contain omega-3 fatty acids) are effective in lowering plasma triglyceride levels.

To summarize,

- Fats are an important constituent of our diet.
- Lipoproteins are complexes that carry lipids, particularly, cholesterol and triglycerides in the plasma.
- They are made up of hundreds of lipid and protein molecules.

- Proteins, called apolipoproteins, occupy the surface of lipoproteins and play crucial roles in lipid transport and lipoprotein metabolism.

- The major classes of lipoproteins based on their densities are :

    1. Chylomicrons
    2. Very low density lipoproteins (VLDL)
    3. Intermediate density lipoproteins (IDL)
    4. Low density lipoproteins (LDL)
    5. High density lipoproteins (HDL)

- The dietary triglycerides are broken down into fatty acids and monoglycerides during digestion. Then, while passing through the intestinal mucosal cells, they are resynthesized into new molecules of triglycerides that form minute droplets called chylomicrons.

- The enzyme lipoprotein lipase (LPL) in fat and muscle tissue hydrolyses triglycerides leading to formation of free fatty acids. Once the triglyceride core of chylomicron has been hydrolyzed, the remaining portion of chylomicron (containing cholesterol) binds to the LDL receptors in the liver.

- The endogenous lipid transport systems carry the lipids from the liver to peripheral tissues and from peripheral tissues back to liver.

  The Apolipoprotein B 100 system is involved in the transport of VLDL, IDL and LDL.

  The apolipoprotein A I system is involved in HDL cholesterol metabolism and ensures that cholesterol is picked up from peripheral tissues and brought back to liver.

- Dyslipidaemia indicates abnormal plasma lipid levels.

- Increased plasma levels of LDL cholesterol are an important risk factor for atherosclerosis.

- On the other hand, HDL-mediated transport of cholesterol from periphery to liver is thought to be the primary mechanism by which HDL protects against atherosclerosis.

- The plasma levels of cholesterol or triglycerides or both could be elevated leading to hyperlipidaemia.

- Several studies have confirmed that plasma triglyceride levels are predictors of coronary heart disease.

- In type II Diabetes mellitus, insulin resistance and obesity combine to cause mild to moderate hypertriglyceridaemia and low HDL cholesterol levels.

- Drug therapy for hyperlipidaemia should not be delayed in patients with type II diabetes as they are at increased risk for coronary heart Disease.

- The principles of management of dyslipidaemia involve both dietary changes and drug therapy.

- In general, whole milk dairy products, egg yolks, meats, palm oil and coconut oil should be replaced with fresh fruits and vegetables, complex carbohydrates (whole-grain products), and low-fat dairy products.

- Drug therapy with HMG-CoA reductase inhibitors ('statins'), Niacin, Bile acid – binding resins, or fibrates should be instituted when the LDL cholesterol level is > 200 mg/dL in patients without CHD / risk factors or > 139 mg/dL in patients with CHD.

- Drug therapy for hypertriglyceridaemia is indicated when plasma triglycerides rise above 500mg/dL or in patients with risk factors (see above) for coronary heart disease when triglyceride levels rise are > 200mg/dl.

  Niacin, Fibrates and Fish oils (which contain omega-3 fatty acids) are effective in lowering plasma triglyceride levels.

We hope that this brief overview of lipid disorders will help you to understand the basic concepts in their causation and principles of managing them with dietary changes as well as drug therapy.

Diabetes mellitus - Review of the Disease and Principles of Management

Introduction:

Diabetes mellitus is characterized by hyperglycaemia - high levels of glucose in blood. This is usually due to inability of pancreas (specifically the β cells in islets of Langerhans) to produce enough insulin, a hormone that helps the uptake of glucose and its utilization by cells thereby keeping the blood glucose levels within normal range (80 - 140 mg/dL).

Besides the impaired metabolism of glucose, diabetes involves the development of vascular, renal, ocular, and neurological complications in late stage.

It is observed that Indians are showing a growing risk for development of diabetes - a possible offshoot of changing lifestyles with less physical activity and Westernized food habits.

Types of diabetes:

The two major types of diabetes mellitus are Type I and Type II diabetes.

Type I diabetes mellitus -

In this type, the patients have little or no insulin secretion from pancreas. This results probably from an autoimmune destruction of β cells. The patients with Type I diabetes are dependent on exogenous insulin for glycaemic control and prevention of late complications. This was formerly known as insulin-dependent diabetes mellitus (IDDM) or 'juvenile-onset diabetes'.

Commonly, this type of diabetes appears suddenly in previously healthy children or young adults. There are symptoms such as polyuria i.e. increased urinary output, polydipsia i.e. excessive intake of water, polyphagia i.e. excessive ingestion of food, and weight loss. In this condition, insulin therapy is essential to restore the metabolism to normal level.

It should be noted that Type I diabetes is less common as compared to Type II diabetes.

Type II diabetes mellitus -

Patients with this type of diabetes retain the capacity to secrete insulin to some extent. However, insulin levels are low relative to the glucose levels present in the blood. Further, there may be a resistance to the actions of insulin in the target tissues. Since, under usual circumstances these patients are not dependent on exogenous insulin for their immediate survival, this was formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or 'adult-onset diabetes'.

Type II diabetes typically appears after the age of 40 years. It has a high degree of genetic influence and is associated with obesity. The classic symptoms like those seen in Type I or insulin-dependent diabetes mellitus (IDDM) are often missing, and the disease may become evident only by the development of complications mentioned above.

There are other specific types of diabetes related to a specific disease, drug/s, or conditions (e.g. gestational diabetes during pregnancy). However, from our point of view, we have to focus on the more prevalent Type II diabetes (or NIDDM) which is treated with oral hypoglycaemic agents for controlling blood glucose levels within normal range.

Let us now try to understand the role of insulin in control of glucose metabolism and the pathogenesis of Type II diabetes in more details.

Metabolic Effects of Insulin :

The concentration of glucose is a key regulator of insulin secretion. Normally, when blood glucose rises above the fasting levels of 75 mg to 100 mg/dL, beta cells in the pancreas secrete insulin. On the other hand, when blood glucose levels decline even slightly (e.g. to 70 mg/dL), the secretion of insulin promptly diminishes.

Insulin acts on insulin-sensitive tissues viz. liver, muscle, & fat and promotes cellular uptake of glucose.

After an overnight fast, low basal levels of insulin diminish glucose uptake in insulin-sensitive tissues. Most glucose uptake occurs in other tissues, primarily the brain. The blood glucose levels are maintained by the release of glucose by the liver (by breakdown of glycogen as well as endogenous glucose synthesis from glycerol, fatty acids etc.) at the rate of 7 to 10 g/hr matching the need of consuming tissues.

In a fed state, ingestion of food stimulates secretion of insulin. Insulin triggers of mechanisms to maintain the glucose levels within normal range, such as –

a] suppression of endogenous glucose synthesis,
b] stimulation of glucose uptake in liver and formation of glycogen (storage form of glucose,
c] stimulation of glucose uptake by peripheral tissues, mainly muscle & fat.

(The rise in insulin that accompanies the consumption of meals also facilitates protein and fat storage. In muscle tissue, insulin inhibits the breakdown of protein and stimulates uptake of amino acids & synthesis of new protein. Similarly, in fatty tissue the action of insulin accelerates formation of triglycerides & reduces breakdown of stored triglycerides).

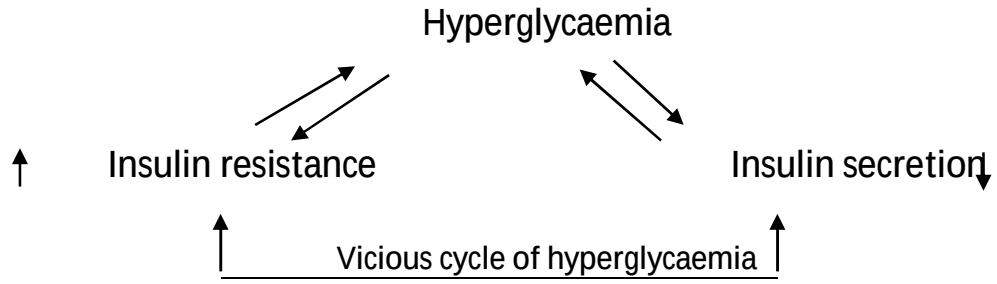
Pathogenesis of Type II diabetes :

Diabetes is characterized by marked fasting & postprandial (after a meal) hyperglycaemia.

In type II diabetes, there is a delayed insulin secretion and insulin resistance in the tissues like liver & muscles. These two together impair the suppression of hepatic glucose production and the ability of liver & muscles to store glucose as glycogen, resulting in hyperglycaemia.

In addition, glucose uptake in peripheral tissues is impaired due to lower insulin secretion and the development of resistance to the action of insulin.

Hyperglycaemia impairs the beta cell response to glucose resulting in reduced insulin secretion and promotes insulin resistance. Thus there is a vicious cycle initiated by which hyperglycaemia leads to more severe hyperglycaemia.



It remains uncertain whether insulin resistance or defective insulin secretion is the primary factor leading to type II diabetes.

Chronic Complications associated with diabetes

When the hyperglycaemia is not controlled for several years, the complications develop that affect a variety of organs and tissues. Glucose levels are increased in non-insulin-sensitive tissues resulting in activation of other metabolic pathways.

Vascular changes accelerating atherosclerosis because of hyperglycaemia lead to symptomatic hypertension, coronary artery disease, peripheral vascular disease that may result in tissue ischaemia & gangrene.

Involvement of retina of the eye is characterized by increased capillary permeability, haemorrhages and oedema. Later the retinal perfusion is decreased causing microinfarcts. Retinopathy may progress to macular oedema leading to blindness (macula is the region of greatest visual acuity in retina). The other complications resulting in blindness in a diabetic patient include cataract, retinal haemorrhage, retinal detachment and intravitreous haemorrhage.

Diabetic polyneuropathy causes sensory changes in the hands and legs such as numbness, tingling and sometimes pain. Foot ulcers develop due to impaired sensory perception of repeated trauma from ill-fitting footwear or walking barefoot. Individual nerves such as a cranial nerve supplying the eye or femoral nerve may be affected as mononeuropathy. Functioning of the autonomic nervous system may be affected leading to impotence, delayed gastric emptying, & impaired bladder function.

Renal function gradually reduces due to diabetic nephropathy. Presence of albumin in urine i.e. albuminuria is the first sign of decreasing glomerular functioning with ultimate development of end-stage renal disease.

There is an increased risk of infection due to fungi and bacteria since the cellular immunity is decreased by the hyperglycaemia as well as circulatory disturbances (diabetic angiopathy). Infections of skin, oral and vaginal candidiasis are most common infections seen in a diabetic.

Principles of Management:

Management of diabetes involves changes in lifestyle as well as pharmacological therapy with insulin or oral hypoglycaemic drugs. In type I diabetes, the primary focus is to replace insulin while in type II diabetes oral antidiabetic agents are employed besides attention to diet and regular exercise.

Although therapeutic strategies for the two forms of diabetes differ, the short- and long-term goals of management are identical.

Goals of Management

Period	Goals
Short - term	Restore metabolic control to near-normal. Improve sense of well-being.
Long-term	Minimize risk of diabetic complications - Accelerated atherosclerosis - Microangiopathy (retinopathy, nephropathy) - Neuropathy

Dietary changes and regular exercise are important non-pharmacological measures in the management of diabetes.

<u>Diet recommendations :</u>

- Ø Weight reduction in obese patients & maintenance of appropriate weight
- Ø Carbohydrates should provide 45 - 60 % of daily caloric intake depending on severity of diabetes
- Ø Restriction of saturated fat to < 10 % of daily caloric intake
- Ø Increased use of monounsaturated fats (e.g. olive oil, peanut oil)
- Ø Decreased cholesterol intake to < 200 mg/d
- Ø Sodium restriction in patients with / prone to hypertension.

Exercise recommendations :

- Aerobic exercise preferred, avoid lifting weights, exercise that involves straining or raises blood pressure
- Intensity to be decided by age and cardiovascular state of the patient
- Duration - 20 to 30 minutes, preceded & followed by stretching / warming up and cooling down exercises for 5 to 10 minutes
- Frequency - 3 to 4 days every week.

Oral hypoglycaemic agents :

Oral agents are favoured as first-line antidiabetic drugs in type II diabetic patients with mild to moderate hyperglycaemia who are older and obese. In patients with severe hyperglycaemia also, after the glucose levels have been stabilized with insulin initially, the patients are treated with oral agents.

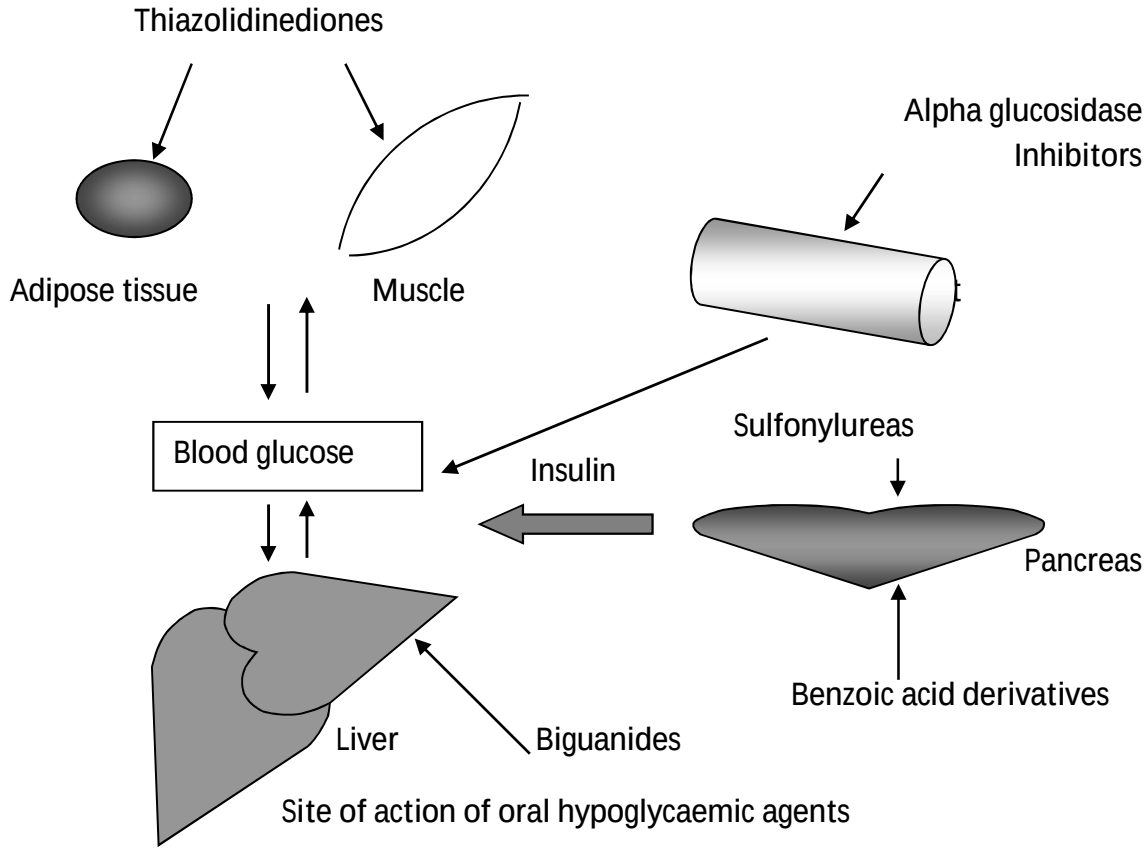
Several new classes of oral glucose-lowering agents have become available in the recent times (see table)

Oral hypoglycaemic agents available

Class & agent	Duration of action (hr)	Total daily dose (mg / d)	Doses per day
Sulfonylureas			
First generation			
Chlorpropamide	>24	100 - 750	1
Tolbutamide	6 - 12	500 - 3000	2 - 3
Second generation			
Glimepiride	24	1 - 8	1
Glibenclamide	Up to 24	1.25 - 20	1 - 2
Gliclazide	>12	40 - 320	1 - 2
Glipizide	Up to 24	2.5 - 40	1 - 2

Biguanide Metformin	Up to 24	500 - 2550	2 - 3
Thiazolidinedione Pioglitazone Rosiglitazone	 24 Up to 24	 15 - 45 4 - 8	 1 1 - 2
a-glucosidase inhibitor Acarbose	 N/A	 75 - 300	 3 (with each meal)
Benzoic acid derivative Repaglinide	 Short	 1 - 16	 3 (with each meal)

Various oral agents have actions at different sites by which they help in controlling the blood glucose levels. This is illustrated in the following figure:



Site of action of oral hypoglycaemic agents

Let us briefly study the role of individual agents in maintaining glycaemic control in the following discussion.

Sulfonylureas:

These drugs enhance insulin secretion by binding with the receptors on the surface of beta cells in the pancreas. The insulin is responsible for lowering the blood glucose levels. The insulin resistance commonly diminishes due to reversal of hyperglycaemia.

Biguanides:

Biguanides, unlike sulfonylureas, act mainly by reducing hepatic glucose production. The exact cellular mechanism is however uncertain.

Benzoic acid derivatives:

Repaglinide, a benzoic acid derivative, interacts with a different portion of the sulfonylurea receptor on the beta cell surface to stimulate insulin secretion.

Thiazolidinediones:

These drugs reduce insulin resistance by activating a receptor, namely, peroxisome proliferator-activated receptor γ, which regulates several insulin-responsive genes. The biologic effect is stimulation of peripheral glucose metabolism. However, there is little effect on hepatic glucose production.

α - glucosidase inhibitors:

α - glucosidase is an intestinal enzyme that breaks down complex sugars into monosaccharides. α - glucosidase inhibitors, such as acarbose, inhibit or delay the absorption of carbohydrates like starch, sucrose etc. thereby lowering the blood glucose levels.

The final decision regarding therapy for type II diabetes will be influenced by various factors viz. severity of the fasting hyperglycaemia, presence of symptoms, obesity, patient's age, and other coexisting diseases.

The dosage of the selected agent/s should be individualized based on results of blood glucose monitoring.

If one is able to diagnose the disease early and control the hyperglycaemia adequately over a period of time through diet, exercise, and drug/s, the chances of developing late complications of diabetes can be substantially lower.

CNS Disorders

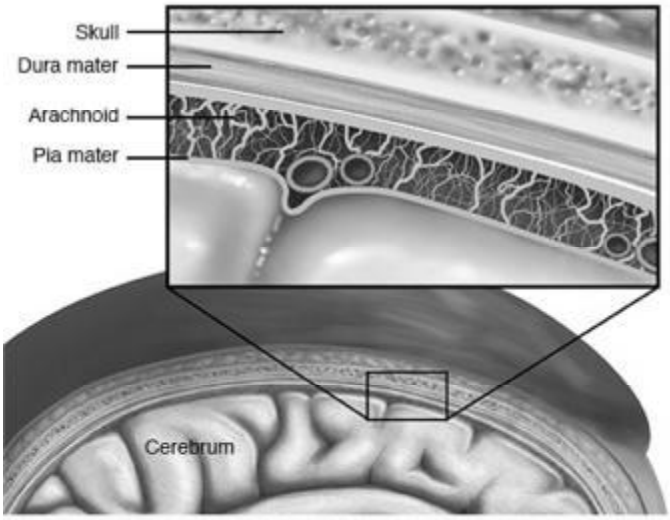
Meningitis

Meningitis is an inflammation of the membranes (meninges) surrounding the brain and spinal cord.

The swelling from meningitis typically triggers symptoms such as headache, fever and a stiff neck.

Other signs and symptoms in anyone older than the age of 2 include:

- Headache with nausea or vomiting
- Confusion or difficulty concentrating
- Seizures ('fits' or 'convulsions')
- Sleepiness or difficulty waking
- Sensitivity to light
- Skin rash (sometimes, such as in meningococcal meningitis)



Causes

Viral infections are the most common cause of meningitis, followed by bacterial infections and, rarely, fungal infections. Because bacterial infections can be life-threatening, identifying the cause is essential.

Bacteria that enter the bloodstream and travel to the brain and spinal cord can cause acute bacterial meningitis. It can also occur when bacteria directly invade the meninges. This may be caused by an ear or sinus infection, a skull fracture, or, rarely, after some surgeries.

Several strains of bacteria can cause acute bacterial meningitis, most commonly:

- Streptococcus pneumoniae (pneumococcus)
- Neisseria meningitidis (meningococcus)
- Haemophilus influenzae
- Listeria monocytogenes

Treatment

The treatment depends on the type of meningitis.

Acute bacterial meningitis must be treated immediately with intravenous antibiotics and, more recently, corticosteroids. This helps to ensure recovery and reduce the risk of complications, such as brain swelling and seizures.

The doctor may drain any infected sinuses or mastoids — the bones behind the outer ear that connect to the middle ear.

Encephalitis

Encephalitis is inflammation of the brain. There are several causes, but the most common is viral infection.

Encephalitis often causes only mild flu-like signs and symptoms or no symptoms at all.

Most people with viral encephalitis have mild flu-like symptoms, such as:

- Headache
- Fever
- Aches in muscles or joints
- Fatigue or weakness

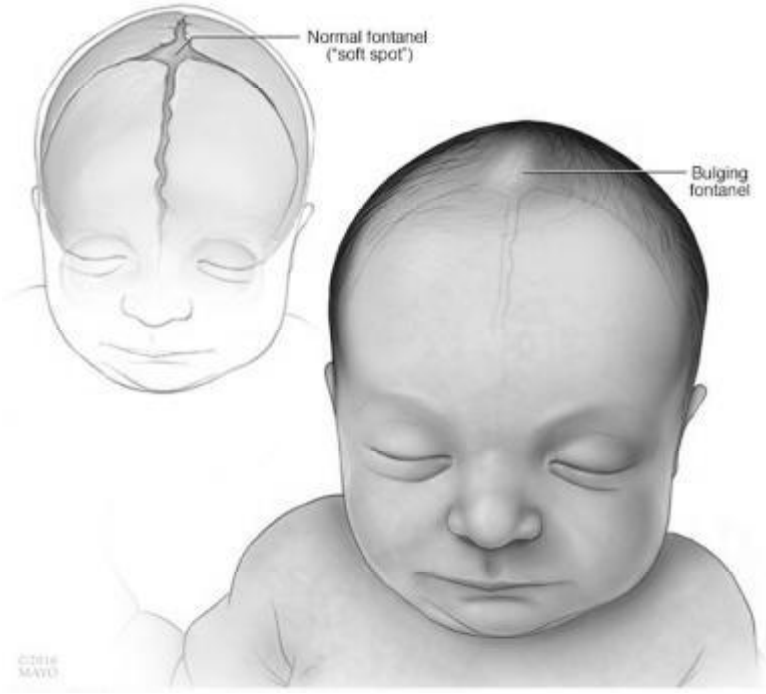
Sometimes the signs and symptoms are more severe, and might include:

- Confusion, agitation or hallucinations
- Seizures

- Loss of sensation or paralysis in certain areas of the face or body
- Muscle weakness
- Problems with speech or hearing
- Loss of consciousness

In infants and young children, signs and symptoms might also include:

- Bulging in the soft spots (fontanels) of an infant's skull
- Nausea and vomiting
- Body stiffness
- Poor feeding or not waking for a feeding
- Irritability



There are two main types of encephalitis:

- Primary encephalitis. This condition occurs when a virus or other agent directly infects the brain.

- Secondary encephalitis. This condition results from a faulty immune system reaction to an infection elsewhere in the body. Instead of attacking only the cells causing the infection, the immune system also mistakenly attacks healthy cells in the brain.

Also known as post-infection encephalitis, secondary encephalitis often occurs two to three weeks after the initial infection.

The viruses that can cause encephalitis include:

- Herpes simplex virus (HSV)

  Both HSV type 1 — associated with cold sores and fever blisters around the mouth — and HSV type 2 — associated with genital herpes — can cause encephalitis. Encephalitis caused by HSV type 1 is rare but can result in significant brain damage or death.

- Other herpes viruses

  These include the Epstein-Barr virus, which commonly causes infectious mononucleosis, and the varicella-zoster virus, which commonly causes chickenpox and shingles.

- Enteroviruses

  These viruses include the poliovirus and the coxsackievirus, which usually cause an illness with flu-like symptoms, eye inflammation and abdominal pain.

- Mosquito-borne viruses

  These viruses can cause infections such as Chikungunya, West Nile, western equine and eastern equine encephalitis. Symptoms of an infection might appear within a few days to a couple of weeks after exposure to a mosquito-borne virus.

- Tick-borne viruses

  The Powassan virus is carried by ticks and causes encephalitis. Symptoms usually appear about a week after a bite from an infected tick.

- Rabies virus

  Infection with the rabies virus, which is usually transmitted by a bite from an infected animal, causes a rapid progression to encephalitis once symptoms begin.

- Childhood infections

  Common childhood infections — such as measles (rubeola), mumps and German measles (rubella) — used to be fairly common causes of secondary encephalitis.

Treatment

Treatment for mild encephalitis usually consists of:

- Bed rest
- Plenty of fluids
- Anti-inflammatory drugs — such as acetaminophen, ibuprofen, and naproxen sodium to relieve headaches and fever

Antiviral drugs

Encephalitis caused by certain viruses usually requires antiviral treatment.

Antiviral medications commonly used to treat encephalitis include:

- Acyclovir
- Ganciclovir
- Foscarnet

Some viruses, such as insect-borne viruses, don't respond to these treatments. But because the specific virus may not be identified immediately or at all, doctors often recommend immediate treatment with acyclovir. Acyclovir can be effective against HSV, which can result in significant complications when not treated promptly.

Antiviral medications are generally well-tolerated. Rarely, side effects can include kidney damage.

Supportive care

People who are hospitalized with severe encephalitis might need:

- Breathing assistance, as well as careful monitoring of breathing and heart function
- Intravenous fluids to ensure proper hydration and levels of essential minerals
- Anti-inflammatory drugs, such as corticosteroids, to reduce swelling and pressure within the skull
- Anticonvulsant medications, such as phenytoin to stop or prevent seizures

There may be a need for additional therapy, such as:

- Physical therapy to improve strength, flexibility, balance, motor coordination and mobility

- Occupational therapy to develop everyday skills and to use adaptive products that help with everyday activities
- Speech therapy to relearn muscle control and coordination to produce speech
- Psychotherapy to learn coping strategies and new behavioral skills to improve mood disorders or address personality changes

Rabies

Rabies is a viral encephalitis transmitted by the saliva of infected mammals. Symptoms include depression and fever, followed by agitation, excessive salivation, and hydrophobia. Vaccination is indicated for people at high risk of exposure.

Postexposure prophylaxis involves wound care and passive and active immunoprophylaxis and, if promptly and meticulously executed, almost always prevents human rabies. Otherwise, the disorder is almost universally fatal. Treatment is supportive.

Rabies causes > 55,000 human deaths worldwide annually, mostly in Latin America, Africa, and Asia, where canine rabies is endemic.

Rabid animals transmit the infection through their saliva, usually by biting. Rarely, the virus can enter through a skin abrasion or across mucous membranes of the eyes, nose, or mouth.

The virus travels from the site of entry via peripheral nerves to the spinal cord (or to the brain stem when the face is bitten), then to the brain. It then spreads from the CNS via peripheral nerves to other parts of the body. Involvement of the salivary glands and oral mucosa is responsible for transmissibility.

Symptoms and Signs

Pain or paresthesias may develop at the site of the bite. The incubation period averages 1 to 2 months but may be > 1 yr.

Initial symptoms are nonspecific: fever, headache, and malaise. Within days, encephalitis (furious rabies; in 80%) or paralysis (dumb rabies; in 20%) develops.

Encephalitis causes restlessness, confusion, agitation, bizarre behavior, hallucinations, and insomnia. Salivation is excessive, and attempts to drink cause painful spasms of the laryngeal and pharyngeal muscles leading to hydrophobia – fear of water.

In the paralytic form, ascending paralysis and quadriplegia develop without delirium and hydrophobia.

Treatment

Treatment once rabies has developed is only supportive and includes heavy sedation (eg, with ketamine and midazolam) and comfort measures. Death usually occurs 3 to 10 days after symptoms begin. Few patients have survived; many received immunoprophylaxis before onset of symptoms.

Prevention

Rabid animals can often be recognized by their strange behavior; they may be agitated and vicious, weak, or paralyzed and may show no fear of people.

Preexposure rabies prophylaxis

Human diploid cell rabies vaccine (HDCV) is safe and recommended for preexposure prophylaxis for people at risk, including veterinarians, animal handlers, spelunkers, workers who handle the virus, and travelers to endemic areas.

A total of three 1-mL doses are given IM, one each on days 0, 7, and between day 21 and 28. Vaccination provides lifetime protection to some degree. However, protection decreases with time; a booster dose of vaccine is given if the antibody titer is below a certain level.

Postexposure rabies prophylaxis

Exposure is considered to be a bite that breaks the skin or any contact between mucous membrane or broken skin and animal saliva. If exposure occurs, the wound is cleansed immediately and thoroughly with soap and water or benzalkonium chloride. Deep puncture wounds are flushed with soapy water using moderate pressure. Wounds are usually left open.

Postexposure prophylaxis (PEP) with rabies vaccine and rabies immune globulin (RIG) is given depending on the biting animal and circumstances

Brain Abscess

A brain abscess is an intracerebral collection of pus. Symptoms may include headache, lethargy, fever, and focal neurologic deficits. Diagnosis is by contrast-enhanced MRI or CT. Treatment is with antibiotics and usually CT-guided stereotactic aspiration or surgical drainage.

An abscess forms when an area of cerebral inflammation becomes necrotic and encapsulated by glial cells and fibroblasts. Edema around the abscess may increase intracranial pressure.

Causes

A brain abscess can result from -

- Direct extension of cranial infections (eg, osteomyelitis, mastoiditis, sinusitis, subdural empyema)
- Penetrating head wounds (including neurosurgical procedures)
- Hematogenous spread (eg, in bacterial endocarditis, congenital heart disease with right-to-left shunt, or IV drug abuse)
- Unknown causes

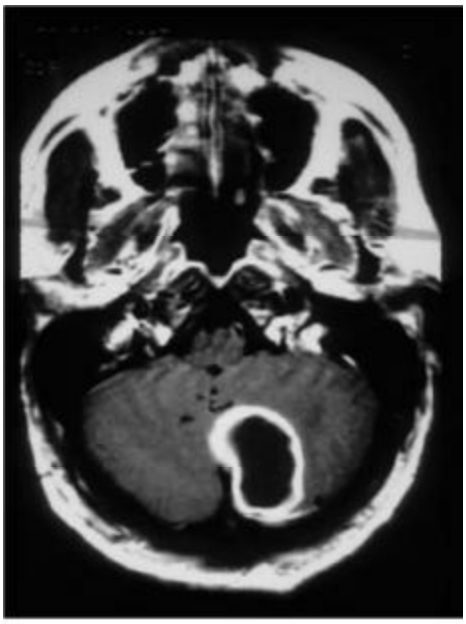
The bacteria involved are usually anaerobic and sometimes mixed, often including anaerobes, such as *Bacteroides* and anaerobic and microaerophilic streptococci. Staphylococci are common after cranial trauma, neurosurgery, or endocarditis. Enterobacteriaceae may be isolated in chronic ear infections.

Fungi (eg, *Aspergillus*) and protozoa (eg, *Toxoplasma gondii*, particularly in HIV-infected patients) can cause abscesses.

Symptoms and Signs

Symptoms result from increased intracranial pressure and mass effect. Classically, headache, nausea, vomiting, lethargy, seizures, personality changes, papilledema, and focal neurologic deficits develop over days to weeks.

Fever, chills, and leukocytosis may develop before the infection is encapsulated, but they may be absent at presentation or subside over time.



Cerebellar Abscess

Treatment

- Antibiotics (initially cefotaxime or ceftriaxone, plus metronidazole for *Bacteroides* sp or vancomycin for *Staphylococcus aureus* based on suspicion, then as guided by culture and susceptibility testing)
- Usually CT-guided stereotactic aspiration or surgical drainage
- Sometimes corticosteroids, anticonvulsants, or both

All patients receive antibiotics for a minimum of 4 to 8 wk. Initial empiric antibiotics include cefotaxime 2 g IV q 4 h or ceftriaxone 2 g IV q 12 h; both are effective against streptococci, Enterobacteriaceae, and most anaerobes but not against *Bacteroides fragilis*.

If clinicians suspect *Bacteroides* sp, metronidazole 15 mg/kg (loading dose) followed by 7.5 mg/kg IV q 6 h is also required. If *S. aureus* is suspected, vancomycin 1 g q 12 h is used (with cefotaxime or ceftriaxone) until sensitivity to nafcillin (2 g q 4 h) is determined. Response to antibiotics is best monitored by serial MRI or CT.

Drainage (CT-guided stereotactic or open) provides optimal therapy and is necessary for most abscesses that are solitary and surgically accessible, particularly those > 2 cm in diameter. If abscesses are < 2 cm in diameter, antibiotics alone may be tried, but abscesses must then be monitored with serial MRI or CT; if abscesses enlarge after being treated with antibiotics, surgical drainage is indicated.

Patients with increased intracranial pressure may benefit from a short course of high-dose corticosteroids (dexamethasone 10 mg IV once, then 4 mg IV q 6 h for 3 or 4 days).

Stroke

A stroke occurs when the blood supply to part of your brain is interrupted or reduced, depriving brain tissue of oxygen and nutrients. Within minutes, brain cells begin to die.

A stroke is a medical emergency. Prompt treatment is crucial. Early action can minimize brain damage and potential complications.

Symptoms

Watch for these signs and symptoms -

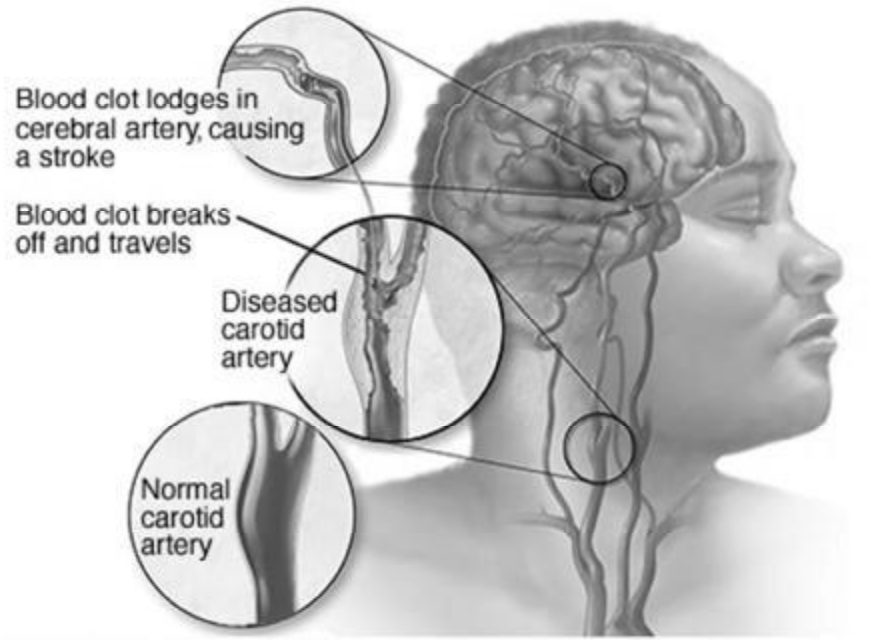
- Trouble with speaking and understanding. You may experience confusion. You may slur your words or have difficulty understanding speech.
- Paralysis or numbness of the face, arm or leg. You may develop sudden numbness, weakness or paralysis in your face, arm or leg. This often happens just on one side of your body. Try to raise both your arms over your head at the same time. If one arm begins to fall, you may be having a stroke. Also, one side of your mouth may droop when you try to smile.
- Trouble with seeing in one or both eyes. You may suddenly have blurred or blackened vision in one or both eyes, or you may see double.
- Headache. A sudden, severe headache, which may be accompanied by vomiting, dizziness or altered consciousness, may indicate you're having a stroke.
- Trouble with walking. You may stumble or experience sudden dizziness, loss of balance or loss of coordination.

Causes

A stroke may be caused by a blocked artery (ischemic stroke) or the leaking or bursting of a blood vessel (hemorrhagic stroke).

Some people may experience only a temporary disruption of blood flow to the brain (transient ischemic attack, or TIA) that doesn't cause permanent damage.

Ischemic stroke



Ischemic stroke

About 80 percent of strokes are ischemic strokes. Ischemic strokes occur when the arteries to the brain become narrowed or blocked, causing severely reduced blood flow (ischemia). The most common ischemic strokes include:

- Thrombotic stroke. A thrombotic stroke occurs when a blood clot (thrombus) forms in one of the arteries that supply blood to the brain. A clot may be caused by fatty deposits (plaque) that build up in arteries and cause reduced blood flow (atherosclerosis) or other artery conditions.

- Embolic stroke. An embolic stroke occurs when a blood clot or other debris forms away from the brain — commonly in the heart — and is swept through the bloodstream to lodge in narrower brain arteries. This type of blood clot is called an embolus.

Hemorrhagic stroke

Hemorrhagic stroke occurs when a blood vessel in the brain leaks or ruptures.

Brain hemorrhages can result from many conditions that affect your blood vessels. These include:

- Uncontrolled high blood pressure (hypertension)
- Overtreatment with anticoagulants (blood thinners)
- Weak spots in your blood vessel walls (aneurysms)

A less common cause of hemorrhage is the rupture of an abnormal tangle of thin-walled blood vessels (arteriovenous malformation).

Types of hemorrhagic stroke include:

- Intracerebral hemorrhage. In an intracerebral hemorrhage, a blood vessel in the brain bursts and spills into the surrounding brain tissue, damaging brain cells. Brain cells beyond the leak are deprived of blood and are also damaged.

  High blood pressure, trauma, vascular malformations, use of blood-thinning medications and other conditions may cause an intracerebral hemorrhage.

- Subarachnoid hemorrhage. In a subarachnoid hemorrhage, an artery on or near the surface of your brain bursts and spills into the space between the surface of your brain and your skull. This bleeding is often signaled by a sudden, severe headache.

  A subarachnoid hemorrhage is commonly caused by the bursting of a small sack-shaped or berry-shaped aneurysm. After the hemorrhage, the blood vessels in the brain may widen and narrow erratically (vasospasm), causing brain cell damage by further limiting blood flow.

Transient ischemic attack (TIA)

A transient ischemic attack (TIA) — sometimes known as a ministroke — is a temporary period of symptoms similar to those you'd have in a stroke. A temporary decrease in blood supply to part of your brain causes TIAs, which may last as little as five minutes.

Like an ischemic stroke, a TIA occurs when a clot or debris blocks blood flow to part of your nervous system — but there is no permanent tissue damage and no lasting symptoms.

Risk factors

Potentially treatable stroke risk factors include:

Lifestyle risk factors

- Being overweight or obese
- Physical inactivity
- Heavy or binge drinking
- Use of illicit drugs such as cocaine and methamphetamines

Medical risk factors

- Blood pressure readings higher than 120/80 millimeters of mercury (mm Hg)
- Cigarette smoking or exposure to secondhand smoke
- High cholesterol
- Diabetes
- Obstructive sleep apnea
- Cardiovascular disease, including heart failure, heart defects, heart infection or abnormal heart rhythm
- Personal or family history of stroke, heart attack or transient ischemic attack.

Other factors associated with a higher risk of stroke include:

- Age —People age 55 or older have a higher risk of stroke than do younger people.
- Sex — Men have a higher risk of stroke than women. Women are usually older when they have strokes, and they're more likely to die of strokes than are men.
- Hormones — use of birth control pills or hormone therapies that include estrogen, as well as increased estrogen levels from pregnancy and childbirth.

Complications

A stroke can sometimes cause temporary or permanent disabilities, depending on how long the brain lacks blood flow and which part was affected. Complications may include:

- Paralysis or loss of muscle movement. One may become paralyzed on one side of the body, or lose control of certain muscles, such as those on one side of the face or one arm. Physical therapy may help return to activities affected by paralysis, such as walking, eating and dressing.
- Difficulty talking or swallowing. A stroke might affect control of the muscles in the mouth and throat, making it difficult to talk clearly (dysarthria), swallow (dysphagia) or eat. You also may have difficulty with language (aphasia), including speaking or understanding speech, reading, or writing. Therapy with a speech-language pathologist might help.

- Memory loss or thinking difficulties. Many people who have had strokes experience some memory loss. Others may have difficulty thinking, making judgments, reasoning and understanding concepts.
- Emotional problems. People who have had strokes may have more difficulty controlling their emotions, or they may develop depression.
- Pain. Pain, numbness or other strange sensations may occur in the parts of the body affected by stroke. For example, if a stroke causes you to lose feeling in your left arm, you may develop an uncomfortable tingling sensation in that arm.

  People also may be sensitive to temperature changes, especially extreme cold, after a stroke. This complication is known as central stroke pain or central pain syndrome. This condition generally develops several weeks after a stroke, and it may improve over time.
- Changes in behavior and self-care ability. People who have had strokes may become more withdrawn and less social or more impulsive. They may need help with grooming and daily chores.

Prevention

Knowing the stroke risk factors, following doctor's recommendations and adopting a healthy lifestyle are the best steps one can take to prevent a stroke.

Many stroke prevention strategies are the same as strategies to prevent heart disease. In general, healthy lifestyle recommendations include:

- Controlling high blood pressure (hypertension). After having had a stroke, lowering the blood pressure can help prevent a subsequent TIA or stroke.

  Exercising, managing stress, maintaining a healthy weight and limiting the amount of sodium and alcohol you eat and drink can all help to keep high blood pressure in check. In addition to recommending lifestyle changes, doctors may prescribe medications to treat high blood pressure.

- Lowering the amount of cholesterol and saturated fat in the diet. Eating less cholesterol and fat, especially saturated fat and trans fats, may reduce the plaque in the arteries.

- Quitting tobacco use. Smoking raises the risk of stroke for smokers and nonsmokers exposed to secondhand smoke. Quitting tobacco use reduces your risk of stroke.
- Controlling diabetes. Diabetes can be managed with diet, exercise, weight control and medication.

- Maintaining a healthy weight. Being overweight contributes to other stroke risk factors, such as high blood pressure, cardiovascular disease and diabetes.

- Eating a diet rich in fruits and vegetables. A diet containing five or more daily servings of fruits or vegetables may reduce the risk of stroke.

- Exercising regularly. Aerobic or "cardio" exercise reduces risk of stroke in many ways. Exercise can lower blood pressure, increase levels of high-density lipoprotein cholesterol, and improve the overall health of the blood vessels and heart. It also helps one lose weight, control diabetes and reduce stress. Gradually work up to 30 minutes of activity — such as walking, jogging, swimming or bicycling — on most, if not all, days of the week.

- Drinking alcohol in moderation, if at all. Alcohol can be both a risk factor and a protective measure for stroke. Heavy alcohol consumption increases the risk of high blood pressure, ischemic strokes and hemorrhagic strokes.

- Treating obstructive sleep apnea (OSA). Doctors may recommend an overnight oxygen assessment to screen for OSA — a sleep disorder in which the oxygen level intermittently drops during the night. Treatment for OSA includes oxygen at night or wearing a small device in the mouth to help obe breathe.

Preventive medications

If one has had an ischemic stroke or TIA, the doctor may recommend medications to help reduce the risk of having another stroke. These include:

- Anti-platelet drugs. Platelets are cells in the blood that form clots. Anti-platelet drugs make these cells less sticky and less likely to clot. The most commonly used anti-platelet medication is aspirin.

  If aspirin doesn't prevent the TIA or stroke the doctor may instead prescribe an anti-platelet drug such as clopidogrel.

- Anticoagulants. These drugs, which include heparin and warfarin, reduce blood clotting. Heparin is fast acting and may be used over a short period of time in the hospital. Slower acting warfarin may be used over a longer term.

  Warfarin is a powerful blood-thinning drug, so one needs to take it exactly as directed and watch for side effects.

Dementia

Introduction

Dementia isn't a specific disease. Instead, dementia describes a group of symptoms affecting memory, thinking and social abilities severely enough to interfere with daily functioning.

Though dementia generally involves memory loss, memory loss alone may have many different causes. So memory loss alone doesn't mean you have dementia.

Alzheimer's disease is the most common cause of a progressive dementia in older adults, but there are a number of causes of dementia.

Symptoms

Dementia symptoms vary depending on the cause, but common signs and symptoms include:

Cognitive changes

- Memory loss, which is usually noticed by a spouse or someone else
- Difficulty communicating or finding words
- Difficulty reasoning or problem-solving
- Difficulty handling complex tasks
- Difficulty with planning and organizing
- Difficulty with coordination and motor functions
- Confusion and disorientation

Psychological changes

- Personality changes
- Depression
- Anxiety
- Inappropriate behavior
- Paranoia
- Agitation
- Hallucinations

Causes

Dementia involves damage of nerve cells in the brain, which can occur in several areas of the brain. Dementia affects people differently, depending on the area of the brain affected.

Dementias are often grouped by what they have in common, such as the part of the brain that's affected or whether they worsen over time (progressive dementias). Some dementias, such as those caused by a reaction to medications or vitamin deficiencies, might improve with treatment.

Progressive dementias

Types of dementias that progress and aren't reversible include:

- Alzheimer's disease. In people age 65 and older, Alzheimer's disease is the most common cause of dementia.

  Although the cause of Alzheimer's disease isn't known, plaques and tangles are often found in the brains of people with Alzheimer's. Plaques are clumps of a protein called beta-amyloid, and tangles are fibrous tangles made up of tau protein.

  Certain genetic factors might make it more likely that people will develop Alzheimer's.

- Vascular dementia. This second most common type of dementia occurs as a result of damage to the vessels that supply blood to your brain. Blood vessel problems can be caused by stroke or other blood vessel conditions.

- Lewy body dementia. Lewy bodies are abnormal clumps of protein that have been found in the brains of people with Lewy body dementia, Alzheimer's disease and Parkinson's disease. This is one of the more common types of progressive dementia.

- Frontotemporal dementia. This is a group of diseases characterized by the breakdown (degeneration) of nerve cells in the frontal and temporal lobes of the brain, the areas generally associated with personality, behavior and language.

  As with other dementias, the cause isn't known.

- Mixed dementia. Autopsy studies of the brains of people 80 and older who had dementia indicate that many had a combination of Alzheimer's disease, vascular dementia and Lewy

body dementia. Studies are ongoing to determine how having mixed dementia affects symptoms and treatments.

Other disorders linked to dementia

- Huntington's disease. Caused by a genetic mutation, this disease causes certain nerve cells in the brain and spinal cord to waste away. Signs and symptoms, including a severe decline in thinking (cognitive) skills usually appear around age 30 or 40.

- Traumatic brain injury. This condition is caused by repetitive head trauma, such as experienced by boxers, football players or soldiers.

  Depending on the part of the brain that's injured, this condition can cause dementia signs and symptoms, such as depression, explosiveness, memory loss, uncoordinated movement and impaired speech, as well as slow movement, tremors and rigidity (parkinsonism).

  Symptoms might not appear until years after the trauma.

- Creutzfeldt-Jakob disease. This rare brain disorder usually occurs in people without known risk factors. This condition might be due to an abnormal form of a protein. Creutzfeldt-Jakob disease can be inherited or caused by exposure to diseased brain or nervous system tissue.

  Signs and symptoms of this fatal condition usually appear around age 60.

- Parkinson's disease. Many people with Parkinson's disease eventually develop dementia symptoms (Parkinson's disease dementia).

Dementia-like conditions that can be reversed

Some causes of dementia or dementia-like symptoms can be reversed with treatment. They include:

- Infections and immune disorders. Dementia-like symptoms can result from fever or other side effects of your body's attempt to fight off an infection. Conditions such as multiple sclerosis that result from the body's immune system attacking nerve cells also can cause dementia.

- Metabolic problems and endocrine abnormalities. People with thyroid problems, low blood sugar (hypoglycemia), too little or too much sodium or calcium, or an impaired ability to absorb vitamin B-12 can develop dementia-like symptoms or other personality changes.

- Nutritional deficiencies. Not drinking enough liquids (dehydration); not getting enough thiamin (vitamin B-1), which is common in people with chronic alcoholism; and not getting enough vitamins B-6 and B-12 in your diet can cause dementia-like symptoms.

- Reactions to medications. A reaction to a medication or an interaction of several medications can cause dementia-like symptoms.

- Subdural hematomas. Bleeding between the surface of the brain and the covering over the brain, which is common in the elderly after a fall, can cause symptoms similar to dementia.

- Poisoning. Exposure to heavy metals, such as lead, and other poisons, such as pesticides, as well as alcohol abuse or recreational drug use can lead to symptoms of dementia.

  Symptoms might resolve with treatment.

- Brain tumors. Rarely, dementia can result from damage caused by a brain tumor.

- Anoxia. This condition, also called hypoxia, occurs when organ tissues aren't getting enough oxygen. Anoxia can occur due to severe asthma, heart attack, carbon monoxide poisoning or other causes.

- Normal-pressure hydrocephalus. This condition, which is caused by enlarged ventricles in the brain, can cause walking problems, urinary difficulty and memory loss.

Risk factors

Many factors can eventually lead to dementia. Some factors, such as age, can't be changed. Others can be addressed to reduce your risk.

Risk factors that can't be changed

- Age. The risk rises as you age, especially after age 65. However, dementia isn't a normal part of aging, and dementia can occur in younger people.
- Family history. Having a family history of dementia puts you at greater risk of developing the condition. However, many people with a family history never develop symptoms, and

many people without a family history do. Tests to determine whether you have certain genetic mutations are available.
- Down syndrome. By middle age, many people with Down syndrome develop early-onset Alzheimer's disease.
- Mild cognitive impairment. This involves difficulties with memory but without loss of daily function. It puts people at higher risk of dementia.

Risk factors one can change

One might be able to control the following risk factors of dementia.

- Heavy alcohol use. If one drinks large amounts of alcohol, he / she might have a higher risk of dementia. Some studies, however, have shown that moderate amounts of alcohol might have a protective effect.
- Cardiovascular risk factors. These include high blood pressure (hypertension), high cholesterol, buildup of fats in artery walls (atherosclerosis) and obesity.
- Depression. Although not yet well-understood, late-life depression might indicate the development of dementia.
- Diabetes. If one has diabetes, one might have an increased risk of dementia, especially if it's poorly controlled.
- Smoking. Smoking might increase the risk of developing dementia and blood vessel (vascular) diseases.
- Sleep apnea. People who snore and have episodes where they frequently stop breathing while asleep may have reversible memory loss.

Complications

Dementia can affect many body systems and, therefore, the ability to function. Dementia can lead to:

- Inadequate nutrition. Many people with dementia eventually reduce or stop their intake of nutrients. Ultimately, they may be unable to chew and swallow.
- Pneumonia. Difficulty swallowing increases the risk of choking or aspirating food into the lungs, which can block breathing and cause pneumonia.
- Inability to perform self-care tasks. As dementia progresses, it can interfere with bathing, dressing, brushing hair or teeth, using the toilet independently and taking medications accurately.
- Personal safety challenges. Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.

- Death. Late-stage dementia results in coma and death, often from infection.

Prevention

There's no sure way to prevent dementia, but there are steps one can take that might help. More research is needed, but it might be beneficial to do the following:

- Keep your mind active. Mentally stimulating activities, such as reading, solving puzzles and playing word games, and memory training might delay the onset of dementia and decrease its effects.
- Be physically and socially active. Physical activity and social interaction might delay the onset of dementia and reduce its symptoms. Move more and aim for 150 minutes of exercise a week.
- Quit smoking. Some studies have shown smoking in middle age and beyond may increase your risk of dementia and blood vessel (vascular) conditions. Quitting smoking might reduce the risk and will improve health.
- Get enough vitamin D. Research suggests that people with low levels of vitamin D in their blood are more likely to develop Alzheimer's disease and other forms of dementia. One can get vitamin D through certain foods, supplements and sun exposure.

- Lower your blood pressure. High blood pressure might lead to a higher risk of some types of dementia.

- Maintain a healthy diet. Eating a healthy diet is important for many reasons, but a diet rich in fruits, vegetables, whole grains and omega-3 fatty acids, commonly found in certain fish and nuts might promote health and lower your risk of developing dementia.

Parkinson's Disease

Introduction

Parkinson's Disease is a slowly progressive, degenerative disorder characterized by resting tremor, stiffness (rigidity), slow and decreased movement (bradykinesia), and gait and/or postural instability.

Treatment aims to restore dopaminergic function in the brain with levodopa plus carbidopa and/or other drugs (eg, dopamine agonists, MAO type B [MAO-B] inhibitors, amantadine).

For refractory, disabling symptoms in patients without dementia, stereotactic deep brain stimulation or lesional surgery and levodopa and an apomorphine pump may help.

Parkinson's disease (PD) affects about -

- 0.4% of people > 40 yr
- 1% of people ≥ 65 yr
- 10% of people ≥ 80 yr

The mean age at onset is about 57 yr.

Rarely, PD begins during childhood or adolescence (juvenile parkinsonism). Onset between ages 21 and 40 yr is sometimes called young or early-onset PD. Genetic causes are more likely in juvenile and early-onset PD; these forms may differ from later-onset PD because they progress more slowly and are very sensitive to dopaminergic treatments and because most disability results from non-motor symptoms such as depression, anxiety, and pain.

Secondary parkinsonism is brain dysfunction that is characterized by basal ganglia dopaminergic blockade and that is similar to PD, but it is caused by something other than PD (eg, drugs, cerebrovascular disease, trauma, postencephalitic changes).

Atypical parkinsonism refers to a group of neurodegenerative disorders that have some features similar to those of Parkinson disease but have some different clinical features, a worse prognosis, a modest or no response to levodopa, and a different pathology (eg, neurodegenerative disorders such as multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal degeneration).

Pathophysiology

Synuclein is a neuronal and glial cell protein that can aggregate into insoluble fibrils and form Lewy bodies.

The pathologic hallmark of PD is synuclein-filled Lewy bodies in the nigrostriatal system.

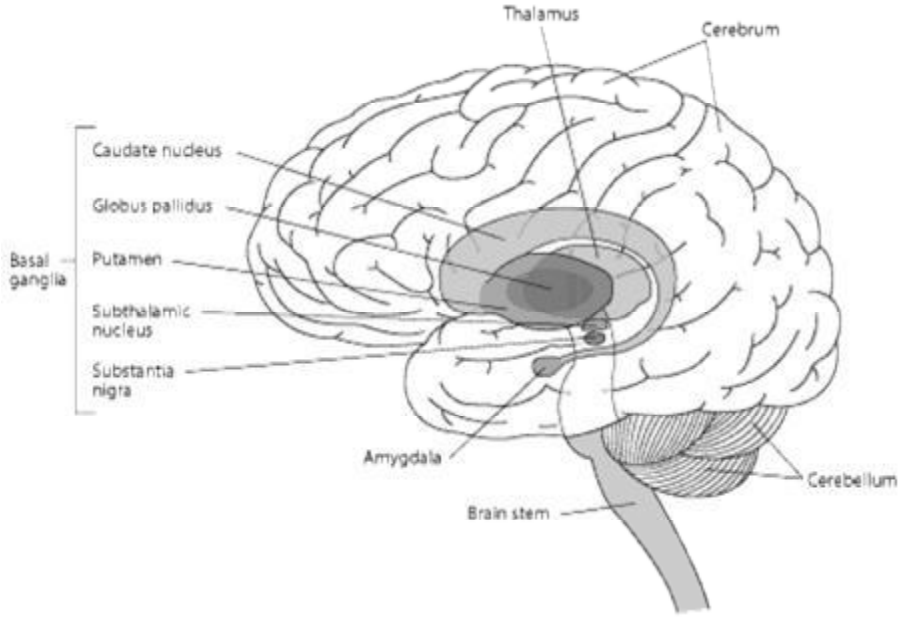
However, synuclein can accumulate in many other parts of the nervous system leading to other synucleinopathies (synuclein deposition disorders) that include dementia with Lewy bodies and multiple system atrophy. PD may share features of other synucleinopathies, such as autonomic dysfunction and dementia.

Rarely, PD occurs without Lewy bodies (eg, in a form due to a mutation in the *PARK 2* gene).

In PD, pigmented neurons of the substantia nigra, locus ceruleus, and other brain stem dopaminergic cell groups degenerate.

Loss of substantia nigra neurons results in depletion of dopamine in the dorsal aspect of the putamen (part of the basal ganglia) and causes many of the motor manifestations of PD.

Basal ganglia



Causes

A genetic predisposition is likely, at least in some cases of PD. About 10% of patients have a family history of PD. Several abnormal genes have been identified. Inheritance is autosomal dominant for some genes and autosomal recessive for others.

In genetic forms, age at onset tends to be younger, but the course is typically more benign than that of later-onset, presumably nongenetic PD.

Symptoms and Signs

In most patients, symptoms of Parkinson disease (PD) begin insidiously.

A resting tremor of one hand is often the first symptom. The tremor is characterized as follows:

- Slow and coarse
- Maximal at rest, lessening during movement, and absent during sleep
- Amplitude increased by emotional tension or fatigue
- Often involving the wrist and fingers, sometimes involving the thumb moving against the index finger (pill rolling), as when people roll a pill in their hand or handle a small object

Usually, the hands or feet are affected first, most often asymmetrically. The jaw and tongue may also be affected, but not the voice. Tremor may become less prominent as the disease progresses.

Rigidity develops independently of tremor in many patients. When a clinician moves a rigid joint, semirhythmic jerks due to variations in the intensity of the rigidity occur, producing a ratchet-like effect (cogwheel rigidity).

Slow movements (bradykinesia) are typical. Movement also becomes decreased in amplitude (hypokinesia) and difficult to initiate (akinesia).

Rigidity and hypokinesia may contribute to muscle aches and sensations of fatigue. The face becomes masklike (hypomimic), with an open mouth and reduced blinking. Excessive drooling (sialorrhea) may contribute to disability. Speech becomes hypophonic, with characteristic monotonous, sometimes stuttering dysarthria.

Hypokinesia and impaired control of distal muscles cause micrographia (writing in very small letters) and make activities of daily living increasingly difficult. Without warning, voluntary movement, including walking, may suddenly halt (called freezing of gait).

Postural instability may develop, resulting in falls, which occur later in PD. Patients have difficulty starting to walk, turning, and stopping. They shuffle, taking short steps, holding their arms flexed to the waist, and swinging their arms little or not at all with each stride. Steps may inadvertently quicken, while stride length progressively shortens; this gait abnormality, called festination, is often a precursor to freezing of gait. A tendency to fall forward (propulsion) or backward (retropulsion) when the center of gravity is displaced results from loss of postural reflexes. Posture becomes stooped.

Dementia develops in about one third of patients, usually late in PD. Early predictors of its development are visuospatial impairment (eg, getting lost while driving) and decreased verbal fluency.

Sleep disorders are common. Insomnia may result from nocturia or from the inability to turn in bed. Rapid eye movement (REM) sleep behavior disorder may develop; in this disorder, violent bursts of physical activity occur during REM sleep because the paralysis that normally occurs during REM sleep is absent.

Sleep deprivation may exacerbate depression and cognitive impairment, as well as contribute to excessive daytime sleepiness.

Neurologic symptoms unrelated to parkinsonism commonly develop because synucleinopathy occurs in other areas of the central, peripheral, and autonomic nervous systems. The following are examples:

- Almost universal sympathetic denervation of the heart, contributing to orthostatic hypotension
- Esophageal dysmotility, contributing to dysphagia and increased risk of aspiration
- Lower bowel dysmotility, contributing to constipation
- Urinary hesitancy and/or urgency, potentially leading to incontinence (common)
- Anosmia (common)

In some patients, some of these symptoms occur before the motor symptoms of PD and frequently worsen over time.

Seborrheic dermatitis is also common.

Treatment

- Carbidopa/levodopa (mainstay of treatment)
- Amantadine, MAO type B (MAO-B) inhibitors, or, in few patients, anticholinergic drugs
- Dopamine agonists
- Catechol *O*-methyltransferase (COMT) inhibitors, always used with levodopa, particularly when response to levodopa is wearing off
- Surgery if drugs do not sufficiently control symptoms or have intolerable adverse effects
- Exercise and adaptive measures

Many oral drugs are commonly used to relieve symptoms of PD.

Levodopa is the most effective treatment. However, when PD is advanced, sometimes soon after diagnosis, response to levodopa can wear off, causing fluctuations in motor symptoms and dyskinesias.

To reduce the time levodopa is taken and thus minimize these effects, clinicians can consider treating younger patients who have mild disability with the following:

- MAO-B inhibitors (selegiline, rasagiline)
- Dopamine agonists (eg, pramipexole, ropinirole, rotigotine)
- Amantadine (which is also the best option when trying to decrease peak-dose dyskinesias)

However, if these drugs do not sufficiently control symptoms, clinicians should promptly initiate levodopa because it can usually greatly improve quality of life. Evidence now suggests that levodopa becomes ineffective because of disease progression rather than cumulative exposure to levodopa, as was previously believed, so early use of levodopa probably does not hasten the drug's ineffectiveness.

Doses are often reduced in the elderly. Drugs that cause or worsen symptoms, particularly antipsychotics, are avoided.

Levodopa

Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier into the basal ganglia, where it is decarboxylated to form dopamine.

Coadministration of the peripheral decarboxylase inhibitor carbidopa prevents levodopa from being decarboxylated into dopamine outside the brain (peripherally), thus lowering the

levodopa dosage required to produce therapeutic levels in the brain and minimizing adverse effects due to dopamine in the peripheral circulation.

Levodopa is most effective at relieving bradykinesia and rigidity, although it often substantially reduces tremor.

Common short-term adverse effects of levodopa are –

- Nausea
- Vomiting
- Light-headedness

Common long-term adverse effects include –

- Mental and psychiatric abnormalities (eg, delirium with confusion, paranoia, visual hallucinations, punding [complex, repetitive, stereotyped behaviors])
- Motor dysfunction (eg, dyskinesias, motor fluctuations)

Hallucinations and paranoia occur most often in the elderly and in patients who have cognitive impairment or dementia.

The dose that causes dyskinesias tends to decrease as the disease progresses. Over time, the dose that is needed for therapeutic benefit and the one that causes dyskinesia converge.

Dosage of carbidopa/levodopa is increased every 4 to 7 days as tolerated until maximum benefit is reached or adverse effects develop. The risk of adverse effects may be minimized by starting at a low dose, such as half of a 25/100 mg of carbidopa/levodopa tablet tid or qid (12.5/50 mg tid or qid), and increasing slowly to about one, two, or three 25/100-mg tablets qid. Most patients with PD require 400 to 1200 mg/day of levodopa in divided doses every 2 to 5 h, but some patients with malabsorption require up to 3000 mg/day.

Preferably, levodopa should not be given with food because protein can reduce absorption of levodopa.

If peripheral adverse effects of levodopa (eg, nausea, vomiting, postural light-headedness) predominate, increasing the amount of carbidopa may help. Carbidopa doses up to 150 mg are safe and do not decrease the efficacy of levodopa.

Psychosis has been treated with oral quetiapine or clozapine; these drugs, unlike other antipsychotics (eg, risperidone, olanzapine, all typical psychotics), do not aggravate parkinsonian symptoms.

Quetiapine can be started at 25 mg at night and increased in 25-mg increments every 1 to 3 days up to 400 mg at night or 200 bid.

Although clozapine is most effective, its use is limited because agranulocytosis is a risk estimated to occur in 1% of patients. When clozapine is used, the dose is 12.5 to 50 mg once/day to 12.5 to 25 mg bid. CBC is done weekly for 6 mo and every 2 wk for another 6 mo and then every 4 wk thereafter. However, the frequency may vary depending on the WBC count.

Amantadine

Amantadine is most often used to do the following:

- Ameliorate dyskinesias secondary to levodopa
- Lessen tremors

Amantadine is useful as monotherapy for early, mild parkinsonism and later can be used to augment levodopa's effects. It may augment dopaminergic activity, anticholinergic effects, or both.

Dopamine agonists

These drugs directly activate dopamine receptors in the basal ganglia. They include –

- Pramipexole (0.75 to 4.5 mg/day po)
- Ropinirole (3 to 6 mg/day po up to 24 mg/day)
- Apomorphine (given by injection)

Oral dopamine agonists can be used as monotherapy but, as such, are rarely effective for more than a few years. Using these drugs early in treatment, with small doses of levodopa, may be useful in patients at high risk of dyskinesias and on-off effects (eg, in patients < 60 yr).

However, dopamine agonists may be useful at all stages of the disease, including as adjunctive therapy in later stages.

Adverse effects may limit the use of oral dopamine agonists. In 1 to 2% of patients, these drugs may cause compulsive gambling, excessive shopping, hypersexuality, or overeating, requiring dose reduction or withdrawal of the causative drug and possibly avoidance of the drug class.

Apomorphine is an injectable dopamine agonist used as rescue therapy when off effects are frequent and severe. Onset of action is rapid (5 to 10 min), but duration is short (60 to 90 min).

Apomorphine 2 to 6 mg sc can be given up to 5 times/day as needed. A 2-mg test dose is given first to check for orthostatic hypotension. BP is checked in the supine and standing positions before treatment and 20, 40, and 60 min afterward.

Other adverse effects are similar to those of other dopamine agonists. Nausea can be prevented by starting trimethobenzamide 300 mg po tid 3 days before apomorphine and continuing it for the first 2 mo of treatment.

Selective MAO-B inhibitors

These drugs include selegiline and rasagiline.

Selegiline inhibits one of the 2 major enzymes that break down dopamine in the brain, thereby prolonging the action of each dose of levodopa. In some patients with mild off effects, selegiline helps prolong levodopa’s effectiveness.

Used initially as monotherapy, selegiline controls mild symptoms; as a result, use of levodopa can be delayed by about 1 yr. A dose of 5 mg po bid does not cause hypertensive crisis, which, because of the drug's amphetamine-like metabolites, is sometimes triggered when patients taking a nonselective MAO inhibitor consume tyramine in foods (eg, some cheeses).

Although virtually free of adverse effects, selegiline can potentiate levodopa-induced dyskinesias, mental and psychiatric adverse effects, and nausea, requiring reduction in the levodopa dose.

Rasagiline inhibits the same enzymes as selegiline. It is effective and well-tolerated in early and late disease; uses of rasagiline 1 to 2 mg po once/day are similar to those of selegiline. Unlike selegiline, it does not have amphetamine-like metabolites, so theoretically, risk of a hypertensive crisis when patients consume tyramine is lower with rasagiline.

Anticholinergic drugs

Anticholinergic drugs can be used as monotherapy in early disease and later to supplement levodopa. They are most effective for tremor.

Doses are increased very slowly. Adverse effects may include cognitive impairment and dry mouth, which are particularly troublesome for the elderly and may be the principal problem with use of these drugs.

Thus, anticholinergic drugs are usually used only in young patients with tremor-predominant PD or with some dystonic components. Rarely, they are used as adjunctive treatment in elderly patients without cognitive impairment or psychiatric disorders.

Commonly used anticholinergic drugs include benztropine and trihexyphenidyl.

Antihistamines with anticholinergic effects (eg, diphenhydramine 25 to 50 mg po bid to qid, orphenadrine 50 mg po once/day to qid) are occasionally useful for treating tremor.

Anticholinergic tricyclic antidepressants (eg, amitriptyline 10 to 150 mg po at bedtime), if used for depression, may be useful as an adjunct to levodopa.

Endocrine System

The endocrine system consists of a group of glands and organs that regulate and control various body functions by producing and secreting hormones. Hormones are chemical substances that affect the activity of another part of the body. In essence, hormones serve as messengers, controlling and coordinating activities throughout the body. *Endocrine* glands release their hormones directly into the *bloodstream* (as opposed to *exocrine* glands, which release hormones or other substances into a *duct*).

The individual organs that make up the endocrine system have different and often unrelated functions. Doctors who specialize in disorders of the endocrine system are known as endocrinologists. Many endocrinologists further subspecialize in the functions and disorders of specific glands.

The major glands of the endocrine system, each of which produces one or more specific hormones, are –

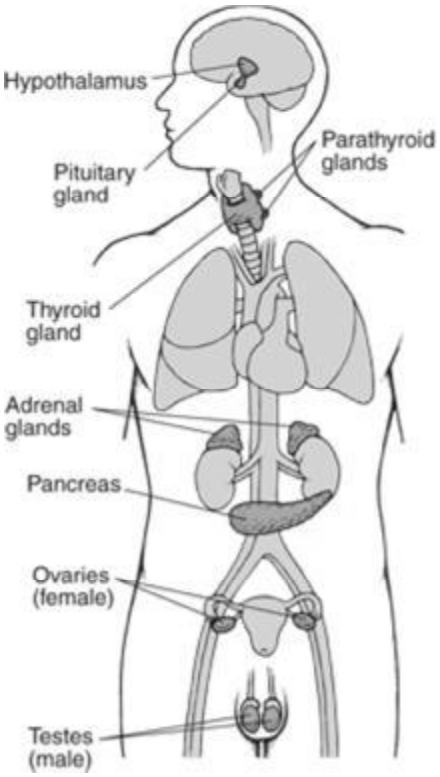
- Hypothalamus
- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Islet cells of the pancreas
- Adrenal glands
- Testes in men, and the ovaries in women

The hypothalamus (a small region of the brain that connects to the pituitary gland) secretes several hormones that control the pituitary gland.

The pituitary gland is sometimes called the master gland because it controls the functions of many other endocrine glands.

During pregnancy, the placenta also acts as an endocrine gland in addition to its other functions.

Major Endocrine Glands

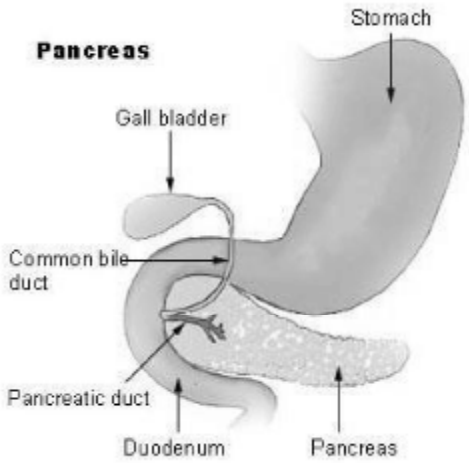


Not all organs that secrete hormones or hormone-like substances are considered part of the endocrine system.

For example, the kidneys produce the hormone renin to help control blood pressure and the hormone erythropoietin to stimulate the bone marrow to produce red blood cells.

In addition, the digestive tract produces a variety of hormones that control digestion, affect insulin secretion from the pancreas, and alter behaviors, such as those associated with hunger. Fat (adipose) tissue also produces hormones that regulate metabolism and appetite.

Additionally, the term "gland" does not necessarily mean that the organ is part of the endocrine system. For example, sweat glands, salivary glands, glands in mucus membranes, and mammary glands are called exocrine glands, because they secrete substances other than hormones and because they secrete the substances into ducts, not directly into the bloodstream.



The pancreas is both an endocrine and exocrine gland.

The main function of endocrine glands is to secrete hormones directly into the bloodstream. Hormones are chemical substances that affect the activity of another part of the body (target site). In essence, hormones serve as messengers, controlling and coordinating activities throughout the body.

Upon reaching a target site, a hormone binds to a receptor, much like a key fits into a lock. Once the hormone locks into its receptor, it transmits a message that causes the target site to take a specific action. Hormone receptors may be within the nucleus or on the surface of the cell.

Ultimately, hormones control the function of entire organs, affecting such diverse processes as growth and development, reproduction, and sexual characteristics. Hormones also influence the way the body uses and stores energy and control the volume of fluid and the levels of salts and sugar (glucose) in the blood. Very small amounts of hormones can trigger very large responses in the body.

Although hormones circulate throughout the body, each type of hormone influences only certain organs and tissues.

Some hormones affect only one or two organs, whereas others have influence throughout the body. For example, thyroid-stimulating hormone, produced in the pituitary gland, affects only the thyroid gland.

In contrast, thyroid hormone, produced in the thyroid gland, affects cells throughout the body and is involved in such important functions as regulating growth of cells, controlling the heart rate, and affecting the speed at which calories are burned.

Insulin, secreted by the islet cells of the pancreas, affects the processing (metabolism) of glucose, protein, and fat throughout the body.

Most hormones are derived from proteins. Others are steroids, which are fatty substances derived from cholesterol.

Major Hormones

Produced by	Hormone	Function
Pituitary gland	Vasopressin (antidiuretic hormone)	Causes kidneys to retain water and, along with aldosterone, helps control blood pressure
	Corticotropin (ACTH)	Controls the production and secretion of hormones by the adrenal glands
	Growth hormone	Controls growth and development Promotes protein production
	Luteinizing hormone and follicle-stimulating hormone	Control reproductive functions, including the production of sperm and semen in men and egg maturation and menstrual cycles in women Control male and female sexual characteristics (including hair distribution, muscle formation, skin texture and thickness, voice, and perhaps even personality traits)
	Oxytocin	Causes muscles of the uterus to contract during childbirth and after delivery and stimulates contractions of milk ducts in the breast, which move milk to the nipple
	Prolactin	Starts and maintains milk production in the ductal glands of the breast (mammary glands)
	Thyroid-stimulating hormone	Stimulates the production and secretion of hormones by the thyroid gland
Parathyroid glands	Parathyroid hormone	Controls bone formation and the excretion of calcium and phosphorus
Thyroid gland	Thyroid hormone	Regulates the rate at which the body functions (metabolic rate)
	Calcitonin	Tends to decrease blood calcium levels and helps regulate calcium balance
Adrenal glands	Aldosterone	Helps regulate salt and water balance by causing the kidneys to retain salt and water and excrete potassium
	Cortisol	Has widespread effects throughout the body Especially has anti-inflammatory action Maintains blood sugar level, blood pressure, and muscle strength Helps control salt and water balance
	Dehydroepiandrosterone (DHEA)	Has effects on bone, mood, and the immune system
	Epinephrine and norepinephrine	Stimulate the heart, lungs, blood vessels, and nervous system
Pancreas	Glucagon	Raises the blood sugar level

Produced by	Hormone	Function
	Insulin	Lowers the blood sugar level Affects the processing (metabolism) of sugar, protein, and fat throughout the body
Kidneys	Erythropoietin	Stimulates red blood cell production
	Renin	Controls blood pressure
Ovaries	Estrogen	Controls the development of female sex characteristics and the reproductive system
	Progesterone	Prepares the lining of the uterus for implantation of a fertilized egg and readies the mammary glands to secrete milk
Testes	Testosterone	Controls the development of male sex characteristics and the reproductive system
Digestive tract	Cholecystokinin	Controls gallbladder contractions that cause bile to enter the intestine Stimulates release of digestive enzymes from the pancreas
	Glucagon-like peptide	Increases insulin release from the pancreas
	Ghrelin	Controls growth hormone release from the pituitary gland Causes sensation of hunger
Adipose (fat) tissue	Resistin	Blocks the effects of insulin on muscle
	Leptin	Controls appetite
Placenta	Chorionic gonadotropin	Stimulates ovaries to continue to release progesterone during early pregnancy
	Estrogen and progesterone	Keep uterus receptive to fetus and placenta during pregnancy
Hypothalamus	Thyrotropin-releasing hormone	Stimulates the release of thyroid-stimulating hormone and prolactin
	Gonadotropin-releasing hormone	Stimulates release of luteinizing hormone and follicle-stimulating hormone
	Corticotropin-releasing hormone	Stimulates release of adrenocorticotropic hormone
	Growth hormone–releasing hormone	Stimulates release of growth hormone
	Somatostatin	Inhibits release of growth hormone, thyroid-stimulating hormone, and insulin

Endocrine Controls

In essence, hormones serve as messengers, controlling and coordinating activities throughout the body. To control endocrine functions, the secretion of each hormone must be regulated within precise limits. The body is normally able to sense whether more or less of a given hormone is needed.

Many endocrine glands are controlled by the interplay of hormonal signals between the hypothalamus, located in the brain, and the pituitary gland, which sits at the base of the brain. This interplay is referred to as the hypothalamic-pituitary axis.

The hypothalamus secretes several hormones that control the pituitary gland.

The pituitary gland, sometimes called the master gland, in turn controls the functions of many other endocrine glands. The pituitary controls the rate at which it secretes hormones through a feedback loop in which the blood levels of other endocrine hormones signal the pituitary to slow down or speed up.

Many other factors can control endocrine function. For example, a baby sucking on its mother's nipple stimulates her pituitary gland to secrete prolactin and oxytocin, hormones that stimulate breast milk production and flow.

Rising blood sugar levels stimulate the islet cells of the pancreas to produce insulin. Part of the nervous system stimulates the adrenal gland to produce epinephrine.

Endocrine Disorders

The endocrine system consists of a group of glands and organs that regulate and control various body functions by producing and secreting hormones. Hormones are chemical substances that affect the activity of another part of the body. In essence, hormones serve as messengers, controlling and coordinating activities throughout the body.

Endocrine disorders involve either -

- Too much hormone secretion
- Too little hormone secretion

Disorders may result from a problem in the gland itself, or because the hypothalamic-pituitary axis provides too much or too little stimulation. Depending on the type of cell they originate in,

tumors can produce excess hormones or destroy normal glandular tissue, decreasing hormone production.

Sometimes the body's immune system attacks an endocrine gland (an autoimmune disorder), decreasing hormone production.

Examples of endocrine disorders include –

- Hyperthyroidism
- Hypothyroidism
- Cushing disease (Oversecretion of glucocorticoids)
- Addison disease
- Acromegaly
- Short stature in children
- Diabetes

Doctors usually measure levels of hormones in the blood to tell how an endocrine gland is functioning. Sometimes blood levels alone do not give enough information about endocrine gland function, so doctors measure hormone levels after giving a stimulus (such as a sugar-containing drink, a drug, or a hormone that can trigger hormone release) or after having the patient take an action (such as fasting).

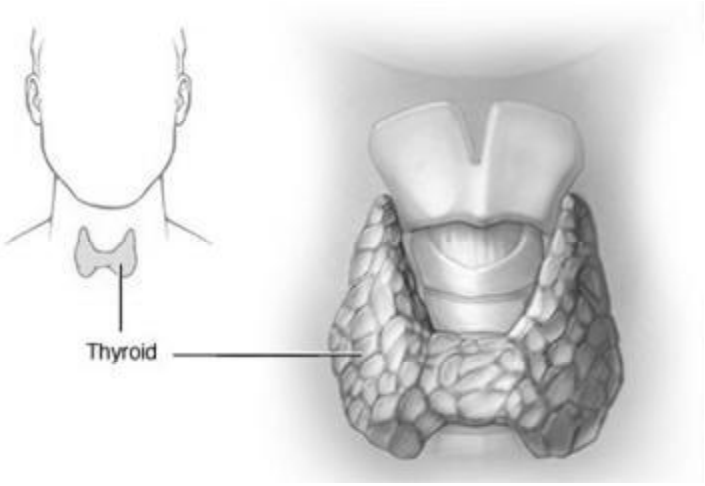
Endocrine disorders are often treated by replacing a hormone that is deficient. However, sometimes the cause of the disorder is treated. For example, a tumor involving an endocrine gland may be removed.

Hyperthyroidism

Hyperthyroidism occurs when the thyroid makes too much T4, T3, or both.

Causes of hyperthyroidism include:

- Grave's disease – an autoimmune disease
- Excess iodine, a key ingredient in T4 and T3
- Thyroiditis, or inflammation of the thyroid, which causes T4 and T3 to leak out of the gland
- Tumors of the ovaries or testes
- Benign tumors of the thyroid or pituitary gland



Symptoms and signs

High amounts of T4, T3, or both can cause an excessively high metabolic rate. This is called a hypermetabolic state. When in a hypermetabolic state, one may experience –

- Rapid heart rate
- Elevated blood pressure
- Hand tremors
- Excessive sweating
- Low tolerance for heat

Hyperthyroidism can cause more frequent bowel movements, weight loss, and, in women, irregular menstrual cycles.

Visibly, the thyroid gland itself can appear swollen - called a goiter. The eyes may also appear quite prominent, which is known as exophthalmos.

Treatment

Antithyroid medications, such as methimazole stop the thyroid from making hormones. They are a common treatment.

Radioactive iodine

Radioactive iodine effectively destroys the cells that produce thyroid hormones.

Common side effects include dry mouth, dry eyes, sore throat, and changes in taste. Precautions may need to be taken for a short time after treatment to prevent radiation spread to others.

Surgery

A section or all of the thyroid gland may be surgically removed. It will then be necessary to take thyroid hormone supplements to prevent hypothyroidism.

Also, beta-blockers such as propranolol can help control the rapid pulse, sweating, anxiety, and high blood pressure.

Hypothyroidism

Hypothyroidism (underactive thyroid) is a condition in which the thyroid gland doesn't produce enough of hormones.

Women are more likely to have hypothyroidism. Over time, untreated hypothyroidism can cause a number of health problems, such as obesity, joint pain, infertility and heart disease.

Symptoms and signs may include:

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarseness
- Muscle weakness

- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods
- Thinning hair
- Slowed heart rate
- Depression
- Impaired memory

In addition, you may become more forgetful, your thought processes may slow, or you may feel depressed.

Advanced hypothyroidism, known as myxedema, is rare, but when it occurs it can be life-threatening. Signs and symptoms include low blood pressure, decreased breathing, decreased body temperature, unresponsiveness and even coma.

Causes

Hypothyroidism may be due to a number of factors, including:

- Autoimmune disease e.g. an inflammatory disorder known as Hashimoto's thyroiditis is the most common cause of hypothyroidism. The immune system produces antibodies that affect the thyroid's ability to produce hormones.
- Thyroid surgery. Removing all or a large portion of the thyroid gland can diminish or halt hormone production. In that case, it is necessary to take thyroid hormone for life.
- Radiation therapy. Radiation used to treat cancers of the head and neck can affect the thyroid gland and may lead to hypothyroidism.
- Medications. A number of medications can contribute to hypothyroidism. One such medication is lithium, which is used to treat certain psychiatric disorders.
- Iodine deficiency. The trace mineral iodine — found primarily in seafood, seaweed, plants grown in iodine-rich soil and iodized salt — is essential for the production of thyroid hormones.

Treatment

Standard treatment for hypothyroidism involves daily use of the thyroid hormone levothyroxine. This oral medication restores adequate hormone levels, reversing the signs and symptoms of hypothyroidism.

Cushing disease

Cushing disease or syndrome occurs when the body is exposed to high levels of the hormone cortisol for a long time. It may be caused by the overuse of oral corticosteroid medication or it can also occur when body makes too much cortisol on its own.

Cortisol, which is produced in the adrenal glands, plays a variety of roles in your body. For example, cortisol helps regulate your blood pressure and keeps your cardiovascular system functioning normally.

Cortisol also helps your body respond to stress and regulates the metabolism of proteins, carbohydrates and fats in the diet into usable energy.

Too much cortisol can produce some of the hallmark signs of Cushing syndrome –

- a fatty hump between shoulders ('buffalo hump')
- a rounded face ('moon face')
- pink or purple stretch marks on skin
- Thinning, fragile skin that bruises easily
- Slow healing of cuts, insect bites and infections

Cushing syndrome can also result in high blood pressure, bone loss and, on occasion, type 2 diabetes.

Causes

Excess levels of the hormone cortisol are responsible for Cushing syndrome.

The condition may be due to body's own overproduction of cortisol (endogenous Cushing syndrome). This may occur from excess production by one or both adrenal glands, or overproduction of the adrenocorticotropic hormone (ACTH), which normally regulates cortisol production.

In these cases, Cushing syndrome may be related to:

- A pituitary gland tumor (pituitary adenoma) - A noncancerous (benign) tumor of the pituitary gland secretes an excess amount of ACTH, which in turn stimulates the adrenal glands to make more cortisol. It occurs much more often in women and is the most common form of endogenous Cushing syndrome.

- An ectopic ACTH-secreting tumor - Rarely, when a tumor develops in an organ that normally does not produce ACTH, the tumor will begin to secrete this hormone in excess, resulting in Cushing syndrome. These tumors are usually found in the lungs, pancreas, thyroid or thymus gland.

- A primary adrenal gland disease - In some people, the cause of Cushing syndrome is excess cortisol secretion that is associated with disorders of the adrenal glands. The most common of these disorders is a noncancerous tumor of the adrenal cortex, called an adrenal adenoma.

    - Cancerous tumors of the adrenal cortex (adrenocortical carcinomas) are rare, but they can cause Cushing syndrome as well. Occasionally, benign, nodular enlargement of both adrenal glands can result in Cushing syndrome.

Cushing syndrome can develop from an outside cause (exogenous Cushing syndrome). One example is taking corticosteroid medications in high doses over an extended period of time. These medications, such as prednisone, have the same effect in the body as does cortisol produced by your body.

Oral corticosteroids may be necessary to treat inflammatory diseases, such as rheumatoid arthritis, asthma etc. or to prevent your body from rejecting a transplanted organ.

Treatment

Treatments for Cushing syndrome are designed to lower the high level of cortisol in the body.

Treatment options include:

- Reducing corticosteroid use - If the cause of Cushing syndrome is long-term use of corticosteroid medications, reducing the dosage over a period of time, while still adequately managing asthma, arthritis or other condition is required.

  Abruptly discontinuing these medications could lead to deficient cortisol levels. Slowly tapering off corticosteroid drugs allows the body to resume normal cortisol production.

- Surgery - If the cause of Cushing syndrome is a tumor, complete surgical removal is needed. Pituitary tumors are typically removed by a neurosurgeon. If a tumor is present in the adrenal glands, lungs or pancreas, a general surgeon can remove it.

After the operation, it is necessary to take cortisol replacement medications to provide the body with the correct amount of cortisol. In most cases, there is eventually a return of normal adrenal hormone production.

- Radiation therapy – Radiation therapy is to be used in conjunction with surgery if the surgeon can't totally remove a pituitary tumor. Additionally, radiation may be used for people who aren't suitable candidates for surgery.

- Medications - Medications can be used to control cortisol production when surgery and radiation don't work. Medications may also be used before surgery in people who have become very sick with Cushing syndrome or to improve signs and symptoms and minimize surgical risk.

  Medications to control excessive production of cortisol at the adrenal gland include ketoconazole, mitotane and metyrapone.

  Mifepristone is useful in people with Cushing syndrome who have type 2 diabetes or glucose intolerance. Mifepristone does not decrease cortisol production, but it blocks the effect of cortisol on your tissues.

  The drug pasireotide works by decreasing ACTH production from a pituitary tumor. It is recommended if pituitary surgery is unsuccessful or cannot be done.

- If none of these treatment options are appropriate or effective, it may be recommended to surgically remove adrenal glands (bilateral adrenalectomy). This procedure will cure excess production of cortisol, but will require lifelong replacement medications.

Addison’s disease

The hormones the adrenal cortex produces are essential for life — the glucocorticoids and the mineralocorticoids.

Glucocorticoid hormones, which include cortisol, control the body's ability to convert food into energy, play a role in immune system's inflammatory response and help the body respond to stress.

Mineralocorticoid hormones, which include aldosterone, maintain the body's balance of sodium and potassium to keep blood pressure normal.

Addison's disease, also called adrenal insufficiency, is a disorder that occurs when body produces insufficient amounts of hormones cortisol and often aldosterone.

Symptoms

Addison's disease symptoms usually develop slowly and may include:

- Extreme fatigue
- Weight loss and decreased appetite
- Darkening of your skin (hyperpigmentation)
- Low blood pressure, even fainting
- Salt craving
- Low blood sugar (hypoglycemia)
- Nausea, diarrhea or vomiting
- Abdominal pain
- Muscle or joint pains
- Irritability
- Depression
- Body hair loss or sexual dysfunction in women

Acute adrenal failure (addisonian crisis)

Sometimes, however, the signs and symptoms of Addison's disease may appear suddenly. In acute adrenal failure (addisonian crisis), the signs and symptoms may also include:

- Pain in lower back, abdomen or legs
- Severe vomiting and diarrhea, leading to dehydration
- Low blood pressure
- Loss of consciousness
- High potassium (hyperkalemia) and low sodium (hyponatremia)

Causes

Primary adrenal insufficiency

Addison's disease occurs when the cortex is damaged and doesn't produce its hormones in adequate quantities as a result of the body attacking itself (autoimmune disease).

Other causes of adrenal gland failure may include:

- Tuberculosis

- Other infections of the adrenal glands
- Spread of cancer to the adrenal glands
- Bleeding into the adrenal glands, which may present as adrenal crisis without any preceding symptoms.

Secondary adrenal insufficiency

Adrenal insufficiency can also occur if the pituitary gland is diseased. The pituitary gland makes a hormone called adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to produce its hormones.

Inadequate production of ACTH can lead to insufficient production of hormones normally produced by adrenal glands, even though adrenal glands are not damaged.

Another common cause of secondary adrenal insufficiency is when people who take corticosteroids for treatment of chronic conditions, such as asthma or arthritis, abruptly stop taking the corticosteroids.

Treatment

All treatment for Addison's disease involves hormone replacement therapy to correct the levels of steroid hormones your body isn't producing. Some options for treatment include:

- Hydrocortisone, prednisone or cortisone acetate may be used to replace cortisol.
- Doctor may prescribe fludrocortisone to replace aldosterone.

An ample amount of sodium is recommended, especially during heavy exercise, when the weather is hot or if there is gastrointestinal upsets, such as diarrhea.

Addisonian crisis

An addisonian crisis is a life-threatening situation that results in low blood pressure, low blood levels of sugar and high blood levels of potassium. This situation requires immediate medical care.

Treatment typically includes intravenous injections of:

- Hydrocortisone
- Saline solution
- Sugar (dextrose)

Acromegaly

Acromegaly is a hormonal disorder that develops when the pituitary gland produces too much growth hormone during adulthood. When this happens, your bones increase in size, including those of your hands, feet and face. Acromegaly usually affects middle-aged adults.

In children who are still growing, too much growth hormone can cause a condition called gigantism. These children have exaggerated bone growth and an abnormal increase in height.

Symptoms

One of the most common signs of acromegaly is enlarged hands and feet.

Acromegaly may also cause you to experience gradual changes in the shape of your face, such as a protruding lower jaw and brow, an enlarged nose, thickened lips, and wider spacing between your teeth.

Acromegaly may produce the following signs and symptoms:

- Coarse, oily, thickened skin
- Excessive sweating and body odor
- Small outgrowths of skin tissue (skin tags)
- Fatigue and muscle weakness
- A deepened, husky voice due to enlarged vocal cords and sinuses
- Severe snoring due to obstruction of the upper airway
- Impaired vision
- Enlarged tongue
- Pain and limited joint mobility
- Menstrual cycle irregularities in women
- Erectile dysfunction in men
- Enlarged liver, heart, kidneys, spleen and other organs
- Increased chest size (barrel chest)

Causes

Acromegaly is caused by the pituitary gland overproducing growth hormone (GH) over time.

In adults, a tumor is the most common cause of too much GH production:

- Pituitary tumors - Most cases of acromegaly are caused by a noncancerous (benign) tumor (adenoma) of the pituitary gland. The tumor secretes excessive amounts of growth hormone, causing many of the signs and symptoms of acromegaly.

- Nonpituitary tumors - In a few people with acromegaly, tumors in other parts of the body, such as the lungs, pancreas or adrenal glands, cause the disorder. Sometimes, these tumors actually secrete GH. In other cases, the tumors produce a hormone called growth hormone-releasing hormone (GH-RH), which stimulates the pituitary gland to make more GH.

Treatment

Surgery

Doctors can remove most pituitary tumors using a method called transsphenoidal surgery. In this procedure, the surgeon works through nose to extract the pituitary tumor.

Removing the tumor can normalize GH production and eliminate the pressure on the tissues surrounding the pituitary gland to relieve associated signs and symptoms.

Drugs used to lower the production or block the action of GH include:

- Somatostatin analogues - The drugs octreotide and lanreotide are synthetic versions of the brain hormone somatostatin. They interfere with the excessive secretion of GH by the pituitary gland, and thus can produce rapid declines in GH levels.

- Dopamine agonists - The medications cabergoline and bromocriptine are taken orally. In some people, these drugs can lower levels of GH. The tumor may decrease in size in some people taking a dopamine agonist or somatostatin analogues.

- Growth hormone antagonist. The medication pegvisomant, a growth hormone antagonist, acts to block the effect of GH on body tissues. Pegvisomant may be particularly helpful for people who haven't had good success with other forms of treatment.

Radiation

Doctor may recommend radiation treatment when tumor cells remain after surgery. Radiation therapy destroys any lingering tumor cells and slowly reduces GH levels.

Short stature in children

Short stature is a general term for people whose height is considerably below average compared to the height of their peers. While it can apply to adults, the term is more commonly used to refer to children.

A child can be significantly shorter than their friends and still be perfectly healthy.

However, short stature can indicate an underlying medical problem. In these cases, many children can grow to a normal height with proper treatment. For others, short stature may be permanent.

Causes

The three major reasons for short stature are constitutional growth delay, genetics, and disease.

Constitutional Growth Delay

Some children simply develop later than others. These children are often referred to as “late bloomers.” These kids are small for their age and often enter puberty later. However, they’ll continue to grow after their friends have stopped. They usually catch up by adulthood.

Genetics

If one or both parents are short, there’s a strong possibility that their child will also be short. If there are no underlying medical reasons why either parent is short, their child’s short stature may be perfectly healthy.

Disease

A number of diseases may cause unusually short stature.

- Endocrine diseases affect hormone production, and often height. These include growth hormone deficiency (GHD), hypothyroidism, or low thyroid hormone levels, and Cushing’s disease.

- Chronic diseases can also decrease height through their effects on overall health. Examples of chronic disease are heart disease, asthma, inflammatory bowel disease, diabetes, kidney problems, sickle cell anemia, and juvenile rheumatoid arthritis.

- Genetic conditions that affect height include Down syndrome, Turner syndrome, and Williams syndrome.

- Bone and skeletal diseases, such as rickets or achondroplasia, may change stature through their effects on bone growth.

- Problems during pregnancy can affect the height of a child.

- Malnutrition can also lead to short stature.

Treatment

Treatment for short stature depends on the cause.

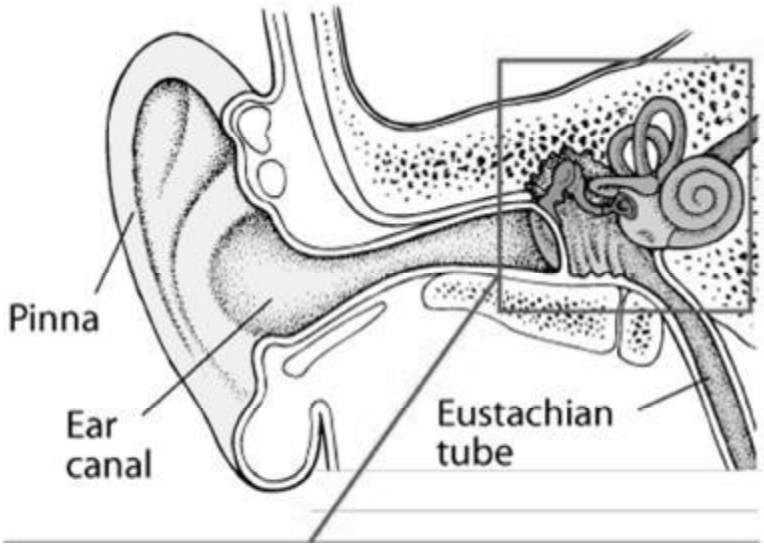
Thyroid hormone replacement can be used to treat hypothyroidism.

Growth hormone injections can treat GHD and a number of other conditions, including Turner syndrome and chronic kidney failure.

Introduction to Some Ear, Nose, and Throat Disorders

The common ENT disorders include acute otitis media, tonsillopharyngitis, sore throat, adenoid disorders, epistaxis, nasal congestion and rhinorrhea, sinusitis etc.

Inside the ear.



The inner ear is in the petrous area of the temporal bone. Within the bone is the osseous labyrinth, which encases the membranous labyrinth. The osseous labyrinth includes the vestibular system (made up of the semicircular canals and the vestibule) and the cochlea.

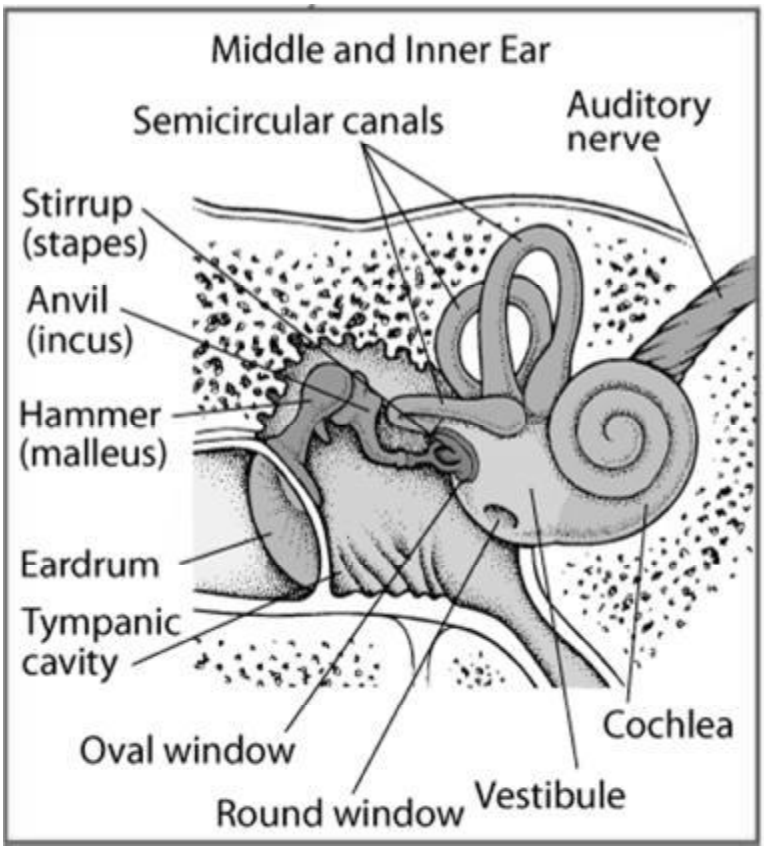
The vestibular system, responsible for balance and posture, consists of the saccule, utricle, and semicircular canals.

The saccule and utricle contain cells that sense movement of the head in a straight line (sensing acceleration) or up and down (sensing gravity).

The 3 semicircular canals sense angular rotation of the head. Depending on the direction the head moves, the fluid movement will be greater in one on the 3 canals than in the others. Hair cells in the canals respond to the fluid movement, initiating nerve impulses so that the brain can take appropriate action to maintain balance.

The cochlea, responsible for hearing, is filled with fluid. Within the cochlea is the organ of Corti, containing about 30,000 hair cells. Cilia from the hair cells extend into the fluid and are embedded in a gelatinous membrane. Sound vibrations are transmitted from the ossicles, through the middle ear and the oval window, into the inner ear where these vibrations cause

the fluid and cilia to vibrate. These vibrations are then transformed into an electric signal that is sent to the brain.



There are many environmental factors that can damage the cells within the inner ear and cause hearing loss. Continued exposure to loud noise causes progressive damage, eventually resulting in hearing loss and sometimes in tinnitus.

Otorrhea

Ear discharge (otorrhea) is drainage exiting the ear. It may be serous, serosanguineous, or purulent. Associated symptoms may include ear ache, fever, pruritus, vertigo, tinnitus, and hearing loss.

Causes may originate from the ear canal, the middle ear, or the cranial vault.
Overall, the most common causes are –

- Acute otitis media with perforation
- Chronic otitis media (with a perforation of the eardrum, cholesteatoma, or both)
- Otitis externa

Some Causes of Ear Discharge

Cause	Suggestive Findings
Acute discharge*	
Acute otitis media with perforated TM	Severe pain, with relief on appearance of purulent discharge
Chronic otitis media	Otorrhea in patients with chronic perforation, sometimes with cholesteatoma (Can also manifest as chronic discharge)
Otitis externa (infectious or allergic)	*Infectious*: Often after swimming, local trauma; marked pain, worse with ear traction Often a history of chronic ear dermatitis with itching and skin changes *Allergic*: Often after use of ear drops; more itching, erythema, less pain than with infectious Typically involvement of earlobe, where drops trickled out of ear canal *Both*: Canal very edematous, inflamed, with debris; normal TM
Chronic discharge	
Cancer of ear canal	Discharge often bloody, mild pain Sometimes visible lesion in canal Easy to confuse with otitis externa early on
Cholesteatoma	History of TM perforation Flaky debris in ear canal, pocket in TM filled with caseous debris Sometimes polypoid mass or granulation tissue over the cholesteatoma
Chronic purulent otitis media	Long history of ear infections or other ear disorders Less pain than with external otitis Canal macerated, granulation tissue TM immobile, distorted, usually visible perforation
Foreign body	Usually in children Drainage foul-smelling, purulent

Cause	Suggestive Findings
	Foreign body often visible on examination unless marked edema or drainage
Mastoiditis	Often fever, history of untreated or unresolved otitis media Redness, tenderness over mastoid
Necrotizing otitis externa	Usually history of immune deficiency or diabetes Chronic severe pain Periauricular swelling and tenderness, granulation tissue in ear canal Sometimes facial nerve paralysis
*< 6 wk. TM = tympanic membrane.	

Acute Otitis Media

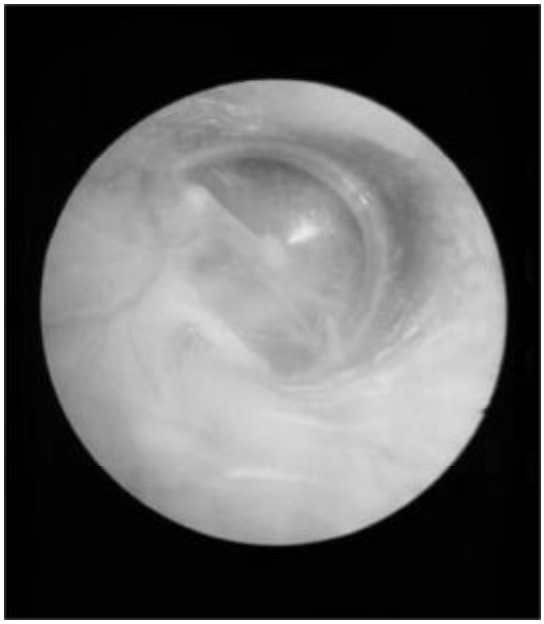
Acute otitis media (AOM) is a bacterial or viral infection of the middle ear, usually accompanying an Upper Respiratory Infection. Symptoms include pain, often with systemic symptoms (eg, fever, nausea, vomiting, diarrhea), especially in the very young. Diagnosis is based on otoscopy. Spontaneous perforation of the TM causes serosanguineous or purulent otorrhea. Severe headache, confusion, or focal neurologic signs may occur with intracranial spread of infection.

The etiology of acute otitis media may be viral or bacterial. Viral infections are often complicated by secondary bacterial infection.

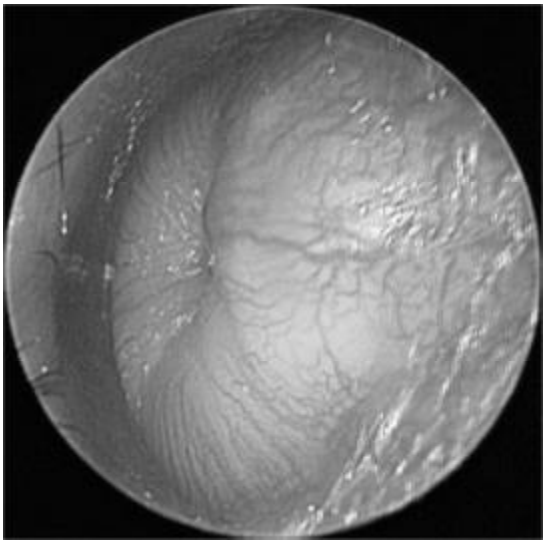
In neonates, gram-negative enteric bacilli, particularly *Escherichia coli,* and *Staphylococcus aureus* cause AOM. In older infants and children < 14 yr, the most common organisms are *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and nontypeable *Haemophilus influenzae*; less common causes are group A β-hemolytic streptococci and *S. aureus*.

In patients > 14 yr, *S. pneumoniae,* group A β-hemolytic streptococci, and *S. aureus* are most common, followed by *H. influenzae*.

Treatment is with analgesics and sometimes antibiotics. Rarely myringotomy may be needed.



Normal Tympanic Membrane



Acute Otitis Media

Antibiotics for Otitis Media

Drug	Dose* (by Age)	Comments
Initial treatment		
Amoxicillin	< 14 yr: 40–45 mg/kg q 12 h > 14 yr: 500 mg q 8 h	Preferred unless the child has one of the following: • Received amoxicillin in the

Drug	Dose* (by Age)	Comments
		past 30 days • Purulent conjunctivitis • Recurrent acute otitis media unresponsive to amoxicillin High-dose regimen for possible resistant organisms
Penicillin-allergic†		
Cefdinir	14 mg/kg once/day or 7 mg/kg q 12 h	—
Cefuroxime	< 14 yr: 15 mg/kg q 12 h > 14 yr: 500 mg q 12 h	Maximum 1000 mg/day
Cefpodoxime	5 mg/kg q 12 h	—
Ceftriaxone	50 mg/kg IM or IV once May repeat at 72 h	Particularly for children with severe vomiting or who will not swallow antibiotic liquids
Resistant cases‡		
Amoxicillin/clavulanate	< 14 yr: 40–45 mg/kg q 12 h ≥ 14 yr: 500 mg q 12 h	Preferred; dose based on amoxicillin component Use new formulation to limit clavulanate to maximum of 10 mg/kg/day
Ceftriaxone	50 mg/kg IM or IV once/day for 3 days	Can use even if failed on oral cephalosporin Considered if adherence is likely to be poor
Clindamycin	10 to 13 mg/kg q 8 h	2nd-line alternative, consider using along with a cephalosporin

* Treatment duration is typically 10 days for children < 2 yr and 7 days for older children unless otherwise specified. Drugs are given orally unless otherwise specified.

† Cross reactivity of 2nd- and 3rd-generation cephalosporins with penicillin is very low.

‡ No improvement after 48 to 72 h of treatment, or previous resistant infection; amoxicillin used in the previous 30 days; or concurrent purulent conjunctivitis

Chronic Otitis Media

Otitis media is a persistent, chronically draining (> 6 wk), suppurative perforation of the tympanic membrane. Symptoms include painless otorrhea with conductive hearing loss. Complications include development of aural polyps, cholesteatoma, and other infections. Treatment requires complete cleaning of the ear canal several times daily, careful removal of granulation tissue, and application of topical corticosteroids and antibiotics. Systemic antibiotics and surgery are reserved for severe cases.

Chronic otitis media can result from acute otitis media, eustachian tube obstruction, mechanical trauma, thermal or chemical burns, blast injuries, or iatrogenic causes (eg, after tympanostomy tube placement). Further, patients with craniofacial abnormalities (eg, Down syndrome, cri du chat syndrome, cleft lip and/or cleft palate, velocardiofacial syndrome [Shprintzen syndrome]) have an increased risk.

Chronic otitis media may become exacerbated after a URI or when water enters the middle ear through a tympanic membrane (TM) perforation during bathing or swimming. Infections often are caused by gram-negative bacilli or *Staphylococcus aureus,* resulting in painless, purulent, sometimes foul-smelling otorrhea.

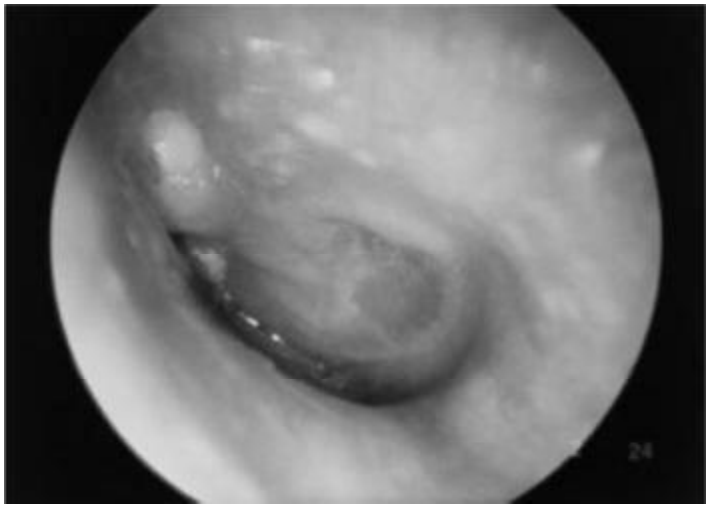
Persistent chronic otitis media may result in destructive changes in the middle ear (such as necrosis of the long process of the incus) or aural polyps (granulation tissue prolapsing into the ear canal through the TM perforation). Aural polyps are a serious sign, almost invariably suggesting cholesteatoma.

A cholesteatoma is an epithelial cell growth that forms in the middle ear, mastoid, or epitympanum after chronic otitis media. Lytic enzymes, such as collagenases, produced by the cholesteatoma can destroy adjacent bone and soft tissue. The cholesteatoma is also a nidus for infection; purulent labyrinthitis, facial paralysis, or intracranial abscess may develop.

Symptoms and Signs

Chronic otitis media usually manifests with conductive hearing loss and otorrhea. Pain is uncommon unless an associated osteitis of the temporal bone occurs. The TM is perforated and draining, and the auditory canal is macerated and littered with granulation tissue.

A patient with cholesteatoma has white debris in the middle ear, a draining polypoid mass protruding through the TM perforation, and an ear canal that appears clogged with mucopurulent granulation tissue.



Cholesteatoma

Diagnosis

Diagnosis of chronic otitis media is usually clinical. Drainage is cultured. When cholesteatoma or other complications are suspected (as in a febrile patient or one with vertigo or otalgia), CT or MRI is done. These tests may reveal intratemporal or intracranial processes (eg, labyrinthitis, ossicular or temporal erosion, abscesses).

Treatment

- Topical antibiotic drops
- Removal of granulation tissue
- Surgery for cholesteatomas

Ten drops of topical ciprofloxacin solution are instilled in the affected ear 2 times/day for 14 days.

When granulation tissue is present, it is removed with microinstruments or cauterization with silver nitrate sticks. Ciprofloxacin 0.3% and dexamethasone 0.1% is then instilled into the ear canal for 7 to 10 days.

Severe exacerbations require systemic antibiotic therapy with amoxicillin 250 to 500 mg po q 8 h for 10 days or a 3rd-generation cephalosporin, subsequently modified by culture results and response to therapy.

Tympanoplasty is indicated for patients with marginal or attic perforations and chronic central TM perforations. A disrupted ossicular chain may be repaired during tympanoplasty as well.

Cholesteatomas must be removed surgically. Because recurrence is common, reconstruction of the middle ear is usually deferred until a 2nd-look operation (using an open surgical approach or a small-diameter otoscope) is done 6 to 8 mo later.

Otitis Externa

External otitis is an acute infection of the ear canal skin typically caused by bacteria (*Pseudomonas* is most common). Symptoms include pain, discharge, and hearing loss if the ear canal has swollen shut; manipulation of the auricle causes pain. Diagnosis is based on inspection.

External otitis may manifest as a localized furuncle or as a diffuse infection of the entire canal (acute diffuse external otitis). The latter is often called swimmer's ear; the combination of water in the canal and use of cotton swabs is the major risk factor. Malignant external otitis is a severe *Pseudomonas* osteomyelitis of the temporal bone, usually affecting the elderly, diabetics, and immunocompromised patients.

Treatment

In mild and moderate acute external otitis, topical antibiotics and corticosteroids are effective. First, the infected debris should be gently and thoroughly removed from the canal with suction or dry cotton swabs under adequate lighting.

Moderate external otitis requires the addition of an antibacterial solution or suspension, such as ciprofloxacin.

Severe external otitis or the presence of cellulitis extending beyond the ear canal may require systemic antibiotics, such as cephalexin 500 mg po qid for 10 days or ciprofloxacin 500 mg po bid for 10 days. An analgesic, such as an NSAID or even an oral opioid, may be necessary for the first 24 to 48 h.

Malignant External Otitis

Malignant external otitis occurs mainly in elderly patients with diabetes or in immunocompromised patients. It is often initiated by *Pseudomonas* external otitis; methicillin-resistant *Staphylococcus aureus* (MRSA) has also been identified as a cause.

It is characterized by persistent and severe, deep-seated ear pain (often worse at night), foul-smelling purulent otorrhea, and granulation tissue or exposed bone in the ear canal (usually at the junction of the bony and cartilaginous portions of the canal).

Varying degrees of conductive hearing loss may occur. In severe cases, facial nerve paralysis, and even lower cranial nerve (IX, X, or XI) paralysis, may ensue as this erosive, potentially life-threatening infection spreads along the skull base (skull base osteomyelitis) from the stylomastoid foramen to the jugular foramen and beyond.

Treatment

Treatment is typically with a 6-wk IV course of a culture-directed fluoroquinolone (eg, ciprofloxacin, 400 mg IV q 8 h) and/or a semisynthetic penicillin (piperacillin–tazobactam or piperacillin)/aminoglycoside combination (for ciprofloxacin resistant *Pseudomonas*).

However, mild cases may be treated with a high-dose oral fluoroquinolone (eg, ciprofloxacin, 750 mg po q 12 h) on an outpatient basis with close follow-up.

Treatment also includes topical ciprofloxacin/dexamethasone preparations (eg, ear drops, impregnated canal dressings).

Hyperbaric oxygen may be a useful adjunctive treatment, but its definitive role remains to be elucidated. Consultation with an infectious disease specialist for optimal antibiotic therapy and duration and with an endocrinologist for strict diabetic control is recommended.

Extensive bone disease may require more prolonged antibiotic therapy. Meticulous control of diabetes is essential. Frequent office debridement is necessary to remove granulation tissue and purulent discharge. Surgery usually is not necessary, but surgical debridement to clear necrotic tissue may be used for more extensive infections.

Herpes Zoster Oticus (Ramsay Hunt Syndrome)

Herpes zoster oticus is an uncommon manifestation of herpes zoster that affects the 8th cranial nerve ganglia and the geniculate ganglion of the 7th (facial) cranial nerve.

Herpes zoster (shingles) is reactivation of varicella-zoster virus infection. Risk factors for reactivation include immunodeficiency secondary to cancer, chemotherapy, radiation therapy, and HIV infection.

Typically, the virus remains latent in a dorsal root ganglion, and reactivation manifests as painful skin lesions following a dermatomal distribution. However, rarely the virus remains latent in the geniculate ganglion and upon reactivation causes symptoms involving the 7th and 8th cranial nerves.

Symptoms and Signs

Symptoms of herpes zoster oticus include –

- Severe ear pain with vesicles in the ear
- Transient or permanent facial paralysis (resembling Bell palsy)
- Vertigo lasting days to weeks
- Hearing loss (which may be permanent or which may resolve partially or completely)

Vesicles occur on the pinna and in the external auditory canal along the distribution of the sensory branch of the facial nerve.

Treatment

Although there is no reliable evidence that corticosteroids, antiviral drugs, or surgical decompression makes a difference, they are the only possibly useful treatments. When used, corticosteroids are started with prednisone 60 mg po once/day for 4 days, followed by gradual tapering of the dose over the next 2 wk. Either acyclovir 800 mg po 5 times/day or valacyclovir 1 g po bid for 10 days may shorten the clinical course and is routinely prescribed for immunocompromised patients.

Vertigo is effectively suppressed with diazepam 2 to 5 mg po q 4 to 6 h. Pain may require oral opioids. Postherpetic neuralgia may be treated with amitriptyline.

Nasal and Pharyngeal Disorders

Nose

The nasal cavity is covered with a highly vascular mucosa that warms and humidifies incoming air. Each lateral wall of the cavity has 3 turbinates, which are bony shelves that increase the surface area, thereby allowing more effective heat and moisture exchange.

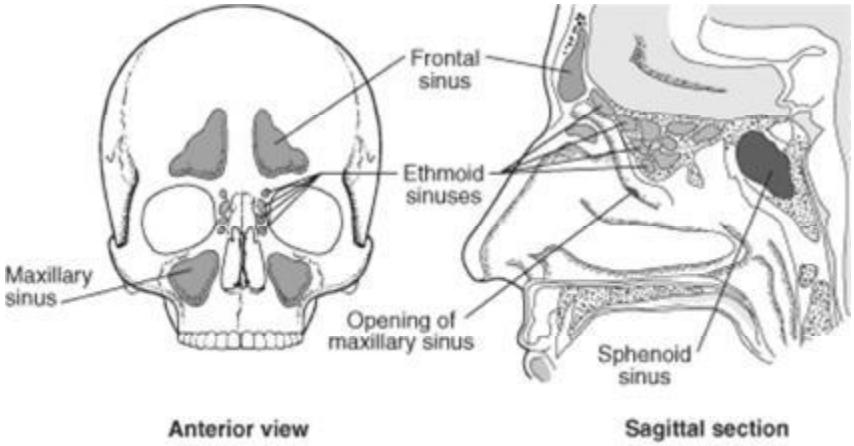
Nasal mucus traps incoming particulate matter. The space between the middle and inferior turbinate is the middle meatus, into which the maxillary and most of the ethmoid sinuses drain.

Polyps may develop between the turbinates, often in association with asthma, allergy, aspirin use, and cystic fibrosis.

Sinuses

The paranasal sinuses are mucus-lined bony cavities that connect to the nasopharynx. The 4 types are maxillary, frontal, ethmoid, and sphenoid sinuses. They are located in the facial and cranial bones. The physiologic role of the sinuses is unclear.

Paranasal sinuses.



Throat

The uvula hangs in the midline at the far end of the soft palate. It varies greatly in length. A long uvula and loose or excess velopharyngeal tissue may cause snoring and occasionally contribute to obstructive sleep apnea.

Tonsils and adenoids are patches of lymphoid tissue surrounding the posterior pharynx in an area termed Waldeyer's ring. Their role is to combat infection.

Nasal Congestion and Rhinorrhea

Nasal congestion and rhinorrhea (runny nose) are extremely common problems that commonly occur together but occasionally occur alone.

The most common causes are the following:

- Viral infections
- Allergic reactions

Causes of Nasal Congestion and Rhinorrhea

Cause	Suggestive Findings
Acute sinusitis	Mucopurulent discharge, often unilateral Red mucosa Sometimes a foul or metallic taste, focal facial pain or headache, and erythema or tenderness over the maxillary or frontal sinus
Allergies	Watery discharge; sneezing; watery, itchy eyes; pale, boggy nasal mucosa Symptoms often seasonal or with exposure to possible triggers
Decongestant overuse	Rebound congestion as decongestant wears off Pale, markedly swollen mucosa
Nasal foreign body	Unilateral, foul-smelling (sometimes blood-tinged) discharge in a child
Vasomotor rhinitis	Recurrent watery discharge; sneezing; red, swollen mucosa No identifiable triggers
Viral URI	Watery to mucoid discharge; accompanied by sore throat, malaise, erythematous nasal mucosa

Dry air may provoke congestion. Acute sinusitis is slightly less common, and a nasal foreign body is unusual (and occurs predominantly in children).

Patients who use topical decongestants for > 3 to 5 days often experience significant rebound congestion when the effects of the drug wear off, causing them to continue using the decongestant in a vicious circle of persistent, worsening congestion.

Treatment

Specific conditions are treated. Symptomatic relief of congestion can be achieved with topical or oral decongestants. Topical decongestants include oxymetazoline, 2 sprays each nostril once/day or bid for 3 days. Oral decongestants include pseudoephedrine 60 mg bid. Prolonged use should be avoided.

Viral rhinorrhea can be treated with oral antihistamines (eg, diphenhydramine 25 to 50 mg po bid), which are recommended because of their anticholinergic properties unrelated to their H_2-blocking properties.

Allergic congestion and rhinorrhea can be treated with antihistamines; in such cases, nonanticholinergic antihistamines (eg, fexofenadine 60 mg po bid) as needed provoke fewer adverse effects. Nasal corticosteroids (eg, mometasone 2 sprays each nostril daily) also help allergic conditions.

Antihistamines and decongestants are not recommended for children < 6 yr.

Nonallergic Rhinitis

It is the inflammation of the nasal mucous membrane, with resultant nasal congestion, rhinorrhea, and variable associated symptoms depending on etiology (eg, itching, sneezing, watery or purulent rhinorrhea, anosmia).

The cause of nonallergic rhinitis is usually viral, although irritants can cause it. Diagnosis is usually clinical.

Treatment includes humidification of room air, sympathomimetic amines, and antihistamines. Bacterial superinfection requires appropriate antibiotic treatment.

Acute rhinitis

Acute rhinitis, manifesting with edema and vasodilation of the nasal mucous membrane, rhinorrhea, and obstruction, is usually the result of a common cold; other causes include streptococcal, pneumococcal, and staphylococcal infections.

Chronic rhinitis

Chronic rhinitis is generally a prolongation of subacute (resolved in 30 to 90 days) inflammatory or infectious viral rhinitis.

It may also rarely occur in syphilis, TB, rhinoscleroma, rhinosporidiosis, leishmaniasis, blastomycosis, histoplasmosis, and leprosy—all of which are characterized by granuloma formation and destruction of soft tissue, cartilage, and bone.

Nasal obstruction, purulent rhinorrhea, and frequent bleeding result. Rhinoscleroma causes progressive nasal obstruction from indurated inflammatory tissue in the lamina propria.

Rhinosporidiosis is characterized by bleeding polyps. Both low humidity and airborne irritants can result in chronic rhinitis.

Atrophic rhinitis

Atrophic rhinitis, a form of chronic rhinitis, results in atrophy and sclerosis of mucous membrane; the mucous membrane changes from ciliated pseudostratified columnar epithelium to stratified squamous epithelium, and the lamina propria is reduced in amount and vascularity.

Atrophic rhinitis is associated with advanced age, granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis), and iatrogenically induced excessive nasal tissue extirpation. Although the exact etiology is unknown, bacterial infection frequently plays a role. Nasal mucosal atrophy often occurs in the elderly.

Vasomotor rhinitis

Vasomotor rhinitis is a chronic condition in which intermittent vascular engorgement of the nasal mucous membrane leads to watery rhinorrhea and sneezing.

Etiology is uncertain, and no allergy can be identified. A dry atmosphere seems to aggravate the condition.

Symptoms and Signs

Acute rhinitis results in cough, low-grade fever, nasal congestion, rhinorrhea, and sneezing.

Chronic rhinitis manifestations are similar to those of acute rhinitis, but in prolonged or severe cases, patients may also have thick, foul-smelling, mucopurulent drainage; mucosal crusting; and/or bleeding.

Atrophic rhinitis results in enlargement of the nasal cavities, crust formation and malodorous bacterial colonization, nasal congestion, anosmia, and epistaxis that may be recurrent and severe.

Vasomotor rhinitis results in sneezing and watery rhinorrhea. The turgescent mucous membrane varies from bright red to purple. The condition is marked by periods of remission and exacerbation.

Treatment

- For viral rhinitis, decongestants, antihistamines, or both
- For atrophic rhinitis, topical treatment

- For vasomotor rhinitis, humidification and sometimes topical corticosteroids and oral pseudoephedrine

Viral rhinitis may be treated symptomatically with decongestants (either topical vasoconstriction with a sympathomimetic amine, such as oxymetazoline q 8 to 12 h or phenylephrine 0.25% q 3 to 4 h for not more than 7 days, or systemic sympathomimetic amines, such as pseudoephedrine 30 mg po q 4 to 6 h).

Antihistamines may be helpful, but those with anticholinergic properties dry mucous membranes and therefore may increase irritation.

Decongestants also may relieve symptoms of acute bacterial rhinitis and chronic rhinitis, whereas an underlying bacterial infection requires culture, pathogen identification, antibiotic sensitivities, and appropriate antimicrobial treatment.

If symptoms persist, particularly in dry, crusted, atrophic rhinitis, biopsy may be necessary to rule out cancer.

Treatment of atrophic rhinitis is directed at reducing the crusting and eliminating the odor with nasal irrigation, topical antibiotics (eg, bacitracin, mupirocin), topical or systemic estrogens, and vitamins A and D.

Occluding or reducing the patency of the nasal cavities surgically decreases the crusting caused by the drying effect of air flowing over the atrophic mucous membrane.

Treatment of vasomotor rhinitis is by trial and error and is not always satisfactory. Patients benefit from humidified air, which may be provided by a humidified central heating system or a vaporizer in the workroom or bedroom.

Topical corticosteroids (eg, mometasone 2 sprays bid) and nasal antihistamines can be of some benefit.

Systemic sympathomimetic amines (eg, for adults, pseudoephedrine 30 mg po q 4 to 6 h) relieve symptoms but are not recommended for long-term use because they thicken the mucus and may cause tachycardia and nervousness.

Topical vasoconstrictors are avoided because they cause the vasculature of the nasal mucous membrane to lose its sensitivity to other vasoconstrictive stimuli—eg, the humidity and temperature of inspired air.

Sinusitis

It is the inflammation of the paranasal sinuses due to viral, bacterial, or fungal infections or allergic reactions.

Symptoms include nasal obstruction and congestion, purulent rhinorrhea, and facial pain or pressure; sometimes malaise, headache, and/or fever are present.

Treatment of suspected bacterial infection is with antibiotics, such as amoxicillin/clavulanate or doxycycline, given for 5 to 7 days for acute sinusitis and for up to 6 wk for chronic sinusitis.

Decongestants, corticosteroid nasal sprays, and application of heat and humidity may help relieve symptoms and improve sinus drainage. Recurrent sinusitis may require surgery to improve sinus drainage.

Sinusitis may be classified as acute (completely resolved in < 30 days); subacute (completely resolved in 30 to 90 days); recurrent (≥ 4 discrete acute episodes per year, each completely resolved in < 30 days but recurring in cycles, with at least 10 days between complete resolution of symptoms and initiation of a new episode); and chronic (lasting > 90 days).

Etiology

Acute sinusitis in immunocompetent patients in the community is almost always viral (eg, rhinovirus, influenza, parainfluenza).

A small percentage develop secondary bacterial infection with streptococci, pneumococci, *Haemophilus influenzae*, *Moraxella catarrhalis,* or staphylococci. Occasionally, a periapical dental abscess of a maxillary tooth spreads to the overlying sinus.

Hospital-acquired acute infections are more often bacterial, typically involving *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis,* and *Enterobacter*. Immunocompromised patients may have acute invasive fungal sinusitis (see Invasive Sinusitis in Immunocompromised Patients).

Chronic sinusitis involves many factors that combine to create chronic inflammation. Chronic allergies, structural abnormalities (eg, nasal polyps), environmental irritants (eg, airborne pollution, tobacco smoke), mucociliary dysfunction, and other factors interact with infectious organisms to cause chronic sinusitis. The organisms are commonly bacterial (possibly as part of a biofilm on the mucosal surface) but may be fungal.

Many bacteria have been implicated, including gram-negative bacilli and oropharyngeal anaerobic microorganisms; polymicrobial infection is common. In a few cases, chronic maxillary sinusitis is secondary to dental infection.

Fungal infections (*Aspergillus*, *Sporothrix*, *Pseudallescheria*) may be chronic and tend to strike the elderly and immunocompromised patients.

Allergic fungal sinusitis is a form of chronic sinusitis characterized by diffuse nasal congestion, markedly viscid nasal secretions, and, often, nasal polyps. It is an allergic response to the presence of topical fungi, often *Aspergillus,* and is not caused by an invasive infection.

Invasive fungal sinusitis is an aggressive, sometimes fatal, infection in immunocompromised patients, usually caused by *Aspergillus* or *Mucor* species.

Symptoms and Signs

Acute and chronic sinusitis cause similar symptoms and signs, including purulent rhinorrhea, pressure and pain in the face, nasal congestion and obstruction, hyposmia, halitosis, and productive cough (especially at night). Often the pain is more severe in acute sinusitis. The area over the affected sinus may be tender, swollen, and erythematous.

- Maxillary sinusitis causes pain in the maxillary area, toothache, and frontal headache.
- Frontal sinusitis causes pain in the frontal area and frontal headache.
- Ethmoid sinusitis causes pain behind and between the eyes, a frontal headache often described as splitting, periorbital cellulitis, and tearing.
- Sphenoid sinusitis causes less well localized pain referred to the frontal or occipital area.

Fever and chills suggest an extension of the infection beyond the sinuses.

The nasal mucous membrane is red and swollen; yellow or green purulent rhinorrhea may be present. Seropurulent or mucopurulent exudate may be seen in the middle meatus with maxillary, anterior ethmoid, or frontal sinusitis and in the area medial to the middle turbinate with posterior ethmoid or sphenoid sinusitis.

Manifestations of complications include periorbital swelling and redness, proptosis, ophthalmoplegia, confusion or decreased level of consciousness, and severe headache.

Treatment

- Local measures to enhance drainage (eg, steam, topical vasoconstrictors)
- Sometimes antibiotics (eg, amoxicillin/clavulanate, doxycycline)

In acute sinusitis, improved drainage and control of infection are the aims of therapy. Steam inhalation; hot, wet towels over the affected sinuses; and hot beverages help alleviate nasal vasoconstriction and promote drainage.

Topical vasoconstrictors, such as phenylephrine 0.25% spray q 3 h or oxymetazoline q 8 to 12 h, are effective but should be used for a maximum of 5 days or for a repeating cycle of 3 days on and 3 days off until the sinusitis is resolved.

Systemic vasoconstrictors, such as pseudoephedrine 30 mg po (for adults) q 4 to 6 h, are less effective.

Saline nasal irrigation may help symptoms slightly but is cumbersome and uncomfortable, and patients require teaching to execute it properly; it may thus be better for patients with recurrent sinusitis, who are more likely to master (and tolerate) the technique.

Corticosteroid nasal sprays can help relieve symptoms but typically take at least 10 days to be effective.

Antibiotic treatment

Although most cases of community-acquired acute sinusitis are viral and resolve spontaneously, previously many patients were given antibiotics because of the difficulty in clinically distinguishing viral from bacterial infection. However, current concerns about creation of antibiotic-resistant organisms have led to a more selective use of antibiotics. The Infectious Diseases Society of America suggests the following characteristics help identify patients who should be started on antibiotics:

- Mild to moderate sinus symptoms persisting for ≥ 10 days
- Severe symptoms (eg, fever ≥ 39°, severe pain) for ≥ 3 to 4 days
- Worsening sinus symptoms after initially improving from a typical viral URI ("double sickening" or biphasic illness)

Because many causative organisms are resistant to previously used drugs, amoxicillin/clavulanate 875 mg po q 12 h (25 mg/kg po q 12 h in children) is the current first-line drug.

Patients at risk of antibiotic resistance are given a higher dose of 2 g po q 12 h (45 mg/kg po q 12 h in children). Patients at risk of resistance include those who are under 2 yr of age or over

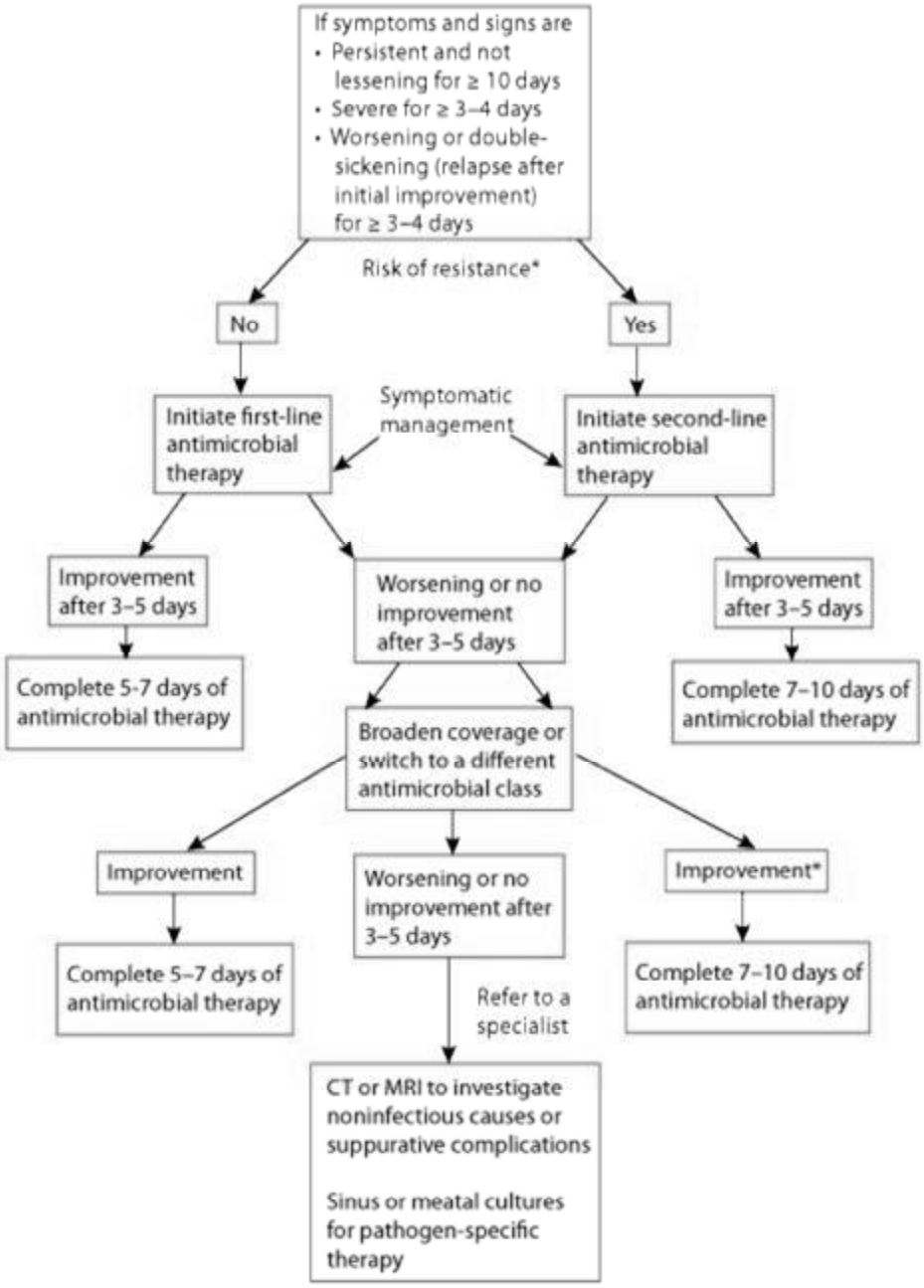
65 yr, who have received antibiotics in the previous month, who have been hospitalized within the past 5 days, and those who are immunocompromised.

Adults with penicillin allergy may receive doxycycline or a respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin). Children with penicillin allergy may receive levofloxacin, or clindamycin plus a 3rd-generation oral cephalosporin (cefixime or cefpodoxime).

If there is improvement within 3 to 5 days, the drug is continued. Adults without risk factors for resistance are treated for 5 to 7 days total; other adults are treated for 7 to 10 days. Children are treated for 10 to 14 days. If there is no improvement in 3 to 5 days, a different drug is used.

Macrolides, trimethoprim/sulfamethoxazole, and monotherapy with a cephalosporin are no longer recommended because of bacterial resistance. Emergency surgery is needed if there is vision loss or an imminent possibility of vision loss.

Algorithm for use of antibiotics in acute sinusitis.



*Risk factors for antibiotic resistance:

- Age < 2 or > 65 yr
- Attendance in daycare
- Prior antibiotic use within the past month
- Prior hospitalization within the past 5 days
- Coexisting disorders
- Immunocompromise

In exacerbations of chronic sinusitis in children or adults, the same antibiotics are used, but treatment is given for 4 to 6 wk. The sensitivities of pathogens isolated from the sinus exudate and the patient's response to treatment guide subsequent therapy.

Sinusitis unresponsive to antibiotic therapy may require surgery (maxillary sinusotomy, ethmoidectomy, or sphenoid sinusotomy) to improve ventilation and drainage and to remove inspissated mucopurulent material, epithelial debris, and hypertrophic mucous membrane. These procedures usually are done intranasally with the aid of an endoscope. Chronic frontal sinusitis may be managed either with osteoplastic obliteration of the frontal sinuses or endoscopically in selected patients. The use of intraoperative computer-aided surgery to localize disease and prevent injury to surrounding contiguous structures (such as the eye and brain) has become common. Nasal obstruction that is contributing to poor drainage may also require surgery.

Sore Throat

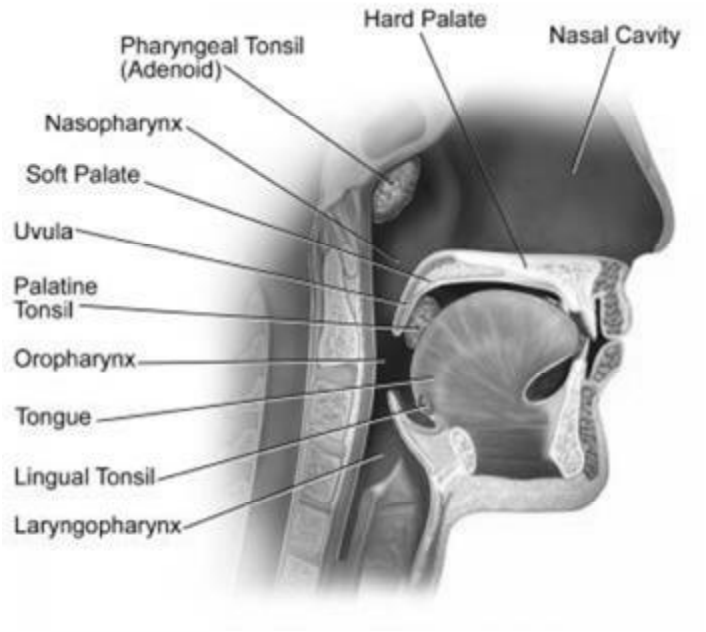
Sore throat is pain in the posterior pharynx that occurs with or without swallowing. Pain can be severe; many patients refuse oral intake.

Sore throat results from infection; the most common cause is tonsillopharyngitis. Rarely, an abscess or epiglottitis is involved; although uncommon, these are of particular concern because they may compromise the airway.

Tonsillopharyngitis

Tonsillopharyngitis is acute infection of the pharynx, palatine tonsils, or both. Symptoms may include sore throat, dysphagia, cervical lymphadenopathy, and fever. Diagnosis is clinical, supplemented by culture or rapid antigen test. Treatment depends on symptoms and, in the case of group A β-hemolytic streptococcus, involves antibiotics.

The tonsils participate in systemic immune surveillance. In addition, local tonsillar defenses include a lining of antigen-processing squamous epithelium that involves B- and T-cell responses.



Anatomy of the Tonsils and Throat (Sagittal View)

Tonsillopharyngitis of all varieties constitutes about 15% of all office visits to primary care physicians.

Etiology

Tonsillopharyngitis is usually viral, most often caused by the common cold viruses (adenovirus, rhinovirus, influenza, coronavirus, and respiratory syncytial virus), but occasionally by Epstein-Barr virus, herpes simplex virus, cytomegalovirus, or HIV.

In about 30% of patients, the cause is bacterial. Group A β-hemolytic streptococcus (GABHS) is most common but *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are sometimes involved.

Rare causes include pertussis, *Fusobacterium*, diphtheria, syphilis, and gonorrhea.

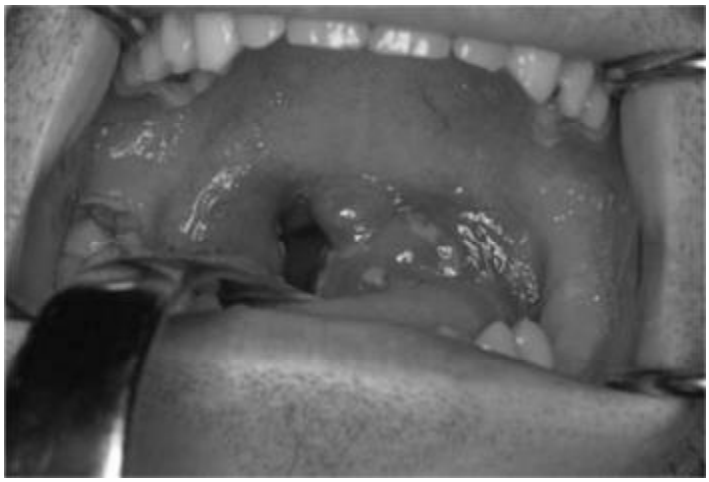
GABHS occurs most commonly between ages 5 and 15 and is uncommon before age 3.

Symptoms and Signs

Pain with swallowing is the hallmark and is often referred to the ears. Very young children who are not able to complain of sore throat often refuse to eat. High fever, malaise, headache, and GI upset are common, as are halitosis and a muffled voice. A rash may also be present. The tonsils are swollen and red and often have purulent exudates. Tender cervical

lymphadenopathy may be present. Fever, adenopathy, palatal petechiae, and exudates are somewhat more common with GABHS than with viral tonsillopharyngitis, but there is much overlap. With GABHS, a scarlatiniform rash (scarlet fever) may be present.

GABHS usually resolves within 7 days. Untreated GABHS may lead to local suppurative complications (eg, peritonsillar abscess or cellulitis) and sometimes to rheumatic fever or glomerulonephritis.



Acute Tonsillitis

Treatment

- Symptomatic treatment
- Antibiotics for GABHS
- Tonsillectomy considered for recurrent GABHS

Symptomatic treatments such as warm saltwater gargles and topical anesthetics (eg, benzocaine, lidocaine, dyclonine) may help temporarily relieve pain in tonsillopharyngitis. Patients in severe pain (even from tonsillopharyngitis) may require short-term use of opioids.

Corticosteroids (eg, dexamethasone, 10 mg IM) are occasionally used, for example, for tonsillopharyngitis that appears to pose a risk of airway obstruction (eg, due to mononucleosis) or very severe tonsillopharyngitis symptoms.

Supportive treatments include analgesia, hydration, and rest. Analgesics may be systemic or topical. NSAIDs are usually effective systemic analgesics. Some clinicians also give a single dose of a corticosteroid (eg, dexamethasone 10 mg IM), which may help shorten symptom duration without affecting rates of relapse or adverse effects.

Topical analgesics are available as lozenges and sprays; ingredients include benzocaine, phenol, lidocaine, and other substances. These topical analgesics can reduce pain but have to be used repeatedly and often affect taste. Benzocaine used for pharyngitis has rarely caused methemoglobinemia.

Penicillin V is usually considered the drug of choice for GABHS tonsillopharyngitis; dose is 250 mg po bid for 10 days for patients < 27 kg and 500 mg for those > 27 kg. Amoxicillin is effective and more palatable if a liquid preparation is required.

If compliance is a concern, a single dose of benzathine penicillin 1.2 million units IM (600,000 units for children ≤ 27 kg) is effective.

Other oral drugs include macrolides for patients allergic to penicillin, a 1st-generation cephalosporin, and clindamycin. Diluting over-the-counter hydrogen peroxide with water in a 1:1 mixture and gargling with it will promote debridement and improve oropharyngeal hygiene.

Treatment may be started immediately or delayed until culture results are known. If treatment is started presumptively, it should be stopped if cultures are negative.

Tonsillectomy

Tonsillectomy has often been considered if GABHS tonsillitis recurs repeatedly (> 6 episodes/yr, > 4 episodes/yr for 2 yr, or > 3 episodes/yr for 3 yr) or if acute infection is severe and persistent despite antibiotics.

Other criteria for tonsillectomy include obstructive sleep disorder, recurrent peritonsillar abscess, and suspicion of cancer.

Numerous effective surgical techniques are used to perform tonsillectomy, including electrocautery dissection, microdebrider, radiofrequency coblation, and sharp dissection.

Significant intraoperative or postoperative bleeding occurs in < 2% of patients, usually within 24 h of surgery or after 7 days, when the eschar detaches. Patients with bleeding should go to the hospital.

Dizziness and Vertigo

Dizziness is an imprecise term patients often use to describe various related sensations, including –

- Faintness (a feeling of impending syncope)
- Light-headedness
- Feeling of imbalance or unsteadiness
- A vague spaced-out or swimmy-headed feeling
- A spinning sensation

Vertigo is a false sensation of movement of the self or the environment. Usually the perceived movement is rotary—a spinning or wheeling sensation—but some patients simply feel pulled to one side. Vertigo is not a diagnosis—it is a description of a sensation.

Both sensations may be accompanied by nausea and vomiting or difficulty with balance, gait, or both.

Perhaps because these sensations are hard to describe in words, patients often use “dizziness,” “vertigo,” and other terms interchangeably and inconsistently. Different patients with the same underlying disorder may describe their symptoms very differently.

However they are described, dizziness and vertigo may be disturbing and even incapacitating, particularly when accompanied by nausea and vomiting. Symptoms cause particular problems for people doing an exacting or dangerous task, such as driving, flying, or operating heavy machinery.

Pathophysiology

The vestibular system is the main neurologic system involved in balance. This system includes –

- The vestibular apparatus of the inner ear
- The 8th (vestibulocochlear) cranial nerve, which conducts signals from the vestibular apparatus to the central components of the system
- The vestibular nuclei in the brain stem and cerebellum

Disorders of the inner ear and 8th cranial nerve are considered peripheral disorders. Those of the vestibular nuclei and their pathways in the brain stem and cerebellum are considered central disorders.

The sense of balance also incorporates visual input from the eyes and proprioceptive input from the peripheral nerves (via the spinal cord). The cerebral cortex receives output from the lower centers and integrates the information to produce the perception of motion.

Etiology

There are numerous structural (trauma, tumors, degenerative), vascular, infectious, toxic (including drug-related), and idiopathic causes but only a small percentage of cases are caused by a serious disorder.

The most common causes of dizziness with vertigo involve some component of the peripheral vestibular system:

- Benign paroxysmal positional vertigo
- Meniere disease
- Vestibular neuronitis
- Labyrinthitis

The most common causes of dizziness without vertigo are less clear cut, but they are usually not otologic and probably are:

- Drug effects
- Multifactorial or idiopathic

Occasionally, dizziness and vertigo may be psychogenic. Patients with panic disorder, hyperventilation syndrome, anxiety, or depression may present with complaints of dizziness.

Treatment

Treatment is directed at the cause, including stopping, reducing, or switching any causative drugs.

If a vestibular disorder is present and thought to be secondary to active Meniere disease or vestibular neuronitis or labyrinthitis, the most effective vestibular nerve suppressants are diazepam (2 to 5 mg po q 6 to 8 h, with higher doses given under supervision for severe vertigo) or oral antihistamine/anticholinergic drugs (eg, meclizine 25 to 50 mg tid).

All of these drugs can cause drowsiness, thereby limiting their use for certain patients. Nausea can be treated with prochlorperazine 10 mg IM qid or 25 mg rectally bid.

Gastroenterology

Overview of Gastro-Intestinal (GI) Symptoms

Upper GI complaints include -

- Chronic and recurrent abdominal pain
- Dyspepsia
- Nausea and vomiting
- Regurgitation

Some upper GI complaints represent functional illness (ie, no physiologic cause found after extensive evaluation).

Lower GI complaints include -

- Constipation
- Diarrhea
- Gas and bloating
- Abdominal pain
- Rectal pain or bleeding

As with upper GI complaints, lower GI complaints result from physiologic illness or represent a functional disorder (ie, no radiologic, biochemical, or pathologic abnormalities are found even after extensive evaluation). The reasons for functional symptoms are not clear.

Causes of Chronic Abdominal Pain

Cause	Suggestive Findings*
Endometriosis	Discomfort before or during menses
Ovarian cyst, ovarian cancer	Vague lower abdominal discomfort, bloating Sometimes a palpable pelvic mass
Renal calculi	Fever, flank pain, dark or bloody urine
Celiac disease	In children, failure to thrive Abdominal bloating, diarrhea, and often steatorrhea Symptoms that worsen when gluten-containing products are ingested
Chronic appendicitis	Several previous discrete episodes of RLQ pain
Chronic cholecystitis	Recurrent colicky RUQ pain
Chronic hepatitis	Upper abdominal discomfort, malaise, anorexia

Cause	Suggestive Findings*
	Jaundice uncommon In about one third of patients, a history of acute hepatitis
Chronic pancreatitis, pancreatic pseudocyst	Episodes of severe epigastric pain Sometimes malabsorption (eg, diarrhea, fatty stool) Usually a history of acute pancreatitis
Colon cancer	Discomfort uncommon but possibly colicky discomfort if left colon is partially obstructed Often occult or visible blood in stool
Crohn disease	Episodic severe pain with fever, anorexia, weight loss, diarrhea Extraintestinal symptoms (joints, eyes, mouth, skin)
Gastric cancer	Dyspepsia or mild pain Often occult blood in stool
Hiatus hernia with gastroesophageal reflux	Heartburn Sometimes cough and/or hoarseness Symptoms relieved by taking antacids Sometimes regurgitation of gastric contents into mouth
Intestinal TB	Chronic nonspecific pain Sometimes palpable RLQ mass Fever, diarrhea, weight loss
Lactose intolerance	Bloating and cramps after ingesting milk products
Pancreatic cancer	Severe upper abdominal pain that • Often radiates to the back • Occurs late in disease, when weight loss is often present • May cause obstructive jaundice
Parasitic infestation (particularly giardiasis)	Cramps, flatulence, diarrhea
Peptic ulcer disease	Upper abdominal pain relieved by food and antacids May awaken patient at night
Ulcerative colitis	Crampy pain with bloody diarrhea
Food allergy	Symptoms developing only after consuming certain foods (eg, seafood)
Sickle cell disease	Family history Severe episodes of abdominal pain lasting over a day Recurrent pain in nonabdominal sites

Dyspepsia

Dyspepsia is a sensation of pain or discomfort in the upper abdomen; it often is recurrent. It may be described as indigestion, gassiness, early satiety, postprandial fullness, gnawing, or burning.

Causes

There are several common causes of dyspepsia as shown in the following table -

Cause	Suggestive Findings
Achalasia	Slowly progressive dysphagia Early satiety, nausea, vomiting, bloating, and symptoms that are worsened by food Sometimes nocturnal regurgitation of undigested food Chest discomfort
Cancer (eg, esophageal, gastric)	Chronic, vague discomfort Later, dysphagia (esophageal) or early satiety (gastric) Weight loss
Coronary ischemia	Symptoms described as gas or indigestion rather than chest pain by some patients May have exertional component Cardiac risk factors
Delayed gastric emptying (caused by diabetes, viral illness, or drugs)	Nausea, bloating, fullness
Esophageal spasm	Substernal chest pain with or without dysphagia for liquids and solids
Gastroesophageal reflux disease	Heartburn Sometimes reflux of acid or stomach contents into mouth Symptoms sometimes triggered by lying down Relief with antacids
Peptic ulcer disease	Burning or gnawing pain relieved by food or antacids

Treatment

Symptoms are treated with Proton Pump Inhibitors (PPIs), H_2 blockers, or a cytoprotective agent.

Prokinetic drugs (eg, metoclopramide) given as a liquid suspension also may be tried in patients with dysmotility-like dyspepsia. However, there is no clear evidence that matching the drug class to the specific symptoms (eg, reflux vs dysmotility) makes a difference. Drugs that alter sensory perception (eg, tricyclic antidepressants) may be helpful.

Some Oral Drugs for Dyspepsia

Drug	Usual Dose	Comments
Proton pump inhibitors		
Esomeprazole	40 mg once/day	With long-term use, elevated gastrin levels, but no evidence that this finding causes dysplasia or cancer May cause abdominal pain or diarrhea
Lansoprazole	30 mg once/day	
Omeprazole	20 mg once/day	
Pantoprazole	40 mg once/day	
Rabeprazole	20 mg once/day	
H_2 blockers		
Cimetidine	800 mg once/day	
Famotidine	40 mg once/day	Doses reduced in elderly patients With cimetidine and to a lesser extent with other drugs, minor antiandrogen effects and, less commonly, erectile dysfunction Delayed metabolism of drugs eliminated by cytochrome P-450 enzyme system (eg, phenytoin, warfarin, diazepam) May cause constipation or diarrhea
Nizatidine	300 mg once/day	
Ranitidine	300 mg once/day or 150 mg bid	
Cytoprotective agent		
Sucralfate	1 g po qid	
		Rarely constipation May bind to other drugs and interfere with absorption Cimetidine, ciprofloxacin, digoxin, norfloxacin, ofloxacin, and ranitidine avoided 2 h before or after taking sucralfate

Nausea and Vomiting

Nausea, the unpleasant feeling of needing to vomit, represents awareness of afferent stimuli (including increased parasympathetic tone) to the medullary vomiting center.

Vomiting is the forceful expulsion of gastric contents caused by involuntary contraction of the abdominal musculature when the gastric fundus and lower esophageal sphincter are relaxed.

Vomiting should be distinguished from regurgitation, the spitting up of gastric contents without associated nausea or forceful abdominal muscular contractions. Patients with achalasia or rumination syndrome or a Zenker diverticulum may regurgitate undigested food without nausea.

Complications

Severe vomiting can lead to symptomatic dehydration and electrolyte abnormalities (typically a metabolic alkalosis with hypokalemia) or rarely to an esophageal tear, either partial (Mallory-Weiss) or complete (Boerhaave syndrome).

Chronic vomiting can result in undernutrition, weight loss, and metabolic abnormalities.

Causes

Nausea and vomiting occur in response to conditions that affect the vomiting center. Causes may originate in the GI tract or CNS or may result from a number of systemic conditions.

The most common causes of nausea and vomiting are the following:

- Gastroenteritis
- Drugs
- Toxins

Some Causes of Nausea and Vomiting

Cause	Suggestive Findings*	Diagnostic Approach
GI disorders		
Bowel obstruction	Constipation, distention, tympany Often bilious vomiting, abdominal surgical scars, or hernia	Flat and upright abdominal x-rays
Gastroenteritis	Vomiting, diarrhea Benign abdominal examination	Clinical evaluation
Gastroparesis or ileus	Vomiting of partially digested food a few hours after ingestion Often in diabetics or after abdominal surgery	Flat and upright abdominal x-rays Succussion splash
Hepatitis	Mild to moderate nausea for many days, sometimes vomiting Jaundice, anorexia, malaise Sometimes slight tenderness over the liver	Serum aminotransferases, bilirubin, viral hepatitis titers
Perforated viscus or other acute abdomen (eg, appendicitis, cholecystitis, pancreatitis)	Significant abdominal pain Usually peritoneal signs	
CNS disorders		
Closed head injury	Apparent based on history	Head CT
CNS hemorrhage	Sudden-onset headache, mental status change Often meningeal signs	Head CT Lumbar puncture if CT is normal
CNS infection	Gradual-onset headache Often meningeal signs, mental status change Sometimes petechial rash due to meningococcemia	Head CT Lumbar puncture
Increased intracranial pressure (eg, caused by hematoma or tumor)	Headache, mental status change Sometimes focal neurologic deficits	Head CT
Labyrinthitis	Vertigo, nystagmus, symptoms worsened by motion, tinnitus	

Cause	Suggestive Findings*	Diagnostic Approach
Migraine	Headache sometimes preceded or accompanied by a neurologic aura or photophobia Often a history of recurrent similar attacks	Clinical evaluation Head CT and lumbar puncture considered if evaluation is unclear
Motion sickness	Apparent based on history	Clinical evaluation
Psychogenic disorders	Occurring with stress Eating food considered repulsive	Clinical evaluation
Systemic conditions		
Advanced cancer (independent of chemotherapy or bowel obstruction)	Apparent based on history	Clinical evaluation
Diabetic ketoacidosis	Polyuria, polydipsia Often significant dehydration With or without history of diabetes	Serum glucose, electrolytes, ketones
Drug adverse effect or toxicity	Apparent based on history	Varies with substance
Liver failure or renal failure	Often apparent based on history Often jaundice in advanced liver disease, uremic odor in renal failure	Laboratory tests of liver and renal function
Pregnancy	Often occurring in morning or triggered by food Benign examination (possibly dehydration)	Pregnancy test
Radiation exposure	Apparent based on history	Clinical evaluation
Severe pain (eg, due to a kidney stone)	Varies with cause	Clinical evaluation

Treatment

Specific conditions, including dehydration, are treated. Even without significant dehydration, IV fluid therapy (0.9% saline 1 L, or 20 mL/kg in children) often leads to reduction of symptoms.

In adults, various antiemetics are effective. Choice of agent varies somewhat with the cause and severity of symptoms.

- Motion sickness: Antihistamines, scopolamine patches, or both

- Mild to moderate symptoms: Prochlorperazine or metoclopramide
- Severe or refractory vomiting and vomiting caused by chemotherapy: 5-HT_3 antagonists

Obviously, only parenteral agents should be used in actively vomiting patients.

For psychogenic vomiting, reassurance indicates awareness of the patient's discomfort and a desire to work toward relief of symptoms, regardless of cause.

Brief symptomatic treatment with antiemetics can be tried. If long-term management is necessary, supportive, regular office visits may help resolve the underlying problem.

Some Drugs for treatment of Vomiting

Drug	Usual Dose	Comments
Antihistamines		
Dimenhydrinate	50 mg po q 4–6 h	Used to treat vomiting of labyrinthine etiology (eg, motion sickness, labyrinthitis)
Meclizine	25 mg po q 8 h	
5-HT_3antagonists		
Granisetron	1 mg po or IV tid	Used to treat severe or refractory vomiting, or vomiting due to chemotherapy
Ondansetron	4–8 mg po or IV q 8 h	
Other drugs		
Metoclopramide	5–20 mg po or IV tid to qid	Used with highly emetogenic chemotherapy regimens Possible adverse effects: Somnolence, fatigue, hiccups
Prochlorperazine	5–10 mg IV or 25 mg per rectum	—
Scopolamine	1-mg patch worn for up to 72 h	Used to treat motion sickness Possible adverse effects: Diminished sweating, dry skin

Constipation

Constipation is difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation.

Many people incorrectly believe that daily defecation is necessary and complain of constipation if stools occur less frequently. Others are concerned with the appearance (size, shape, color) or consistency of stools.

Sometimes the major complaint is dissatisfaction with the act of defecation or the sense of incomplete evacuation after defecation.

Constipation is blamed for many complaints (abdominal pain, nausea, fatigue, anorexia) that are actually symptoms of an underlying problem (eg, irritable bowel syndrome [IBS], depression).

Patients should not expect all symptoms to be relieved by a daily bowel movement, and measures to aid bowel habits should be used judiciously.

Causes

Acute constipation suggests an organic cause, whereas chronic constipation may be organic or functional.

In many patients, constipation is associated with sluggish movement of stool through the colon. This delay may be due to drugs, organic conditions, or a disorder of defecatory function (ie, pelvic floor dysfunction), or a disorder that results from diet.

Patients with disordered defecation do not generate adequate rectal propulsive forces, do not relax the puborectalis muscle and the external anal sphincter during defecation, or both.

In IBS, patients have symptoms (eg, abdominal discomfort and altered bowel habits) but generally normal colonic transit and anorectal functions.

Excessive straining, perhaps secondary to pelvic floor dysfunction, may contribute to anorectal pathology (eg, hemorrhoids, anal fissures, and rectal prolapse) and possibly even to syncope.

Fecal impaction, which may cause or develop from constipation, is also common among elderly patients, particularly with prolonged bed rest or decreased physical activity. It is also common after barium has been given by mouth or enema.

Causes of Constipation

Causes	Examples
Acute constipation*	
Bowel obstruction	Volvulus, hernia, adhesions, fecal impaction
Adynamic ileus	Peritonitis, major acute illness (eg, sepsis), head or spinal trauma, bed rest
Drugs	Anticholinergics (eg, antihistamines, antipsychotics, antiparkinsonian drugs, antispasmodics), cations (iron, aluminum, calcium, barium, bismuth), opioids, calcium channel blockers, general anesthetics Constipation shortly after start of therapy with the drug
Chronic constipation*	
Colonic tumor	Adenocarcinoma of sigmoid colon
Metabolic disorders	Diabetes mellitus, hypothyroidism, hypocalcemia or hypercalcemia, pregnancy, uremia, porphyria
CNS disorders	Parkinson disease, multiple sclerosis, stroke, spinal cord lesions
Peripheral nervous system disorders	Hirschsprung disease, neurofibromatosis, autonomic neuropathy
Systemic disorders	Systemic sclerosis, amyloidosis, autoimmune myositis, myotonic dystrophy
Functional disorders	Slow-transit constipation, irritable bowel syndrome, pelvic floor dysfunction (functional defecatory disorders)
Dietary factors	Low-fiber diet, sugar-restricted diet, chronic laxative abuse
*There is some overlap between acute and chronic causes of constipation. In particular, drugs are common causes of chronic constipation.	

Foods Often Affecting GI Function

Foods likely to cause loose bowel movements and/or excessive gas
All caffeine-containing beverages especially coffee with chicory
Peaches, pears, cherries, apples
Fruit juices: Orange, cranberry, apple
Asparagus and cruciferous vegetables such as broccoli, cauliflower, cabbage, and Brussels sprouts
Bran cereal, whole wheat bread, high-fiber foods

Foods likely to cause loose bowel movements and/or excessive gas
Pastry, candy, chocolate, waffle syrup, doughnuts
Wine (> 3 glasses in susceptible people)
Milk and milk products (in lactose-sensitive people)
Foods likely to cause constipation or help control loose bowel movements
Rice, bread, potatoes, pasta
Meat, veal, poultry, fish
Cooked vegetables
Bananas

Treatment

- Possibly discontinuation of causative drugs (some may be necessary)
- Increase in dietary fiber
- Possibly trial with a brief course of osmotic laxatives

Any identified conditions should be treated.

Laxatives should be used judiciously. Some substances (eg, phosphate, bran, cellulose) bind drugs and interfere with absorption. Rapid fecal transit may rush some drugs and nutrients beyond their optimal absorptive locus.

Contraindications to laxative use include acute abdominal pain of unknown origin, inflammatory bowel disorders, intestinal obstruction, GI bleeding, and fecal impaction.

Diet and behavior

The diet should contain enough fiber (typically 15 to 20 g/day) to ensure adequate stool bulk.

Vegetable fiber, which is largely indigestible and unabsorbable, increases stool bulk. Certain components of fiber also absorb fluid, making stools softer and facilitating their passage. Fruits and vegetables are recommended sources, as are cereals containing bran.

Fiber supplementation is particularly effective in treating normal-transit constipation but is not very effective for slow-transit constipation or defecatory disorders.

Behavioral changes may help. Patients should try to move their bowels at the same time daily, preferably 15 to 45 min after breakfast, because food ingestion stimulates colonic motility. Initial efforts at regular, unhurried bowel movements may be aided by glycerin suppositories.

Explanation is important, but it is difficult to convince obsessive-compulsive patients that their attitude toward defecation is abnormal. Physicians must explain that daily bowel movements are not essential, that the bowel must be given a chance to function, and that frequent use of laxatives or enemas (> once/3 days) denies the bowel that chance.

Laxatives -

Bulking agents (eg, psyllium, calcium polycarbophil, methylcellulose) act slowly and gently and are the safest agents for promoting defecation.

Bloating may be reduced by gradually titrating the dose of dietary fiber to the recommended dose, or by switching to a synthetic fiber preparation such as methylcellulose.

Osmotic agents contain poorly absorbed polyvalent ions (eg, magnesium, phosphate, sulfate), polymers (eg, polyethylene glycol), or carbohydrates (eg, lactulose, sorbitol) that remain in the bowel, increasing intraluminal osmotic pressure and thereby drawing water into the intestine. The increased volume stimulates peristalsis. These agents usually work within 3 h.

In general, osmotic laxatives are reasonably safe even when used regularly. However, in large or frequent doses, these drugs may upset fluid and electrolyte balance.

Secretory or stimulant cathartics (eg, phenolphthalein, bisacodyl, anthraquinones, castor oil, anthraquinones) act by irritating the intestinal mucosa or by directly stimulating the submucosal and myenteric plexus.

Bisacodyl is an effective rescue drug for chronic constipation.

The anthraquinones senna, cascara sagrada, aloe, and rhubarb are common constituents of herbal and OTC laxatives. They pass unchanged to the colon where bacterial metabolism converts them to active forms.

Adverse effects include allergic reactions and electrolyte depletion.

Enemas can be used, including tap water and commercially prepared hypertonic solutions.

Emollient agents (eg, docusate, mineral oil) act slowly to soften stools, making them easier to pass. However, they are not potent stimulators of defecation.

Docusate is a surfactant, which allows water to enter the fecal mass to soften and increase its bulk.

Diarrhea

Diarrhea is defined as passing frequent and/or watery stools.

Complications of diarrhea

Complications may result from diarrhea of any etiology.

Fluid loss with consequent dehydration, electrolyte loss (sodium, potassium, magnesium, chloride), and even vascular collapse sometimes occur. Collapse can develop rapidly in patients who have severe diarrhea (eg, patients with cholera) or are very young, very old, or debilitated.

Bicarbonate loss can cause metabolic acidosis.

Hypokalemia can occur when patients have severe or chronic diarrhea or if the stool contains excess mucus.

Hypomagnesemia after prolonged diarrhea can cause tetany.

Causes of diarrhoea

Normally, the small intestine and colon absorb 99% of fluid resulting from oral intake and GI tract secretions—a total fluid load of about 9 of 10 L daily. Thus, even small reductions (ie, 1%) in intestinal water absorption or increases in secretion can increase water content enough to cause diarrhea.

There are a number of causes of diarrhea. Several basic mechanisms are responsible for most clinically significant diarrheas: increased osmotic load, increased secretions, and decreased contact time/surface area.

In many disorders, more than one mechanism is active. For example, diarrhea in inflammatory bowel disease results from mucosal inflammation, exudation into the lumen, and from multiple secretagogues and bacterial toxins that affect enterocyte function.

Increased secretions

Diarrhea occurs when the bowels secrete more electrolytes and water than they absorb. Causes of increased secretions include infections, unabsorbed fats, certain drugs, and various intrinsic and extrinsic secretagogues.

Infections (eg, gastroenteritis) are the most common causes of secretory diarrhea. Infections combined with food poisoning are the most common causes of acute diarrhea (< 4 days in duration). Most enterotoxins block sodium-potassium exchange, which is an important driving force for fluid absorption in the small bowel and colon.

Unabsorbed dietary fat and bile acids (as in malabsorption syndromes) can stimulate colonic secretion and cause diarrhea.

Drugs may stimulate intestinal secretions directly (eg, quinidine, quinine, colchicine, anthraquinone cathartics, castor oil, prostaglandins) or indirectly by impairing fat absorption (eg, orlistat).

Various endocrine tumors produce secretagogues, including vipomas (vasoactive intestinal peptide), gastrinomas (gastrin), mastocytosis (histamine), medullary carcinoma of the thyroid (calcitonin and prostaglandins), and carcinoid tumors (histamine, serotonin, and polypeptides). Some of these mediators (eg, prostaglandins, serotonin, related compounds) also accelerate intestinal transit, colonic transit, or both.

Reduced contact time/surface area

Rapid intestinal transit and diminished surface area impair fluid absorption and cause diarrhea.

Common causes include small-bowel or large-bowel resection or bypass, gastric resection, and inflammatory bowel disease.

Other causes include microscopic colitis (collagenous or lymphocytic colitis) and celiac disease.

Stimulation of intestinal smooth muscle by drugs (eg, magnesium-containing antacids, laxatives, cholinesterase inhibitors, SSRIs) or humoral agents (eg, prostaglandins, serotonin) also can speed transit.

Some common Causes of Diarrhea

Type	Examples
Acute	
Viral infection	Norovirus, rotavirus
Bacterial infection	Salmonella, Campylobacter, or Shigella sp; Escherichia coli; Clostridium difficile

Type	Examples
Parasitic infection	Giardia sp, Entamoeba histolytica, Cryptosporidia sp
Food poisoning	Staphylococci, *Bacillus cereus,*Clostridium perfringens
Drugs	Laxatives, magnesium-containing antacids, caffeine, antineoplastic drugs, many antibiotics, colchicine, quinine/quinidine, prostaglandin analogs, excipients (eg, lactose) in elixirs
Chronic	
Drugs	See Acute (above)
Functional	Irritable bowel syndrome
Dietary factors	See table: Dietary Factors That May Worsen Diarrhea
Inflammatory bowel disease	Ulcerative colitis, Crohn disease
Surgery	Intestinal or gastric bypass or resection
Malabsorption syndromes	Celiac disease, pancreatic insufficiency Carbohydrate intolerance (particularly lactose intolerance)
Tumors	Colon carcinoma, lymphoma, villous adenoma of the colon
Endocrine tumors	Vipoma, gastrinoma, carcinoid tumors, mastocytosis, medullary carcinoma of the thyroid
Endocrine	Hyperthyroidism Diabetes (multifactorial concurrent celiac disease, pancreatic insufficiency, autonomic neuropathy)

Treatment

- Fluid and electrolytes for dehydration
- Possibly antidiarrheals for nonbloody diarrhea in patients without systemic toxicity

Severe diarrhea requires fluid and electrolyte replacement to correct dehydration, electrolyte imbalance, and acidosis.

Parenteral fluids containing sodium chloride, potassium chloride, and glucose are generally required.

Salts to counteract acidosis (sodium lactate, acetate, bicarbonate) may be indicated if serum bicarbonate is < 15 mEq/L.

An oral glucose-electrolyte solution can be given if diarrhea is not severe and nausea and vomiting are minimal. Oral and parenteral fluids are sometimes given simultaneously when water and electrolytes must be replaced in massive amounts (eg, in cholera).

Oral rehydration solution (ORS) should contain

- Complex carbohydrate or 2% glucose
- 50 to 90 mEq/L of sodium

Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little sodium and too much carbohydrate to take advantage of sodium/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss. The sodium/glucose cotransport in the gut is optimized with a sodium:glucose ratio of 1:1.

Oral rehydration solution is recommended by the WHO and is widely available in the US without prescription. Most solutions come as powders that are mixed with tap water. An ORS packet is dissolved in 1 L of water to produce a solution containing the following (in mmol/L)

- Standard WHO ORS: Sodium 90, potassium 20, chloride 80, citrate 10, and glucose 111
- WHO reduced-osmolarity ORS: Sodium 75, potassium 20, chloride 65, citrate 10, and glucose 75

It can also be made manually by adding 1 L of water to 3.5 g table salt, 2.9 g trisodium citrate (or 2.5 g sodium bicarbonate), 1.5 g potassium chloride, and 20 g glucose.

ORS is effective in patients with dehydration regardless of age, cause, or type of electrolyte imbalance (hyponatremia, hypernatremia, or isonatremia) as long as their kidneys are functioning adequately.

Administration

Generally, 50 mL/kg is given over 4 h for mild dehydration and 100 mL/kg for moderate dehydration. For each diarrheal stool, an additional 10 mL/kg (up to 240 mL) is given. After 4 h, the patient is reassessed. If signs of dehydration persist, the same volume is repeated. Patients with cholera may require many liters of fluid/day.

Vomiting usually should not deter oral rehydration (unless there is bowel obstruction or other contraindication) because vomiting typically abates over time. Small, frequent amounts are used, starting with 5 mL every 5 min and increasing gradually as tolerated. The calculated volume required over a 4-h period can be divided into 4 separate aliquots. These 4 aliquots can

then be divided into 12 smaller aliquots and given every 5 min over the course of an hour with a syringe if needed.

In children with diarrhea, oral intake often precipitates a diarrheal stool, so the same volume should be given in fewer aliquots.

Once the deficit has been replaced, an oral maintenance solution containing less sodium should be used. Children should eat an age-appropriate diet as soon as they have been rehydrated and are not vomiting. Infants may resume breastfeeding or formula.

Diarrhea is a symptom. When possible, the underlying disorder should be treated, but symptomatic treatment is often necessary.

Diarrhea may be decreased by oral loperamide 2 to 4 mg tid or qid (preferably given 30 min before meals), diphenoxylate 2.5 to 5 mg (tablets or liquid) tid or qid, codeine phosphate 15 to 30 mg bid or tid.

Pathophysiology of Acid – Peptic Disorders

The focus is on the identification and treatment of potential causes of symptoms such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and medication side effects.

The upper G-I tract when exposed to the acid and pepsin secretion from stomach is prone to develop certain ailments, such as –

- Gastro-oesophageal Reflux Disease (GERD) or Reflux Oesophagitis
- Duodenal Ulcer
- Gastric Ulcer
- Stress Ulcers

Gastro-oesophageal Reflux Disease (GERD) or Reflux Oesophagitis

GERD indicates inflammatory changes leading to damage to the mucosal lining of oesophagus following reflux of acid gastric contents into the oesophagus.

The normal anti-reflux mechanism consisting of the lower oesophageal sphincter does not allow stomach contents to reenter oesophagus. However, such a reflux of stomach contents occurs when:

- Volume of stomach increases e.g. after meals, due to acid hypersecretion or pyloric obstruction
- Pressure inside stomach increases e.g. due to obesity, pregnancy or *ascites*
- Stomach contents are located near the gastro-oesophageal junction e.g. lying down or bending down soon after meals or when a *hiatus hernia* is present
- Anti-reflux mechanism is not fully functional e.g. due to muscle weakness, smoking, use of smooth muscle relaxing drugs like beta-blockers, calcium channel blockers, nitrates or aminophylline, and during pregnancy

Oesophagitis is the result when oesophageal protective mechanisms are overwhelmed by the onslaught of refluxed acid peptic contents. Initially, a mild oesophagitis characterized by microscopic mucosal changes of infiltration by WBCs and proliferation of basal mucosal cells. A more severe condition viz. erosive oesophagitis shows visible damage to oesophageal mucosa along with redness, bleeding and *ulceration*.

The clinical features of GERD include –

- Heartburn i.e. a burning sensation or pain behind chest bone (*sternum*) particularly at night or on lying down
- Dysphagia or difficulty in swallowing, usually seen in later stages
- Morning hoarseness of voice resulting from *laryngitis* i.e. irritation of throat by refluxed acid

Management of a patient with GERD calls for reduction in gastro-oesophageal reflux, improve oesophageal clearance and protect the oesophageal mucosa from acid.

The non-pharmacological measures helpful in achieving these goals include:

- Weight reduction
- Sleeping with head end of bed elevated
- Avoiding smoking
- Avoiding fatty foods, coffee, alcohol, citrus juices, calcium antagonists, an smooth muscle relaxants
- Avoiding consumption of large quantities of fluids with meals etc.

The drug therapy for moderate to severe cases of oesophagitis requires an agent to control gastric acid secretion and a gastric prokinetic agent that raises lower oesophageal sphincter pressure, hastens gastric emptying and improves oesophageal clearance.

Peptic Ulcer

Peptic ulcer is a sharply circumcised loss of tissue lining those parts of the G-I tract exposed to gastric juice containing acid & pepsin.

The common sites are stomach – gastric ulcer, and duodenum – duodenal ulcer.

The causative processes leading to peptic ulcer can be outlined in a nutshell as below:

- An increase in the gastric acid secretion due to various causes viz. genetic predisposition, smoking, alcoholism, and stressful environment
- A decrease in the ability of the mucosal lining to protect against acid due to changes in cell turnover, prostaglandin synthesis (NSAIDs), local blood flow
- Infection by the pathogen Helicobacter pylori

Stress Ulcers

In seriously ill hospitalized patients stress ulcers are very common. They occur due to a decrease in blood flow the mucosal surface leading to ulceration.

Therapeutic approach to acid-peptic disorders

Antacids still have a role as primary treatment for most acid-peptic disorders as they are inexpensive, readily available, and safe in most populations. Antacids work nearly instantaneously and find utility for rapid relief of mild or sporadic symptoms. The primary effect of antacids on the stomach is due to partial neutralization of gastric hydrochloric acid and inhibition of the proteolytic enzyme pepsin. Neutralization of acid in the gut lumen bypasses the need for systemic absorption of the drug. They are all administered orally.

The commonly used agents are the insoluble antacids aluminum hydroxide and magnesium hydroxide. Aluminum-containing products can cause constipation. To counteract this, these agents are often combined with magnesium hydroxide, which, when administered alone, can cause diarrhea and loose stools.

Proton Pump Inhibitors

An empiric Proton Pump Inhibitor (PPI) trial or 'test and treat' strategy for *H. pylori* are among the initial approaches to a patient with GERD, medication-induced gastritis, and peptic ulcers.

H. pylori eradication regimens

Regimen	Comment
Triple therapy	First line treatment
PPI; amoxicillin 1 g BID; clarithromycin 500mg BID for 10–14 days	
Sequential therapy	
PPI and amoxicillin 1 g BID for 5 days followed by PPI, clarithromycin 500mg BID, tinidazole 500mg BID for 5 days	May be first line where macrolide resistance is common
Quadruple therapy	
PPI; bismuth 525mg QID; metronidazole 500mg QID; and tetracycline 500mg QID for 14 days	Treatment for failure

Haematology

Introduction

Blood is a complex mixture of

- Plasma (the liquid component)
- White blood cells (WBCs)
- Red blood cells (RBCs)
- Platelets

The body contains about 5 to 6 quarts (about 5 liters) of blood. Once blood is pumped out of the heart, it takes 20 to 30 seconds to make a complete trip through the circulation and return to the heart.

Blood performs various essential functions as it circulates through the body.

- It delivers oxygen and essential nutrients (such as fats, sugars, minerals, and vitamins) to the body's tissues.
- It carries carbon dioxide to the lungs and other waste products to the kidneys for elimination from the body.
- It transports hormones (chemical messengers) to allow various parts of the body to communicate with each other.
- It also carries components that fight infection and stop bleeding.

Components of Blood

The main components of blood include -

Plasma

Plasma is the liquid component of blood, in which the red blood cells, white blood cells, and platelets are suspended. It constitutes more than half of the blood's volume and consists mostly of water that contains dissolved salts (electrolytes) and proteins.

The major protein in plasma is albumin. Albumin helps keep fluid from leaking out of blood vessels and into tissues, and albumin binds to and carries substances such as hormones and certain drugs.

Other proteins in plasma include antibodies (immunoglobulins), which actively defend the body against viruses, bacteria, fungi, and cancer cells, and clotting factors, which control bleeding.

Plasma has other functions. It acts as a reservoir that can either replenish insufficient water or absorb excess water from tissues. When body tissues need additional liquid, water from plasma is the first resource to meet that need.

Plasma also prevents blood vessels from collapsing and clogging and helps maintain blood pressure and circulation throughout the body simply by filling blood vessels and flowing through them continuously.

Plasma circulation also plays a role in regulating body temperature by carrying heat generated in core body tissues through areas that lose heat more readily, such as the arms, legs, and head.

Red Blood Cells

Red blood cells (also called erythrocytes) make up about 40% of the blood's volume.

Red blood cells contain hemoglobin, a protein that gives blood its red color and enables it to carry oxygen from the lungs and deliver it to all body tissues. Oxygen is used by cells to produce energy that the body needs, leaving carbon dioxide as a waste product.

Red blood cells carry carbon dioxide away from the tissues and back to the lungs. When the number of red blood cells is too low (anemia), blood carries less oxygen, and fatigue and weakness develop.

When the number of red blood cells is too high (erythrocytosis, as in polycythemia vera), blood can become too thick, which may cause the blood to clot more easily and increase the risk of heart attacks and strokes.

Red Blood Cells

White Blood Cells

White blood cells (also called leukocytes) are fewer in number than red blood cells, with a ratio of about 1 white blood cell to every 600 to 700 red blood cells.

White blood cells are responsible primarily for defending the body against infection. There are five main types of white blood cells.

Neutrophils, the most numerous type, help protect the body against infections by killing and ingesting bacteria and fungi and by ingesting foreign debris.

Lymphocytes consist of three main types: T lymphocytes and natural killer cells, which both help protect against viral infections and can detect and destroy some cancer cells, and B lymphocytes, which develop into cells that produce antibodies.

Monocytes ingest dead or damaged cells and help defend against many infectious organisms.

Eosinophils kill parasites, destroy cancer cells, and are involved in allergic responses.

Basophils also participate in allergic responses.

Some white blood cells flow smoothly through the bloodstream, but many adhere to blood vessel walls or even penetrate the vessel walls to enter other tissues. When white blood cells reach the site of an infection or other problem, they release substances that attract more white blood cells.

The white blood cells function like an army, dispersed throughout the body but ready at a moment's notice to gather and fight off an invading organism. White blood cells accomplish this by engulfing and digesting organisms and by producing antibodies that attach to organisms so that they can be more easily destroyed.

When the number of white blood cells is too low (leukopenia), infections are more likely to occur.

A higher than normal number of white blood cells (leukocytosis) may not directly cause symptoms, but the high number of cells can be an indication of an underlying disorder such as an infection, inflammatory process or leukemia.

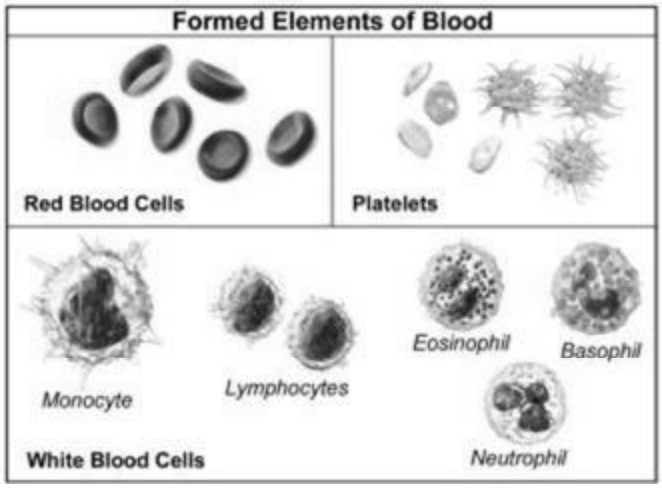
Platelets

Platelets (also called thrombocytes) are cell-like particles that are smaller than red or white blood cells. Platelets are fewer in number than red blood cells, with a ratio of about 1 platelet to every 20 red blood cells.

Platelets help in the clotting process by gathering at a bleeding site and clumping together to form a plug that helps seal the blood vessel. At the same time, they release substances that help promote further clotting.

When the number of platelets is too low (thrombocytopenia), bruising and abnormal bleeding become more likely.

When the number of platelets is too high (thrombocythemia), blood may clot excessively causing a transient ischemic attack. When the number of platelets is extremely high, the platelets can absorb clotting proteins and paradoxically cause bleeding.



Types of Blood Cells

Overview of Blood Disorders

Disorders that affect the blood are called blood disorders or hematologic disorders. There are many blood disorders, and they can affect the quantity as well as the functionality of the cells in the blood (blood cells) or proteins in the blood clotting system or immune system.

Some blood disorders cause the number of cells in the blood to decrease:

- A decreased number of red blood cells is called anemia.
- A decreased number of white blood cells is called leukopenia.
- A decreased number of platelets is called thrombocytopenia.

Common Causes of Anemia

Mechanism	Examples
Decreased red blood cell production	Aplastic anemia Folate deficiency Iron deficiency Leukemia Lymphoma Myelodysplasia (abnormalities in bone marrow tissue) Vitamin B12 deficiency
Increased red blood cell destruction	Autoimmune reactions against red blood cells An enlarged spleen Glucose-6-phosphate dehydrogenase (G6PD) deficiency Sickle cell disease Thalassemia

Other blood disorders cause the numbers of blood cells to increase:

- An increased number of red blood cells is called erythrocytosis.
- An increased number of white blood cells is called leukocytosis.
- An increased number of platelets is called thrombocytosis or thrombocythemia.

Other blood disorders affect proteins within the blood cells or blood plasma (the liquid portion of the blood):

- Hemoglobin, the oxygen-carrying protein inside red blood cells
- Immune system proteins, such as antibodies (also called immunoglobulins)
- Blood clotting factors

Blood flows to every cell in the body and is important to the health and function of all of the body's organs. Blood cells and blood proteins provide the following functions:

- Red blood cells contain hemoglobin, which carries oxygen to every part of the body.
- White blood cells and antibodies fight infections and cancers.
- Platelets and blood clotting factors make bleeding stop or prevent bleeding from occurring.

Blood disorders cause symptoms resulting from disruption of these functions, and symptoms can arise from any tissues and organs that are adversely affected.

Doctors discover the presence of a blood disorder by a blood test such as the complete blood count (CBC) that is done when the doctor is investigating why a person is not feeling well. The doctor usually must do further blood tests to diagnose a person's blood disorder, and sometimes a bone marrow biopsy is necessary.

Symptoms of Blood Disorders

Blood disorders can cause various symptoms in almost any area of the body. Most commonly, symptoms are caused by decreases in the blood components.

- Decreased red blood cells and hemoglobin can cause symptoms of anemia, such as fatigue, weakness, and shortness of breath.
- Decreased white blood cells or immune system proteins can cause recurrent fever and infections.
- Decreased platelets or blood clotting factors can cause abnormal bleeding and bruising.

Occasionally, symptoms may relate to increases in blood components.

- Increased red blood cells can cause headache and a red complexion (plethora).
- Increased white blood cells or immune system proteins can cause increased blood viscosity (thickening of the blood).
- Increased platelets or blood clotting factors can cause thrombosis (inappropriate excessive blood clotting).

Some blood disorders cause a person's blood to become thickened by increased quantities of immune-related proteins, red blood cells, white blood cells, or platelets. This thickened (more viscous) blood may have difficulty passing through small blood vessels, decreasing blood flow to certain areas of the body, which is a serious condition called hyperviscosity syndrome. Affected people may experience symptoms such as shortness of breath, headaches, dizziness, and confusion. Hyperviscosity syndrome can occur in people who have multiple myeloma, in which it is caused by increased immune system proteins.

Some symptoms are more suggestive of a blood disorder. Just a few examples include the following:

- Blood clot (phlebitis), usually in a leg (most often causing swelling, redness, and/or warmth of the leg or shortness of breath)
- Petechiae (a fine pin-point red skin rash) caused by low platelet count
- Blood blisters in the mouth (caused by too few platelets or clotting problems)
- Swollen lymph nodes caused by white blood cell cancers (leukemias, lymphomas)
- Pallor (pale skin) caused by anemia
- Pica (eating of ice, dirt, or clay) suggests iron deficiency anemia

Laboratory Tests for Blood Disorders

When a blood disorder is suspected, a complete blood count and other tests may need to be done to determine the specific diagnosis.

How Blood Is Obtained

Blood is obtained from a vein with a needle and syringe or sometimes from the fingertip by a needle prick.

A vein, usually one on the inside surface of the person's elbow is used. A tourniquet is applied around the upper arm, causing the veins below it to fill with blood so that they may be more easily seen or felt.

After the skin immediately surrounding the vein is cleaned thoroughly, a needle is inserted into the vein. A stinging sensation is usually felt when the needle is first inserted, but otherwise the procedure is painless.

Blood moves through the needle and into a collecting tube. Once enough blood is collected, the tourniquet is removed, the needle is then removed from the vein, and pressure is applied to the area to prevent bleeding from the puncture site.

If only a small amount of blood is needed, the area, usually a finger (the heel in infants), is cleaned and a needle is used to prick the skin.

Complete blood count

The blood test most commonly done is the complete blood count (CBC). The CBC is an evaluation of all the cellular components (red blood cells, white blood cells, and platelets) in the blood.

Automated machines do this test in less than 1 minute on a small amount of blood. The CBC is supplemented in some instances by examination of blood cells under a microscope.

Red blood cell parameters evaluated by CBC include –

- Number of red blood cells (red blood cell count, RBCs)
- Proportion of blood made up of red blood cells (hematocrit, Hct)
- Amount of hemoglobin (the oxygen-carrying protein in red blood cells) in the blood (hemoglobin, Hb)
- Average size of red blood cells (mean cellular volume, MCV)
- Variability of size of red blood cells (red cell distribution width, RDW)
- Amount of hemoglobin in an individual red blood cell (mean cellular hemoglobin, MCH)
- Concentration of hemoglobin in an individual red blood cell (mean cellular hemoglobin concentration, MCHC)

Abnormalities in these parameters can alert laboratory workers to the presence of abnormalities in the red blood cells (which may then be further evaluated by examination under a microscope).

Abnormal red blood cells may be fragmented or shaped like teardrops, crescents (sickle-shaped), or a variety of other forms.

Knowing the specific shape and size of red blood cells can help a doctor diagnose a particular cause of anemia. For example, sickle-shaped cells are characteristic of sickle cell disease, small cells containing insufficient amounts of hemoglobin are likely due to iron deficiency anemia, and large oval cells suggest anemia due to a deficiency of folate (folic acid) or vitamin B_{12}.

White blood cell parameters evaluated by the CBC include –

- Total number of white blood cells
- Percentages and numbers of the different types of white blood cells

The white blood cells are the major component of the body's immune system. There are normally five types of white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and different types are recruited into service when the immune system responds to different stresses or disorders.

Counting the number of white blood cells of each type (differential white blood cell count) can suggest possible causes of a change in the total white blood cell count. For example, if a person with cold symptoms has an increased white blood cell count due to increased neutrophils, the doctor would likely suspect a bacterial pneumonia rather than a viral infection because neutrophils are more often recruited to fight bacterial infections.

To provide more information about the white blood cells, the doctor can examine these cells under a microscope. The microscopic examination can identify features of the cells that are characteristic of certain diseases. For example, large numbers of white blood cells that have a very immature appearance (blasts) may indicate leukemia (cancer of the white blood cells).

Platelets are also counted as part of a CBC. The number of platelets is an important measure of the blood's ability to form blood clots for stopping bleeding. Too few platelets may impair blood clotting.

A high number of platelets (thrombocytosis) can lead to excessive blood clotting in small blood vessels, especially those in the heart or brain. However, in some disorders, a high number of platelets may paradoxically result in excess bleeding.

Reticulocyte count

The reticulocyte count measures the number of newly formed (young) red blood cells (reticulocytes) in a specified volume of blood. Reticulocytes normally make up about 0.5 to 2.5% of the total number of red blood cells. When the body needs more red blood cells, as in

anemia, the bone marrow normally responds by producing more reticulocytes. Thus, the reticulocyte count is a measure of the capacity of the bone marrow to make new red blood cells.

Special tests of blood cells

Clotting tests

One measure of the body's ability to stop bleeding is the count of the number of platelets. Sometimes doctors need to test how well the platelets function. Other tests can measure the overall function of the many proteins needed for normal blood clotting (clotting factors). The most common of these tests are the prothrombin time (PT) and the partial thromboplastin time (PTT). The levels of individual clotting factors can also be determined.

Measures of proteins and other substances

Blood plasma (the liquid portion of blood) contains many proteins. Urine contains very small amounts of protein. Doctors sometimes measure these proteins to look for abnormalities in their quantity or structure.

For example, in multiple myeloma, certain bone marrow cells, called plasma cells, become cancerous and produce unusual antibody (immunoglobulin) proteins (including Bence Jones proteins) that can be measured in blood and urine.

Erythropoietin is a protein made in the kidneys that stimulates the bone marrow to produce red blood cells. The level of this protein can be measured in the blood.

Levels of iron and certain vitamins (for example, B_{12} and folate) that are necessary for the production of healthy blood cells also can be measured.

Blood typing

Blood type, which is determined by the presence of certain proteins on the surface of red blood cells, can be identified by measuring the reaction of a small sample of a person's blood to certain antibodies. Blood typing requires evaluation of both the plasma and red blood cells.

Blood typing must be done before blood can be transfused.

Complete Blood Count (CBC)*

Test	What It Measures	Normal Values
Hemoglobin	Amount of this oxygen-carrying protein within a volume of blood	Men: 14 to 17 grams per deciliter Women: 12 to 16 grams per deciliter
Hematocrit	Proportion of the total amount of blood (blood volume) made up of red blood cells (plasma makes up the rest)	Men: 41 to 51% Women: 36 to 47%
Mean cellular (or corpuscular) volume (MCV)	Average volume of a red blood cell	80 to 100 femtoliters per cell
Mean cellular (or corpuscular) hemoglobin (MCH)	Amount of hemoglobin per red blood cell	28 to 32 picograms per cell
Mean cellular (or corpuscular) hemoglobin concentration (MCHC)	Average concentration of hemoglobin within red blood cells	32 to 36 grams per deciliter of red blood cells
Red blood cell (RBC) count	Number of RBCs in a volume of blood	Men: 4.5 to 5.9 million cells per microliter Women: 4.0 to 5.2 million cells per microliter
Red cell distribution width	Amount of variability in the sizes of the red blood cells	11.5 to 14.5%
White blood cell count	Number of white blood cells in a specified volume of blood	4,500 to 11,000 per microliter
Differential white blood cell count	Percentages and numbers of the different types of white blood cells	Segmented neutrophils: 40 to 70%, or 1800 to 7700 per microliter Lymphocytes: 22 to 44%, or 1000 to 4800 per microliter Monocytes: 4 to 11%, or 200 to 1200 per microliter Eosinophils: 0 to 8%, or 0

Test	What It Measures	Normal Values
		to 900 per microliter Basophils: 0 to 3%, or 0 to 300 per microliter
Platelet count	Number of platelets in a specified volume of blood	140,000 to 450,000 per microliter

*Normal values vary from laboratory to laboratory.

Bone Marrow Examination

Sometimes a sample of bone marrow must be examined to determine why blood cells are abnormal or why there are too few or too many of a specific kind of blood cell. A doctor can take two different types of bone marrow samples:

- Bone marrow aspirate: Removes fluid and cells by inserting a needle into the bone marrow and sucking out fluid and cells
- Bone marrow core biopsy: Removes an intact piece of bone marrow using a coring device (similar to a larger diameter needle)

The bone marrow aspirate shows what cells, normal and abnormal, are present in the bone marrow. Special tests, such as cultures for bacteria, fungi, or viruses, chromosomal analysis, and analysis of cell surface proteins (flow cytometry), can be done on the sample.

The core biopsy shows how full the bone marrow is with cells and where the cells are located within the marrow.

Both types of samples are usually taken from the hipbone (iliac crest), although aspirates are rarely taken from the breastbone (sternum). In very young children, bone marrow samples are occasionally taken from one of the bones in the lower leg (tibia).

Although the aspirate often provides enough information for a diagnosis to be made, the process of drawing the marrow into the syringe breaks up the fragile bone marrow. As a result, determining the original arrangement of the cells is difficult.

When the exact anatomic relationships of cells must be determined and the structure of the tissues evaluated, the doctor also does a core biopsy. A small core of intact bone marrow is

removed with a special bone marrow biopsy needle and sliced into thin sections that are examined under a microscope.

A bone marrow sampling begins with cleaning, sterilizing, and anesthetizing the skin over the bone. The procedure generally involves a slight jolt of pain, followed by minimal discomfort. The procedure takes a few minutes and causes no lasting damage to the bone.

Bone marrow samples are usually taken from the hipbone (iliac crest). The person may lie on one side, facing away from the doctor, with the knee of the top leg bent. After disinfecting the skin and numbing the area over the bone with a local anesthetic, the doctor inserts a needle into the bone and withdraws the marrow.

Leukemia

The leukemias are cancers of the WBCs involving bone marrow, circulating WBCs, and organs such as the spleen and lymph nodes.

Risk of developing leukemia is increased in patients with –

- History of exposure to ionizing radiation (eg, post–atom bomb in Nagasaki and Hiroshima) or to chemicals (eg, benzene)
- Prior treatment with certain antineoplastic drugs, particularly procarbazine, nitrosureas (cyclophosphamide, melphalan), and epipodophyllotoxins (etoposide, teniposide)
- Infection with a virus (eg, human T-lymphotropic virus 1 and 2, Epstein-Barr virus)
- Chromosomal translocations
- Preexisting conditions, including immunodeficiency disorders, chronic myeloproliferative disorders, and chromosomal disorders (eg, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Down syndrome, infantile X-linked agammaglobulinemia)

Pathophysiology

Malignant transformation usually occurs at the pluripotent stem cell level. Abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

Manifestations of leukemia are due to –

- Suppression of normal blood cell formation

  Inhibitory factors produced by leukemic cells and replacement of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia.

- Organ infiltration by leukemic cells

  Organ infiltration results in enlargement of the liver, spleen, and lymph nodes and, occasionally, in kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure (eg, cranial nerve palsies).

Classification

Acute leukemias

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms). Acute leukemias are divided into acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML).

Chronic leukemias

Chronic leukemias have more mature cells than do acute leukemias. They usually manifest as abnormal leukocytosis with or without cytopenia in an otherwise asymptomatic person. Findings and management differ significantly between chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML).

Findings at Diagnosis in the Most Common Leukemias

Feature	Acute Lymphocytic	Acute Myelogenous	Chronic Lymphocytic	Chronic Myelogenous
Peak age of incidence	Childhood	Any age	Middle and old age	Young adulthood
WBC count	High in 50% Normal or low in 50%	High in 60% Normal or low in 40%	High in 98% Normal or low in 2%	High in 100%
Differential WBC count	Many lymphoblasts	Many myeloblasts	Small lymphocytes	Entire myeloid series

Feature	Acute Lymphocytic	Acute Myelogenous	Chronic Lymphocytic	Chronic Myelogenous
Anemia	Severe in >90%	Severe in >90%	Mild in about 50%	Mild in 80%
Platelets	Low in > 80%	Low in > 90%	Low in 20 to 30%	High in 60% Low in 10%
Lymphadenopathy	Common	Occasional	Common	Infrequent
Splenomegaly	In 60%	In 50%	Usual and moderate	Usual and severe

Treatment of Acute Leukemias

The goal of treatment is complete remission, including resolution of abnormal clinical features, restoration of normal blood counts and normal hematopoiesis with < 5% blast cells in the bone marrow, and elimination of the leukemic clone.

The 4 general phases of chemotherapy for ALL include –

- Remission induction

  Remission can be induced with daily oral prednisone and weekly IV vincristine with the addition of an anthracycline or asparaginase. Other drugs and combinations that may be introduced early in treatment are cytarabine and etoposide as well as cyclophosphamide. In some regimens, intermediate-dose or high-dose IV methotrexate is given with leucovorin rescue.

- CNS prophylaxis

  Prophylaxis and treatment may include intrathecal methotrexate, cytarabine, and corticosteroids in combination or methotrexate and cytarabine singly.

- Postremission consolidation or intensification

  Usually lasts a few months and combines drugs that have different mechanisms of action than drugs used in induction regimens.

- Maintenance

  Therapy with methotrexate and mercaptopurine.

Treatment for AML includes –

- Induction therapy

  Basic regimen includes cytarabine by continuous IV infusion or high doses for 5 to 7 days; daunorubicin or idarubicin is given IV for 3 days during this time.

- Consolidation therapy

  High-dose cytarabine regimens may lengthen remission duration.

Stem cell transplantation and new immunotherapies may be helpful for relapse.

Supportive care for acute leukemias

Supportive care is similar in the acute leukemias and may include –

- Transfusions
- Antibiotics or antifungal drugs
- Hydration and urine alkalinization
- Psychologic support

Treatment of chronic leukemias

Specific therapy for CLL includes –

- Chemotherapy

  Alkylating drugs, especially chlorambucil, alone or with corticosteroids, have long been the usual therapy for B-cell CLL. However, fludarabine is more effective. Combination chemotherapy with fludarabine, cyclophosphamide, and rituximab more often induces complete remissions.

- Corticosteroids

  Prednisone 1 mg/kg po once/day may be used in patients who have immunohemolytic anemia and thrombocytopenia.

- Monoclonal antibody therapy

Rituximab combined with fludarabine and with fludarabine and cyclophosphamide markedly improved the complete remission rate.

- Radiation therapy

  Local irradiation for palliation may be given to areas of lymphadenopathy or for liver and spleen involvement that does not respond to chemotherapy.

Supportive care includes –

- Transfusion of packed RBCs or erythropoietin injections for anemia
- Platelet transfusions for bleeding associated with thrombocytopenia
- Antimicrobials for bacterial, fungal, or viral infections

Treatment for CML includes –

- A tyrosine kinase inhibitor, sometimes with chemotherapy
- Sometimes stem cell transplantation

Except when stem cell transplantation is successful, treatment is not known to be curative.

Imatinib and several newer drugs (dasatinib, nilotinib) that inhibit the specific tyrosine kinase that results from the *BCR-ABL* gene product, are dramatically effective in achieving complete clinical and cytogenetic remissions of CML.

Older chemotherapy regimens are reserved for *BCR-ABL*–negative patients, patients who relapse after receiving a TKI, and patients in the blast phase. The main agents are busulfan, hydroxyurea, and interferon.

Lymphoma

Lymphomas are a heterogeneous group of tumors arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin lymphoma and non-Hodgkin lymphoma.

Comparison of Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Feature	Hodgkin Lymphoma	Non-Hodgkin Lymphoma
Nodal involvement	Localized to a specific group of nodes	Usually disseminated among > 1 nodal group
Spread	Tends to spread in an orderly,	Spreads noncontiguously

Feature	Hodgkin Lymphoma	Non-Hodgkin Lymphoma
	contiguous fashion	
Effect on Waldeyer ring and mesenteric lymph nodes	Usually does not affect	Commonly affects mesenteric nodes May affect Waldeyer ring
Extranodal involvement	Infrequent	Frequent
Stage at diagnosis	Usually early	Usually advanced
Histologic classification in children	Usually one with a favorable prognosis	Usually aggressive

Hodgkin Lymphoma

Hodgkin lymphoma is a localized or disseminated malignant proliferation of cells of the lymphoreticular system, primarily involving lymph node tissue, spleen, liver, and bone marrow.

Symptoms include painless lymphadenopathy, sometimes with fever, night sweats, unintentional weight loss, pruritus, splenomegaly, and hepatomegaly.

Hodgkin lymphoma results from the clonal transformation of cells of B-cell origin, giving rise to pathognomic binucleated Reed-Sternberg cells.

Treatment

- Chemotherapy
- Radiation therapy
- Surgery
- Sometimes hematopoietic stem cell transplantation

In early stage, patients may be treated with abbreviated chemotherapy regimen of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus radiation therapy or with longer-course chemotherapy alone.

In later stages disease is usually treated with ABVD combination chemotherapy alone as standard. Other effective drugs include nitrosoureas, ifosfamide, procarbazine, cisplatin or carboplatin, and etoposide.

Other drug combinations are bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone (known as BEACOPP);

and melchlorethamine, doxorubicin, vinblastine, vincristine, etoposide, bleomycin, and prednisone (known as Stanford V).

Non-Hodgkin Lymphomas

Non -Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, the spleen, the liver, and the GI tract.

Most (80 to 85%) NHL arise from B lymphocytes; the remainder arise from T lymphocytes or natural killer cells.

Non-Hodgkin lymphomas are commonly also categorized as indolent or aggressive:

- Indolent: Slowly progressive and responsive to therapy but not typically curable with standard approaches
- Aggressive: Rapidly progressive but responsive to therapy and often curable

Treatment

- Chemotherapy, radiation therapy, or both
- Immunotherapy with anti-CD20 monoclonal antibody, with or without chemotherapy
- Sometimes hematopoietic stem cell transplantation

External beam radiation therapy is used for stage I non-Hodgkin lymphoma.

Most patients with all types of NHL who have stage II to IV disease are candidates for chemoimmunotherapy.

In patients with the aggressive B-cell lymphomas (eg, diffuse large B cell), the standard drug combination is rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (R-CHOP).

In patients with peripheral T-cell NHL and primary CNS lymphoma autologous stem cell transplantation is offered to initial responders before relapse.

Infectious Diseases

Introduction to Microbiology

Life on our planet can be divided into plant kingdom and animal kingdom. This is the simplest way of classifying the living organisms. The plants were different from the animals since they produced energy directly from the sunlight while animals were dependent on the plants or other animals to provide them with energy. On the other hand, animals were freely mobile but the plants could not move from one place to another on their own.

Following the discovery of the magnifying glass and later the microscope, it was seen that plant cells possessed a rigid wall around the cell while animal cells only had a cell membrane but no cell wall.

Microscope also opened up a new world of living things that could not be seen with the naked eye. There were microorganisms (the organisms seen only through a microscope) that resembled the plants in some features while their other features were more close to the animals. Therefore a new kingdom called protista* was established that included these microorganisms.

This is how the science or the study of microorganisms i.e. *microbiology* has developed over the years helping us in our understanding of the fascinating world of microorganisms including viruses, bacteria, fungi etc.; their properties, and their impact on human beings.

Bacteria

Bacteria (singular – bacterium) are unicellular microorganisms that possess a cell wall & multiply by cell division. They belong to the kingdom Protista. The bacteria are named by the genus i.e. a larger group or type & the species i.e. an individual strain with certain characteristics. For example, Staphylococcus is the genus and aureus is the species.

Structure of bacterial cell

The bacterial cell consists of a cell envelope and the cytoplasm.

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* *Protista* - a kingdom comprising of both animal-like and plant-like unicellular organisms. (From Greek protista = the very first.)

Cell Envelope

It is the outermost covering of bacterial cell. It consists of the following:

a) Cell wall – It is a rigid structure made up of proteins and polysaccharides. In some bacteria there are lipid-containing layers too.

b) Cell membrane – it is the boundary between the cytoplasm and the cell wall. It is also known as the cytoplasmic membrane.

The cell wall functions as a protective coat. It may be further fortified by an outer *capsule* in some bacteria.

Cytoplasmic membrane regulates the biochemical exchange process involving nutrients and waste materials.

Cytoplasm

The cytoplasm is a jelly-like material which contains the following:

a) Nucleus – It is composed of the chromosomes carrying the genetic information.

b) Cytoplasmic organelles – These are the structures performing various metabolic functions vital for the cell. They include mitochondria, ribosomes, endoplasmic reticulum etc.

Classification of bacteria

The vast variety of bacteria needs to be classified into a smaller number of groups in order to understand them better.

There are various ways by which we can classify the bacteria. For example, they may be divided into aerobes and anaerobes depending on their need for oxygen.

Or they may be grouped as pathogens or non-pathogens depending on their ability to cause illness in man.

A very important method of classifying the bacteria is based on their staining characteristics. This involves the use of certain chemical agents (called dyes or stains) that impart a specific colour to the organism thus helping in identifying and differentiating the bacteria.

Gram staining is one such important staining method. In this method, a purple dye & a dilute iodine solution is applied to the bacterial sample and then washed off with alcohol. Next, a red dye is applied to the sample and washed off with tap water.

Using this differential staining we can distinguish between Gram positive bacteria that retain the first purple dye and appear purple (or deep violet), and Gram negative bacteria that do not retain the purple dye and hence take up the second red dye to appear pinkish red when seen under the microscope.

Another important basis for classification is the shape of bacteria. Thus, we have cocci that are spherical in shape. They may be arranged in pairs –diplococci, in chains – streptococci, or bunches – staphylococci.

Bacilli are rod-shaped bacteria. Bacteria with a spiral shape are called spirilla while vibrios are curved, comma-shaped bacteria.

The important bacteria and diseases caused by them can be summarized as follows:

Organism	Diseases
A] Aerobes	
1) Gram positive	
a. Cocci	
i. Staphylococcus aureus	boils, cellulitis, endocarditis, eye infections, food poisoning, hospital-acquired infections, impetigo, osteomyelitis, otitis externa, pneumonia, septicaemia, toxic shock syndrome
ii. Staphylococcus epidermidis	abscess, endocarditis, endometritis, hospital-acquired infections, neonatal meningitis, urinary tract infections, wound infections

Organism	Diseases
iii. Streptococcus pyogenes (grp A)	cellulitis, erysipelas, glomerulonephritis, impetigo, pyoderma, respiratory tract infections, rheumatic fever, septicaemia, toxic shock syndrome, wound infections
iv. Streptococcus agalactiae (grp B)	endocarditis, neonatal meningitis, respiratory tract infections, urinary tract infections, wound infections
v. Streptococcus faecalis (grp D)	endocarditis, urinary tract infections
vi. Streptococcus pneumoniae	bronchitis, eye infections, meningitis, otitis media, pneumonia, septicaemia
b. Bacilli	
i. Bacillus anthracis	anthrax
ii. Corynebacterium diphtheriae	diphtheria
iii. Listeria monocytogenes	meningitis, meningoencephalitis, septicaemia
2) Gram negative	
a. Cocci	
i. Neisseria meningitides	meningitis, septicaemia
ii. Neisseria gonorrhoeae	gonorrhoea, endocarditis, meningitis, ophthalmia neonatorum, septic arthritis, septicaemia
b. Bacilli	
i. Escherichieae coli	cholecystitis, gastroenteritis, liver abscess, neonatal meningitis, peritonitis, septicaemia, urinary tract infections

Organism		Diseases
ii.	Haemophilus influenzae	arthritis, cellulitis, chronic bronchitis, conjunctivitis, meningitis, otitis media, pneumonia, sinusitis
iii.	Haemophilus ducreyi	chancroid
iv.	Klebsiella pneumoniae	cholecystitis, pneumonia, infections in immunocompromised patients
v.	Pseudomonas aeruginosa	abscess, burns infections, endocarditis, hospital-acquired infections, malignant otitis externa, meningitis, pneumonia, urinary tract infections, wound infections
vi.	Salmonella spp.	typhoid, paratyphoid, gastroenteritis
vii.	Shigella spp.	bacillary dysentery
viii.	Vibrio cholerae	cholera
ix.	Yersinia pestis	plague
x.	Bordetella pertusis	whooping cough

3) Others

i.	Mycobacterium tuberculosis	tuberculosis
ii.	Mycobacterium leprae	leprosy

B] Anaerobes

1) Gram positive

a. Cocci

Organism	Diseases
i. Peptostreptococcus spp.	abdominal infections, acute necrotising gingivitis, aspiration pneumonia, brain abscess, periodontitis, wound infections

b. Bacilli

i. Clostridium botulinum	botulism
ii. Clostridium welchii	gas gangrene, food poisoning, necrotic enteritis, septic abortion
iii. Clostridium tetani	tetanus
iv. Clostridium difficile	antibiotic-associated colitis
v. Actinomyces spp.	actinomycosis

2) Gram negative

a. Cocci

i. Veillonella spp.	periodontitis, lung infections

b. Bacilli

i. Bacteroides fragilis	abscess, intra-abdominal infections
ii. Fusobacterium spp.	aspiration pneumonia, necrotising gingivitis

Antibacterial Agents

Mode of action	Chemical group	Antibacterial agents
Inhibition of cell wall synthesis	Penicillins (beta lactam)	Benzylpenicillin, ampicillin, amoxycillin, cloxacillin, piperacillin
	Cephalosporins (beta lactam)	Cephalexin, cefadroxil, cefuroxime, cefotaxime, ceftazidime, ceftriaxone
	Glycopeptides	Vancomycin, teicoplanin

Mode of action	Chemical group	Antibacterial agents
Inhibition of protein synthesis	Aminoglycosides	Streptomycin, gentamicin, amikacin, tobramycin
	Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
	Tetracyclines	Tetracycline, doxycycline
	Chloramphenicol	Chloramphenicol
	Lincosamides	Clindamycin
Inhibition of bacterial DNA synthesis	Quinolones	Norfloxacin, ciprofloxacin, ofloxacin, gatifloxacin
	Sulphonamides	Sulphadoxine, sulphmethoxazole, co-trimoxazole
	Metronidazole	Metronidazole

Viruses

A virus is a tiny, infectious particle that can reproduce only by infecting a host cell. Viruses "commandeer" the host cell and use its resources to make more viruses, basically reprogramming it to become a virus factory.

Because they can't reproduce by themselves (without a host), viruses are not considered living. Nor do viruses have cells: they're very small, much smaller than the cells of living things, and are basically just packages of nucleic acid and protein.

Still, viruses have some important features in common with cell-based life. For instance, they have nucleic acid genomes based on the same genetic code that's used in the cells of all living creatures. Also, like cell-based life, viruses have genetic variation and can evolve. So, even though they don't meet the definition of life, viruses seem to be in a "questionable" zone.

Differences between viruses and bacteria

Even though they can both make us sick, bacteria and viruses are very different at the biological level. Bacteria are small and single-celled, but they are living organisms that do not depend on a host cell to reproduce. Because of these differences, bacterial and viral infections are treated very differently. For instance, antibiotics are only helpful against bacteria, not viruses.

Bacteria are also much bigger than viruses. The diameter of a typical virus is about 20 - 300 nanometers. This is considerably smaller than a typical *E. coli* bacterium, which has a diameter of roughly 1000 nm! Thus, tens of millions of viruses could fit on the head of a pin.

At the moment, the largest known virus is called *Pithovirus*. It infects amoebas and is rod-shaped, with a length of 1.5 µm and diameter of 0.5 µm. That's larger than some cells!

To be clear, *Pithovirus* is definitely an exception to the rule. The vast majority of viruses fall into the range of 20 - 300 nm in diameter and are much smaller than cells.

The structure of a virus

There are a lot of different viruses in the world. So, viruses vary a lot in their sizes, shapes, and life cycles.

Viruses do, however, have a few key features in common. These include:

- A protective protein shell, or capsid
- A nucleic acid genome made of DNA or RNA, tucked inside of the capsid
- A layer of membrane called the envelope (some but not all viruses)

Virus capsids

The capsid, or protein shell, of a virus is made up of many protein molecules (not just one big, hollow one). The proteins join to make units called capsomers, which together make up the capsid. Capsid proteins are always encoded by the virus genome.

Virus envelopes

In addition to the capsid, some viruses also have a lipid membrane known as an envelope. Virus envelopes can be external, surrounding the entire capsid, or internal, found beneath the capsid.

Although envelopes are common, especially among animal viruses, they are not found in every virus (i.e., are not a universal virus feature).

Virus genomes

All viruses have genetic material (a genome) made of nucleic acid. Viruses may use either RNA or DNA, both of which are types of nucleic acid.

What is a viral infection?

In everyday life, we tend to think of a viral infection as the nasty collection of symptoms we get when catch a virus, such as the flu or the chicken pox. But what's actually happening in your body when you have a virus?

At the microscopic scale, a viral infection means that many viruses are using your cells to make more copies of themselves. The viral lifecycle is the set of steps in which a virus recognizes and enters a host cell, "reprograms" the host by providing instructions in the form of viral DNA or RNA, and uses the host's resources to make more virus particles (the output of the viral "program").

For a typical virus, the lifecycle can be divided into five broad steps (though the details of these steps will be different for each virus):

1. Attachment - Virus binds to receptor on cell surface.
2. Entry - Virus enters cell by endocytosis. In the cytoplasm, the capsid comes apart, releasing the RNA genome.
3. Replication and gene expression - The RNA genome is copied (this would be done by a viral enzyme, not shown) and translated into viral proteins using a host ribosome. The viral proteins produced include capsid proteins.
4. Assembly - Capsid proteins and RNA genomes come together to make new viral particles.
5. Release - The cell lyses (bursts), releasing the viral particles, which can then infect other host cells.

In some cases, the release of the new viruses kills the host cell. (For instance, a host cell that bursts will not survive.) In other cases, the exiting viruses leave the host cell intact so it can continue cranking out more virus particles.

Fungi

There are millions of different fungal species on Earth, but only about 300 of those are known to make people sick. Fungal diseases are often caused by fungi that are common in the environment. Fungi live outdoors in soil and on plants and trees as well as on many indoor surfaces and on human skin.

Tinea is the name of a group of diseases caused by a fungus. It is also called as “ringworm” because it can cause a circular rash (shaped like a ring) that is usually red and itchy. Anyone can get ringworm.

The fungi that cause this infection can live on skin, surfaces, and on household items such as clothing, towels, and bedding.

Ringworm goes by many names. The medical terms are “tinea” or “dermatophytosis.” Other names for ringworm are based on its location on the body – for example, ringworm on the feet is also called “athlete’s foot.”

These infections are usually not serious, but they can be uncomfortable.

Symptoms

Ringworm can affect skin on almost any part of the body as well as fingernails and toenails. The symptoms of ringworm often depend on which part of the body is infected, but they generally include:

- Itchy skin
- Ring-shaped rash
- Red, scaly, cracked skin
- Hair loss

Symptoms typically appear between 4 and 14 days after the skin comes in contact with the fungi that cause ringworm.

<u>Symptoms of ringworm by location on the body:</u>

- Feet (tinea pedis or “athlete’s foot”): The symptoms of ringworm on the feet include red, swollen, peeling, itchy skin between the toes (especially between the pinky toe and the one next to it). The sole and heel of the foot may also be affected. In severe cases, the skin on the feet can blister.

- Scalp (tinea capitis): Ringworm on the scalp usually looks like a scaly, itchy, red, circular bald spot. The bald spot can grow in size and multiple spots might develop if the infection spreads. Ringworm on the scalp is more common in children than it is in adults.

- Groin (tinea cruris or “jock itch”): Ringworm on the groin looks like scaly, itchy, red spots, usually on the inner sides of the skin folds of the thigh.

- Beard (tinea barbae): Symptoms of ringworm on the beard include scaly, itchy, red spots on the cheeks, chin, and upper neck. The spots might become crusted over or filled with pus, and the affected hair might fall out.

Treatment

Tinea pedis: Athlete’s foot can usually be treated with over-the-counter topical antifungal products; terbinafine appears to be most effective, but other agents can also be used. Chronic or extensive tinea pedis may require treatment with oral antifungal agents such as terbinafine, itraconazole, or fluconazole.[6] In addition, chronic tinea pedis may require adjunctive therapy such as foot powder or talcum powder to prevent skin maceration.

Tinea capitis: Treatment with systemic antifungal medication is required, as topical antifungal products are ineffective for treatment of tinea capitis. Many experts consider griseofulvin to be the drug of choice. Terbinafine is also FDA-approved for the treatment of tinea capitis in patients four years of age and older. Itraconazole and fluconazole have been shown to be safe and effective. Selenium sulfide shampoos can be used as adjunctive therapy.

Tinea corporis/cruris: Tinea corporis and tinea cruris can usually be treated with over-the-counter antifungal products. Patients who have tinea cruris should be advised to keep the groin area clean and dry and to wear cotton underwear. Persons who have extensive or recurrent infections may require systemic antifungal therapy.

Fungal Nail Infections

Fungal nail infections are common infections of the fingernails or toenails that can cause the nail to become discolored, thick, and more likely to crack and break. Infections are more common in toenails than fingernails. The technical name for a fungal nail infection is “onychomycosis.”

Symptoms

Nails with a fungal infection are often:

- Discolored (yellow, brown, or white)
- Thick
- Fragile or cracked

A fungal nail infection usually isn't painful unless it becomes severe.

Some people who have fungal toenail infections also have a fungal skin infection on the foot, especially between the toes (commonly called “athlete’s foot”).

Treatment

Fungal nail infections can be difficult to cure, and they typically don't go away without antifungal treatment. It can take several months to a year for the infection to go away.

Topical antifungal agents can be used but are often ineffective. Oral terbinafine is considered to be the first-line treatment for confirmed onychomycosis; the treatment course is generally 6 weeks for fingernails and 12 weeks for toenails. Azoles can also be used. Surgical debridement or removal of the affected nail is also a consideration for cases that are resistant to antifungals.

Candidiasis

Candidiasis is a fungal infection caused by yeasts that belong to the genus *Candida*. There are over 20 species of *Candida* yeasts that can cause infection in humans, the most common of which is *Candida albicans*. *Candida* yeasts normally reside in the intestinal tract and can be found on mucous membranes and skin without causing infection; however, overgrowth of these organisms can cause symptoms to develop. Symptoms of candidiasis vary depending on the area of the body that is infected.

Candidiasis that develops in the mouth or throat is called “thrush” or oropharyngeal candidiasis.

People who are at higher risk for getting candidiasis in the mouth and throat include babies, especially those younger than one month old, and people who:

- Wear dentures
- Have diabetes
- Have cancer
- Have HIV/AIDS
- Take antibiotics or corticosteroids, including inhaled corticosteroids for conditions like asthma
- Take medications that cause dry mouth or have medical conditions that cause dry mouth
- Smoke

Most people who get candidiasis in the esophagus have weakened immune systems, meaning that their bodies don't fight infections well. This includes people living with HIV/AIDS and people who have blood cancers such as leukemia and lymphoma.

Treatment

Candidiasis in the mouth, throat, or esophagus is usually treated with antifungal medicine. The treatment for mild to moderate infections in the mouth or throat is usually an antifungal medicine applied to the inside of the mouth for 7 to 14 days. These medications include clotrimazole, miconazole, or nystatin.

For severe infections, the treatment is usually fluconazole or another type of antifungal medicine given by mouth or through a vein for people who don't get better after taking fluconazole. The treatment for candidiasis in the esophagus is usually fluconazole.

Vaginal Candidiasis

Candidiasis in the vagina is commonly referred to as a "yeast infection".

Candida can multiply and cause an infection if the environment inside the vagina changes in a way that encourages its growth. Candidiasis in the vagina is commonly called a "vaginal yeast infection." Other names for this infection are "vaginal candidiasis," "vulvovaginal candidiasis," or "candidal vaginitis."

Symptoms

The symptoms of vaginal candidiasis include:

- Vaginal itching or soreness
- Pain during sexual intercourse
- Pain or discomfort when urinating
- Abnormal vaginal discharge

Women who are more likely to get vaginal candidiasis include those who:

- Are pregnant
- Use hormonal contraceptives (for example, birth control pills)
- Have diabetes

- Have a weakened immune system (for example, due to HIV infection or medicines that weaken the immune system, such as steroids and chemotherapy)
- Are taking or have recently taken antibiotics

Treatment

Vaginal candidiasis is usually treated with antifungal medicine. For most infections, the treatment is an antifungal medicine applied inside the vagina or a single dose of fluconazole taken by mouth.

For more severe infections, infections that don't get better, or keep coming back after getting better, other treatments might be needed. These treatments include more doses of fluconazole taken by mouth or other medicines applied inside the vagina such as boric acid, nystatin, or flucytosine.

Invasive Candidiasis

Invasive candidiasis occurs when *Candida* species enter the bloodstream and spread throughout the body.

The most common species that cause infections are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei.*

Invasive candidiasis is a serious infection that can affect the blood, heart, brain, eyes, bones, and other parts of the body & may include endocarditis, peritonitis, meningitis, osteomyelitis, arthritis, and endophthalmitis.

Candidemia, a bloodstream infection with *Candida*, is a common infection in hospitalized patients.

The most common symptoms of invasive candidiasis are fever and chills that don't improve after antibiotic treatment for suspected bacterial infections.

Invasive candidiasis may occur when a person's own *Candida* yeasts enter the bloodstream, for example, where an intravenous (IV) catheter was inserted or during surgery. Medical equipment or devices, particularly intravenous catheters, can also become contaminated with *Candida* and allow the fungus to enter the bloodstream. Healthcare workers can also carry *Candida* on their hands.

Treatment

The specific type and dose of antifungal medication used to treat invasive candidiasis usually depends on the patient's age, immune status, and location and severity of the infection.

For most adults, the initial recommended antifungal treatment is an echinocandin (caspofungin, micafungin, or anidulafungin) given through the vein (intravenous or IV). Fluconazole, amphotericin B, and other antifungal medications may also be appropriate in certain situations.

For candidemia, treatment should continue for 2 weeks after signs and symptoms have resolved and *Candida* yeasts are no longer in the bloodstream. Other forms of invasive candidiasis, such as infections in the bones, joints, heart, or central nervous system, usually need to be treated for a longer period of time.

Inflammatory Disorders

Pain

Pain is one of the most common complaints for which people seek medical attention.

Pain can be defined as an unpleasant sensation usually associated with tissue damage.

Certain chemical substances, such as, prostaglandins, histamine etc. are released following tissue damage. They stimulate the pain receptors located at the site of tissue damage. This pain sensation is transmitted by nervous pathways via spinal cord to a part of brain known as thalamus and to the cerebral cortex. The brain analyzes the sensory inputs to identify the location, intensity, and nature of the pain.

Types of pain

Pain may be described in various ways as follows:

1. Acute pain

   Pain that is recent in origin or of short duration is called 'acute' pain. It generally responds well to pain-relieving drugs called analgesics. (Analgesics inhibit the production of prostaglandins and possibly also reduce the sensitivity of pain receptors.)

2. Chronic pain

   Pain that has been felt for a long duration is called 'chronic' pain. Analgesics alone may not be very efficient in relieving chronic pain.

3. Somatic pain

   Pain sensations arising from skin, muscles, or joints represent the 'somatic' (soma = body) pain. It is well localized and responds to analgesic treatment fairly well.

4. Visceral pain

   The pain arising from the internal organs (i.e. viscera) like intestines, gall bladder, ureters, heart etc. is called 'visceral' pain.

Visceral pain is often poorly localized and does not respond that well to commonly used analgesic agents.

5. Neuropathic pain

   This type of pain results from damage to the nerves. Neuralgia is a painful condition in which pain is experienced along the area of distribution of the nerve.

   Neuropathic pain is often poorly localized and is only partially relieved by analgesics.

Inflammation

Inflammation can be defined as the response of living tissue to injury.

It consists of a series of changes that take place in the tissues in response to the injury.

Pathophysiology of Inflammatory response

Inflammation can result from any of the following :

1. Physical agents

   For example, heat, cold, mechanical trauma etc.

2. Chemical agents

   Examples - acids, alkalis etc.

3. Microorganisms

   Examples - bacteria, viruses, fungi etc.

4. Immunological damage

   i.e. body's reaction to a foreign substance resulting in tissue damage.

The changes taking place in the tissues include:

1. Increase in the local blood flow

Dilatation or widening of small arteries results in increased blood flow through the local capillaries.

2. Outpouring of fluid from the capillaries

   Increase in the permeability of capillary walls leads to outpouring of fluids from the capillaries into the damaged tissue. This fluid consists of water and plasma proteins such as fibrinogen & immunoglobulins.

3. Migration of leukocytes (WBCs) into the tissue

   Normally, the blood cells are not allowed to leave the capillaries. But during the inflammatory response, leucocytes, which are the defense forces of the body, are able to move out of capillary blood into the inflamed tissue.

   This process of leukocyte migration is helped by chemotaxis – attraction of leucocytes by the chemical substances e.g. prostaglandins, histamine etc. that are released in the inflamed tissue.

Prostaglandins

Prostaglandins are derivatives of fatty acids obtained from tissue phospholipids. They were named after prostate gland from where they were first identified. However, it is now known that they occur throughout the body, including the CNS, adrenal glands, liver, kidneys, G-I tract, and reproductive system.

Synthesis of prostaglandins

The inflammatory stimuli lead to breakdown of tissue phospholipids into arachidonic acid by the action of enzyme phospholipase.

Arachidonic acid is further converted to prostaglandin G2 (PGG2) by the enzyme cyclooxygenase.

PGG2 can then be converted to different types of prostaglandins such as PGD2, PGE2, PGF2, prostacyclin (PGI2), and thromboxane (TXA2) by the action of other enzymes.

Actions of prostaglandins

Prostaglandins have many actions that differ according to the particular compound, and target organ.

1. Prostacyclin causes dilatation of small blood vessels while thromboxane A2 causes vasoconstriction.

2. PGI2 inhibits aggregation of platelets while TXA2 promotes aggregation of platelets.

3. PGE2 contracts or relaxes smooth muscles such as those in bronchial airways, G-I tract, and uterus.

4. PGEs and PGI2 inhibits gastric acid secretion. In addition, these prostaglandins increase the blood flow to the lining of stomach. Mucus secretion in the stomach and intestines is increased by prostaglandins. These effects serve to protect the stomach lining against injury.

5. Prostaglandins influence salt & water excretion by the kidneys by altering the blood flow as well as by direct effect.

6. Prostaglandins are important mediators of inflammation. Their action at the local site of injury leads to dilatation of small blood vessels. This results in increased blood flow to the affected site causing redness and swelling.

7. PGs sensitize the free nerve endings in the tissues that act as pain receptors, and increase their responsiveness to mechanical and chemical stimulation resulting in pain sensation.

Signs of inflammation

These microscopic changes at the tissue level are not visible to the naked eye. However, the visible signs of inflammation that tell us of the underlying tissue damage are:

- Pain (*dolor*)
- Redness (*rubor*)
- Local heat (*calor*)
- Swelling (*tumor*)
- Loss of function (*functio laesa*)

The inflammatory disorders are usually described by attaching the suffix "*-itis*" to the name of the tissue, for example, meningitis indicates an inflammatory condition of meninges.

Some of the common and important inflammatory conditions are listed below:

Arthritis

Arthritis is an inflammatory disorder of a joint.

Rheumatoid arthritis (R. A.) is a commonly seen inflammatory condition affecting small joints particularly of hands & feet.

RA usually starts in late adulthood i.e. around 40 yrs of age and is three times more common in women than men.

The exact cause of RA is not known, but it is suspected that it involves an autoimmune response. There are inflammatory changes in joints and later destruction of joint surfaces & synovial membranes. Clinical features include swelling of joints, painful movements, 'morning stiffness', and deformities of fingers & joints.

Osteoarthritis –

Osteoarthritis (O. A.) is a disease affecting large weight-bearing joints such as knee joint.

OA usually starts in middle age & is slightly more common in women than in men.

The underlying cause seems to be the degeneration (wear & tear) occurring with ageing. The affected joint shows destruction of articular cartilage, inflammation of synovial membrane, and formation of new bone tissue at the edges (osteophytes). Clinical features include pain & swelling of the joint, and an increasing stiffness as the disease progresses.

Ankylosing spondylitis –

Ankylosing spondylitis (A. S.) is a disease affecting the vertebral column. It begins in young adult males between the age of 17 yrs to 25 yrs.

Although the exact cause of AS is notclearly known, it probably is related to the immune system. The inflammation involving the vertebrae is followed by laying down of bone in the ligaments & at the intervertebral joints. The X-ray appearance is called 'Bamboo spine'.

The clinical features include a low backache and increasing restriction of vertebral column movements.

Soft tissue inflammations

Besides the joints, other soft tissue structures such as tendons, ligaments, and bursae are also commonly affected by painful inflammatory conditions.

a) Lumbago

It simply means a 'low back pain'. The pain may be because of muscle strain, bad posture or lumbar spondylosis – a degenerative condition of vertebrae.

b) Sciatica

This term is used to describe the radiating pin in the legs along the course of sciatic nerve. Most common cause for sciatica is a prolapsed intervertebral disc, which presses on the sciatic nerve root as it emerges from the vertebral column.

c) Bursitis

A bursa is a fluid – filled sac located at sites of friction between skin, ligaments, tendons, and bones e.g. olecrenon bursa at the elbow. Overuse and trauma result in an inflammation of the bursa and is known as 'bursitis.

d) Tenosynovitis

Tendons i.e. the fibrous attachment of a muscle to a bone are covered by a synovial covering. An inflammation of such tendon sheaths is known as tenosynovitis. It causes pain, swelling, and restriction of movements of the related joints.

'Carpal tunnel syndrome' is the term given to a symptom complex resulting from pressure on the median nerve of hand as it passes through the wrist. The pressure is due to a tenosynovitis of flexor tendons in the wrist and resultanat inflammation and swelling. The symptoms include pain, burning, and tingling in the fingers and hand.

Dental inflammatory conditions

'Periodontitis' is a condition marked by a loss of bone support to teeth along with inflamed gums (gingivitis), swelling and pain. Poor oral hygiene, tobacco abuse and diabetes are important causative factors leading to infection and inflammation.

'Impacted' third molar (wisdom tooth) is a condition that results when the normal eruption of the tooth is obstructed. There is pain and swelling of the surrounding soft tissue.

Management of pain

Analgesics are the drugs that relieve pain. They are divided into two broad groups:

A. Narcotic analgesics, and
B. Non-narcotic or non-opioid analgesics

A) Narcotic analgesics

Narcotic analgesics are drugs with morphine-like actions. Morphine itself is derived from opium, which is the dried juice of poppy fruit. The term 'narcotic' denotes an ability to induce sleep – an effect seen with opium and its derivatives.

The narcotic analgesics include opium derivatives like morphine & codeine, and synthetic compounds like pethidine and propoxyphene.

Narcotic analgesics relieve pain by their interaction with opioid receptors at different sites in brain & spinal cord. They are very useful in treating painful conditions such as cancer pain, pain of myocardial infarction etc.

However, besides analgesic effect, these drugs also cause drowsiness, mood changes, respiratory depression, decreased G-I motility, nausea and vomiting.

Moreover, narcotic analgesics induce tolerance and dependence resulting in excessive consumption of these drugs.

Hence, use of these drugs is strictly regulated and only when indicated.

B) Non-narcotic analgesics

These include phenacetin, paracetamol, analgin etc. Currently, paracetamol is the only agent favoured in clinical practice.

Paracetamol

Paracetamol is a derivative of phenacetin. It is probably the sagest analgesic and is therefore preferred in clinical practice.

Paracetamol has excellent analgesic and antipyretic (fever-reducing) activity but rather weak anti-inflammatory action.

Paracetamol is a potent inhibitor of prostaglandin production within the central nervous system. This makes it an effective analgesic for relieving pain of mild to moderate intensity arising from musculoskeletal disorders.

It is rapidly and almost completely absorbed from the G-I tract. Peak plasma concentrations are reached in 10 to 60 minutes (Tmax), and the plasma half-life is about 1 to 3 hours.

Paracetamol is metabolized in liver and the metabolites are excreted in the urine.

At recommended therapeutic doses, paracetamol is safe and very well tolerated. It does not produce the gastric irritation or G-I bleeding that may occur after the use of some NSAIDs. It is also less likely to produce any effects on platelets or on bleeding time.

Skin rash and other allergic reactions may be seen occasionally.

The usual oral dose of paracetamol in adults is 325 mg to 1000 mg up to 4 times daily, total daily dose not exceeding 4 g.

In children, the usual single dose is 40 mg to 480 mg, depending on age & body weight, not more than five times daily.

Management of inflammatory conditions

Just as analgesics are used to relieve painful conditions, inflammatory disorders are treated with ‘anti-inflammatory drugs’. Often these drugs have both anti-inflammatory as well as analgesic activity.

The anti-inflammatory drugs are broadly divided into two categories –

- Corticosteroids
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Corticosteroids have pharmacological actions similar to the hormones produced by adrenal glands in the human body. Although they are potent anti-inflammatory agents their use may be associated with a high risk of severe adverse reactions. Hence they are usually used for short-term therapy of severe acute inflammatory disorders.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are the mainstay of treatment of painful inflammatory disorders.

The NSAIDs are classified on the basis of their chemical nature as below:

1. Salicylic acid derivatives e.g. aspirin
2. Propionic acid derivatives e.g. ibuprofen
3. Acetic acid derivatives e.g. diclofenac
4. Indole acetic acid derivatives e.g. indomethacin
5. Oxicams e.g. piroxicam
6. Anthranilic acid derivatives e.g. mefenamic acid

All NSAIDs have a common mechanism of action. They inhibit the enzyme cyclooxygenase, which is responsible for the production of prostaglandins – important chemical mediators of inflammatory changes. Thus the inflammatory response is controlled and there is relief from pain, redness, and swelling.

The Immune system

The human body has a series of nonspecific defenses that make up the innate immune system. These defenses are not directed against any one pathogen but instead, provide a guard against all infection.

First line of defense

The body's most important nonspecific defense is the skin, which acts as a physical barrier to keep pathogens out. Even openings in the skin (such as the mouth and eyes) are protected by saliva, mucus, and tears, which contain an enzyme that breaks down bacterial cell walls.

Second line of defense

If a pathogen does make it into the body, there are secondary nonspecific defenses that take place.

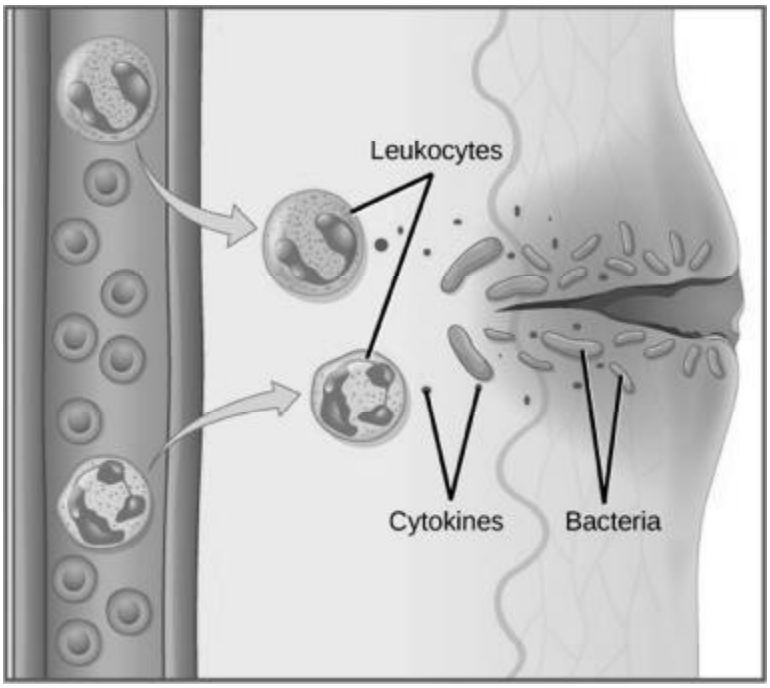


Image showing white blood cells releasing chemicals to induce inflammatory response

An inflammatory response begins when a pathogen stimulates an increase in blood flow to the infected area. Blood vessels in that area expand, and white blood cells leak from the vessels to

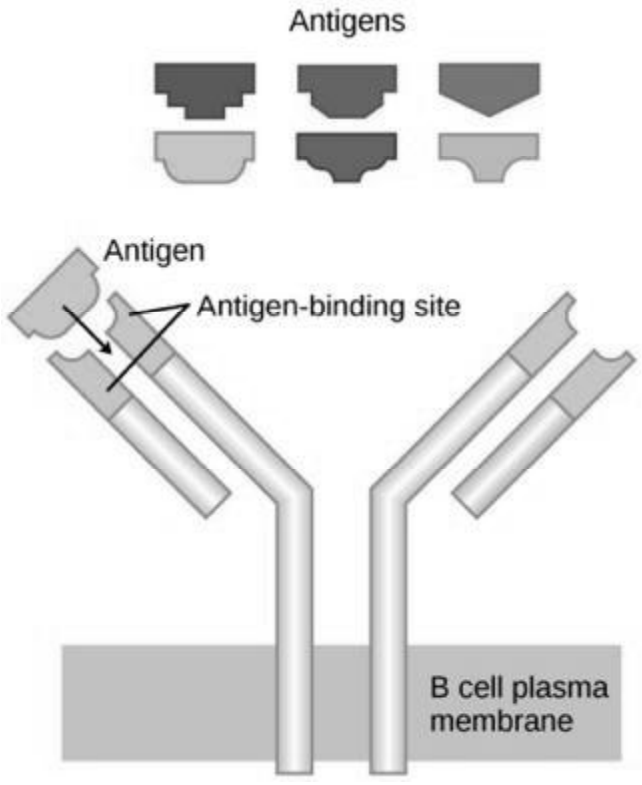
invade the infected tissue. These white blood cells, called phagocytes engulf and destroy bacteria. The area often becomes red, swollen, and painful during an inflammatory response.
When a pathogen has invaded, the immune system may also release chemicals that increase body temperature, producing a *fever*. Increased body temperature may slow or stop pathogens from growing and helps speed up the immune response.

Specific defense: the adaptive immune system

When pathogens are able to bypass innate immune defenses, the adaptive immune system is activated.

Cells that belong in the body carry specific markers that identify them as "self" and tell the immune system not to attack them.

Once the immune system recognizes a pathogen as "non-self," it uses cellular and chemical defenses to attack it. After an encounter with a new pathogen, the adaptive immune system often "remembers" the pathogen, allowing for a faster response if the pathogen ever attacks again.

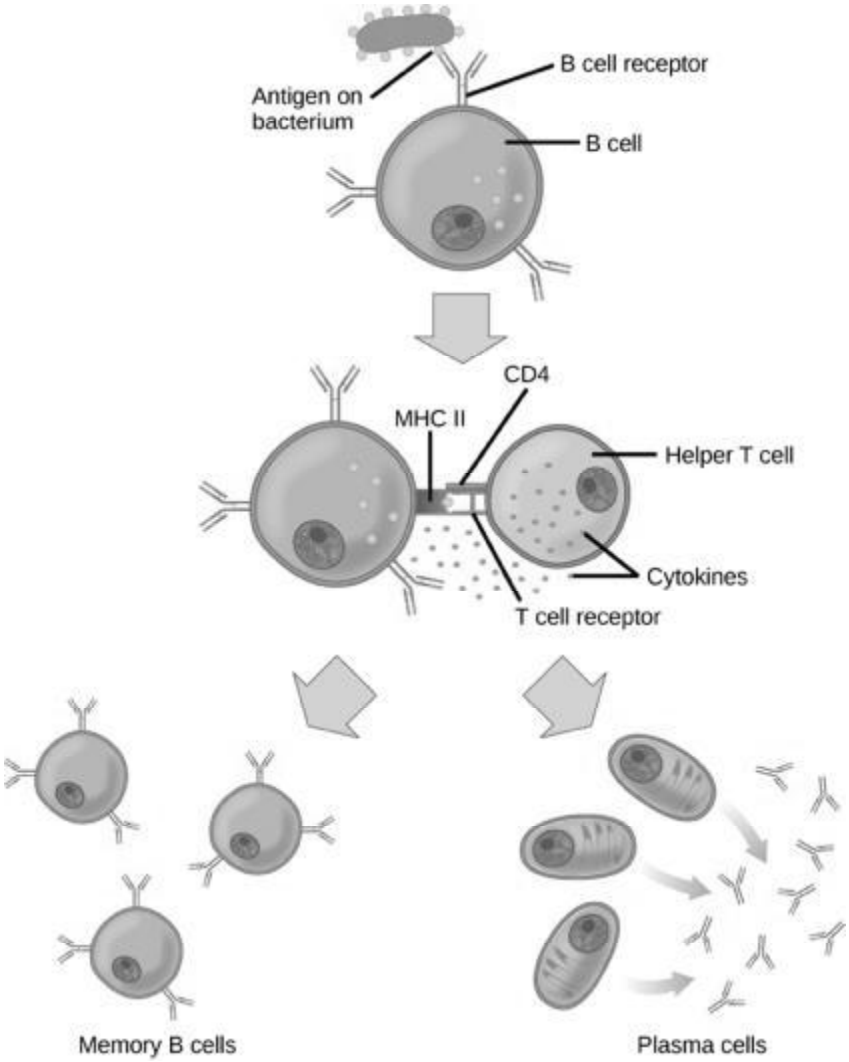


Specific immune responses are triggered by antigens. Antigens are usually found on the surface of pathogens and are unique to that particular pathogen. The immune system responds to antigens by producing cells that directly attack the pathogen, or by producing special proteins called antibodies. Antibodies attach to an antigen and attract cells that will engulf and destroy the pathogen.

The main cells of the immune system are lymphocytes known as B cells and T cells. B cells are produced and mature in bone marrow. T cells are also produced in bone marrow, but they mature in the thymus.

Humoral immunity

Humoral immunity relies on the actions of antibodies circulating through the body.

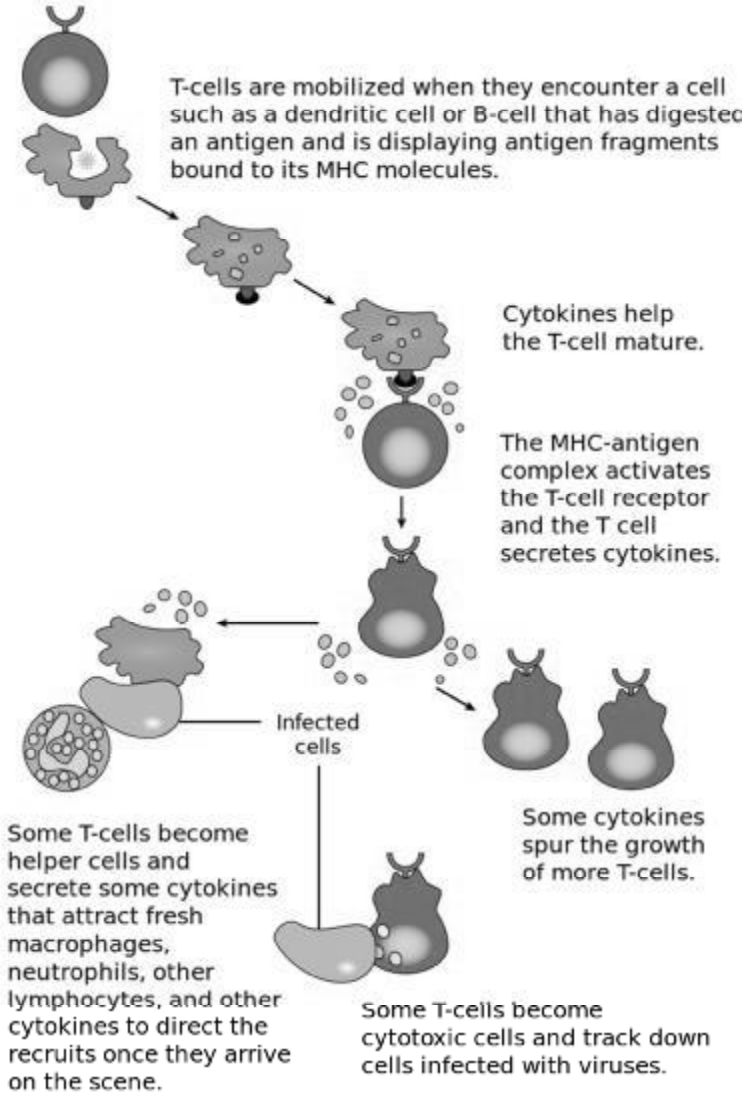


Humoral immunity begins when an antibody on a B cell binds to an antigen. The B cell then internalizes the antigen and presents it to a specialized helper T cell, which in turn activates the B cell.

Activated B cells grow rapidly, producing plasma cells, which release antibodies into the bloodstream, and memory B cells, which store information about the pathogen in order to provide future immunity.

Cell-mediated immunity

Antibodies alone are often not enough to protect the body against pathogens. In these instances, the immune system uses cell-mediated immunity to destroy infected body cells.



T cells are responsible for cell-mediated immunity. Killer T cells (cytotoxic T cells) assist with the elimination of infected body cells by releasing toxins into them and promoting apoptosis. Helper T cells act to activate other immune cells.

Types of allergic reactions

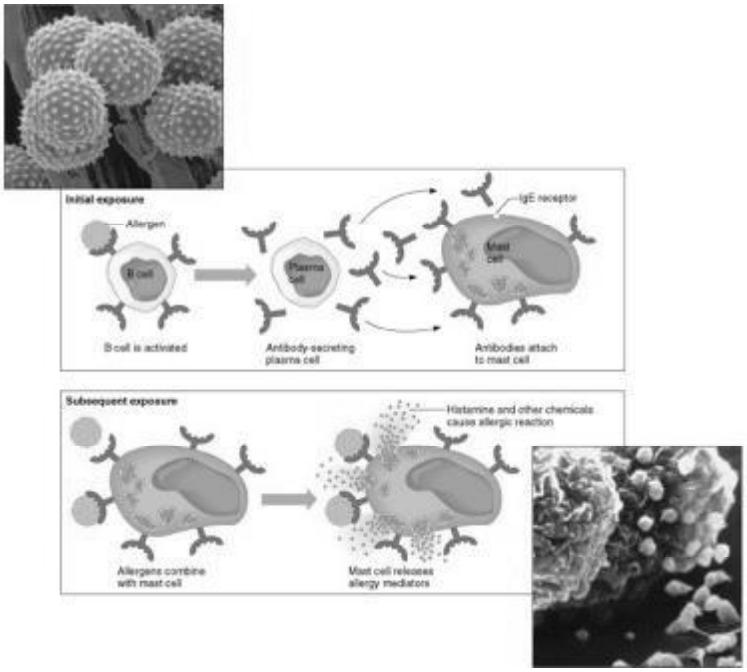
Depending on the type of antibody response and the cascade of events that result from it, the following types of allergic reactions are seen:

- Type I - immediate, anaphylactic (IgE)
    - e.g. urticaria, angioedema, asthma, anaphylactic shock with penicillins

- Type II - cytotoxic antibody (IgG, IgM)
    - e.g., methyldopa and hemolytic anemia; agranulocytosis, aplastic anemia

- Type III - serum sickness (IgG, IgM)
    - antigen-antibody complex e.g., procainamide-induced lupus; Steven Johnson Syndrome

- Type IV - delayed hypersensitivity (T cell)
    - e.g., contact dermatitis, photosensitisation



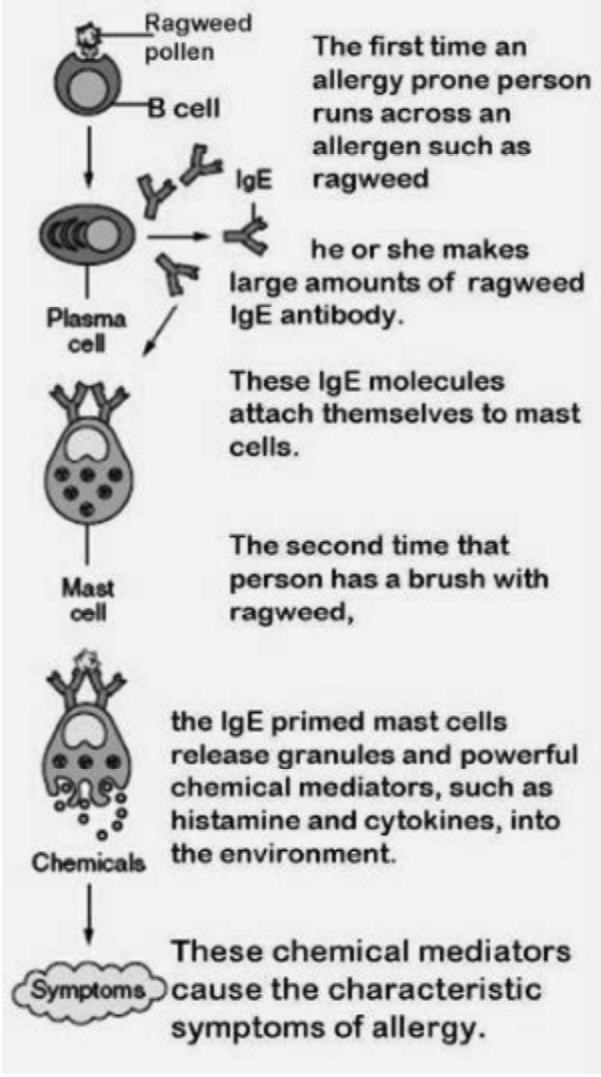
Type 1 or Immediate Hypersensitivity Reaction

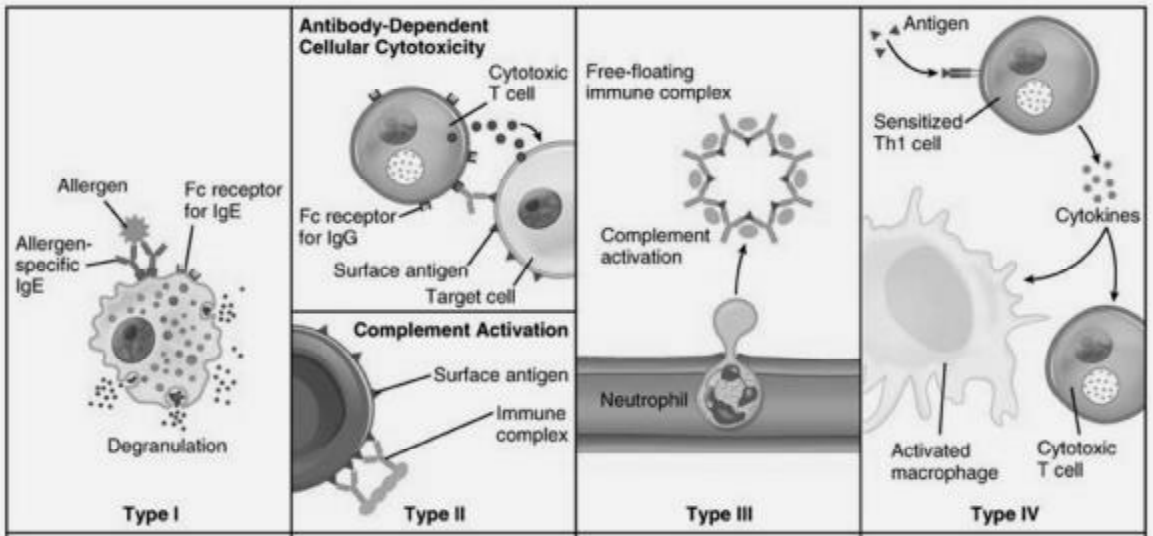
The type I reaction is also known as an immediate hypersensitivity reaction and can be life threatening.

It is caused by an inherited tendency to overproduce the IgE antibodies in response to a specific antigen.

The first exposure generally does not produce symptoms due to the time it takes for B-cell activation.

However, the second exposure can be quite severe producing large amounts of inflammation. The most severe reaction is known as anaphylaxis and produces a number of adverse effects within a very brief time period. These include hives, constriction of bronchioles, and peripheral vasodilation that can cause shock.





IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

Type II hypersensitivity, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis.

Type III hypersensitivity occurs with diseases such as systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings.

These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called sensitization, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages.

A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal.

Overview of Cancer

Introduction

Cancer is the out-of-control growth of cells in your body. Cells are the tiny building blocks of your body. Cells specialize in what they do. For example, your intestines have muscle cells to make them contract, nerve cells to control the muscle cells, and other cells to absorb food.

Normally, new cells in the body grow only to replace cells that have died or gotten too old. Each new cell looks and functions just like its parent cell.

Cancerous (malignant) cells are different from normal cells in many ways because they:

- Multiply very quickly
- Keep on multiplying even though the organ they're in doesn't need more cells
- Look abnormal and usually don't function properly
- Don't stay where they belong—they invade nearby organs or spread to distant parts of the body (metastasize)

Some kinds of cancer cells group together to form a solid mass called a tumor. However, not all tumors are cancerous. Tumors that aren't cancerous are called benign (harmless).

When doctors talk about the “stage” of cancer (stage I, stage II, stage III, or stage IV), they're describing how big the cancer is and if and where it has spread. Some cancers grow and spread faster than others. These are called aggressive cancers.

What causes cancer?

Genetic mutations are responsible for the generation of cancer cells and are thus present in all cancers. These mutations alter the quantity or function of protein products that regulate cell growth and division and DNA repair. Two major categories of mutated genes are oncogenes and tumor suppressor genes.

Oncogenes

These are abnormal forms of normal genes (proto-oncogenes) that regulate various aspects of cell growth. Mutation of these genes may result in direct and continuous stimulation of the pathways (eg, cell surface growth factor receptors, intracellular signal transduction pathways, transcription factors, secreted growth factors) that control cellular growth and division, DNA repair, angiogenesis, and other physiologic processes.

Tumor suppressor genes

Genes such as the *p53* gene play a role in normal cell division and DNA repair and are critical for detecting inappropriate growth signals or DNA damage in cells. If these genes, as a result of inherited or acquired mutations, become unable to function, the system for monitoring DNA integration becomes inefficient, cells with spontaneous genetic mutations persist and proliferate, and tumors result.

Chromosomal abnormalities

Gross chromosomal abnormalities can occur through deletion, translocation, or duplication. If these alterations activate or inactivate genes that result in a proliferative advantage over normal cells, then a tumor may develop. Chromosomal abnormalities occur in most human cancers.

Environmental Factors

A carcinogen is a substance that can cause cancer.

There has to be exposure to a carcinogen for a long time to get cancer. On the other hand, lots of people who are exposed never get cancer.

Carcinogens include –

- Sunlight
- Tobacco
- Certain chemicals
- Certain viruses
- Radiation

Infections

Viruses contribute to the pathogenesis of human cancers. Pathogenesis may occur through the integration of viral genetic elements into the host DNA. These new genes are expressed by the host; they may affect cell growth or division or disrupt normal host genes required for control of cell growth and division. Alternatively, viral infection may result in immune dysfunction, leading to decreased immune surveillance for early tumors.

Cancer-Associated Viruses

Virus	Associated Cancer
Epstein-Barr virus	Burkitt lymphoma Nasopharyngeal carcinoma
Hepatitis B or hepatitis C virus	Hepatocellular carcinoma
Human herpesvirus 8	Kaposi sarcoma
Human papillomaviruses	Anal carcinoma Cervical carcinoma Head and neck carcinoma
Human T-lymphotropic virus	T-cell lymphomas

Bacteria may also cause cancer. *Helicobacter pylori* infection increases the risk of several kinds of cancer (gastric adenocarcinoma, gastric lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma).

Parasites of some types can lead to cancer. *Schistosoma haematobium* causes chronic inflammation and fibrosis of the bladder, which may lead to cancer. *Opisthorchis sinensis* has been linked to carcinoma of the pancreas and bile ducts.

Radiation

Ultraviolet radiation may induce skin cancer (eg, basal and squamous cell carcinoma, melanoma) by damaging DNA. This DNA damage consists of formation of thymidine dimers, which may escape excision and resynthesis of a normal DNA strand because of inherent defects in DNA repair (eg, xeroderma pigmentosum) or through rare, random events.

Ionizing radiation is also carcinogenic. For example, survivors of the atomic bomb explosions in Hiroshima and Nagasaki have a higher-than-expected incidence of leukemia and other cancers.

Similarly, exposure to therapeutic irradiation may lead to leukemia, breast cancer, and other solid tumors years after exposure. Use of x-rays in diagnostic imaging studies is thought to increase risk of cancer.

Industrial exposure (eg, to uranium by mine workers, to asbestos) is linked to development of lung cancer after a 15- to 20-yr latency. Long-term exposure to occupational irradiation or to internally deposited thorium dioxide predisposes people to angiosarcomas and acute nonlymphocytic leukemia.

Drugs and chemicals

Estrogen in oral contraceptives may slightly increase the risk of breast cancer, but this risk decreases over time. Estrogen and progestin used for hormone replacement therapy also increase the risk of breast cancer.

Diethylstilbestrol (DES) increases the risk of breast cancer in women who took the drug and increases the risk of vaginal carcinoma in daughters of these women who were exposed before birth.

Long-term use of anabolic steroids may increase the risk of liver cancer.

Treatment of cancer with chemotherapy drugs alone or with radiation therapy increases the risk of developing a second cancer.

Dietary substances

Certain substances consumed in the diet can increase the risk of cancer. For instance, a diet high in fat and obesity itself have been linked to an increased risk of colon, breast, and possibly prostate cancer.

People who drink large amounts of alcohol are at much higher risk of developing head and neck and esophageal cancer.

A diet high in smoked and pickled foods or in meats cooked at a high temperature increases the risk of developing stomach cancer.

People who are overweight or obese have a higher risk of cancer of the breast, endometrium, colon, kidney, and esophagus.

Common types of cancers

Cancer can develop from almost any cell, including those in your blood, bones, and organs. Each type of cancer is different depending on what type of cell it started from. Cancers are named by the organ they started in. For example, "lung cancer."

The 5 most common cancers in men, from most to least common:

- Prostate
- Lung
- Colon and rectum
- Bladder
- Kidney

The 5 most common cancers in women, from most to least common:

- Breast
- Lung
- Colon and rectum
- Uterus
- Thyroid

That said, skin cancer is probably the most common.

How does cancer spread?

Cancer cells can spread:

- By expanding directly into nearby tissues or organs
- By traveling through the lymphatic system or blood vessels to other organs

The lymphatic system is part of the body's defenses. It's a network of lymph nodes and lymph vessels that carry lymph fluid through the body. Lymph fluid carries away the cells and substances left over from the body's fight against disease. Body's defenses fight and kill cancer cells too, but sometimes living cancer cells get into lymph fluid.

Cancer cells may travel in lymph fluid or in blood to reach other organs. Sometimes cancer cells land in organs far away from the original cancer.

The original cancer is called the primary cancer. Cancer that has spread to other organs is called metastatic cancer.

Warning Signs of Cancer

- Weight loss for no known reason
- Tiredness and fatigue

- Night sweats
- Not being hungry or eating as much
- New pain that doesn't go away
- A recurring feeling of sickness to your stomach or throwing up
- Blood in your urine or stool
- Change in your stool (too hard or too loose)
- Fever that keeps coming back
- Cough that doesn't go away
- Changes in the size or color of a mole
- Spot on skin that doesn’t heal
- Larger than normal lymph nodes
- A lump in the breast

Symptoms of cancer

Symptoms vary depending on the kind of cancer. Some cancers won't show symptoms until they have grown a lot. Others show symptoms at an early stage. Symptoms of cancer may include:

Pain

- Most cancers are painless at first
- As the cancer grows, there may be mild discomfort
- Then, the pain gets worse as cancer gets bigger
- Not all cancers cause severe pain

Bleeding and blood clots

Cancer may cause bleeding inside your body, depending on where your cancer is located:

- Cancer in the digestive tract can cause blood in the stool (poop)
- Cancer in the urinary tract can cause blood in the urine
- Cancer near the lungs can make one cough up blood
- Cancer near a major artery can cause a hole in the artery that will bleed severely
- Cancer in the bone marrow can stop the body from producing the cells that make blood clot

In advanced cancer, severe bleeding may cause death.

Many types of cancer increase the risk of developing blood clots in the veins in the legs. These blood clots sometimes break off and travel to a lung and block blood flow. This can cause serious difficulty breathing and sometimes death.

Weight loss and feeling weak

- One may lose weight and become very thin
- Food may make one feel sick to the stomach or one may have trouble swallowing
- If there is anemia, one may feel very weak and tired as the cancer grows

Muscle and brain symptoms

If cancer grows into or squeezes the nerves or spinal cord, one may have:

- Pain
- Weakness
- Changes in sense of feeling, such as tingling

If cancer starts in or spreads to the brain, one may have:

- Confusion
- Dizziness
- Headaches
- Feel sick to your stomach
- Changes in your vision
- Seizures

Lung symptoms

If cancer squeezes or blocks the airways in the lungs one may have:

- Trouble breathing
- Cough
- Pneumonia

Diagnosis of cancer

Screening tests are done when one doesn't have any symptoms. The doctor might suggest screening tests if one has a higher risk of having cancer based on the age, sex, family history, health, or lifestyle.

Some common screening tests include:

- A Pap test for cervical cancer
- A mammogram (x-ray of breast) for breast cancer
- PSA test (prostate specific antigen) for prostate cancer
- Colonoscopy for colon cancer

Doctors will also do tests to see the stage of the cancer (stage I, stage II, stage III, or stage IV).

Staging tests include:

- Imaging tests, such as x-ray, CT and MRI scan, bones scans, and PET scans depending on the type of cancer
- Biopsy from the tumor or tissues around the tumor
- Blood tests to see if the liver, bones, and kidneys are working normally

Cancer Treatment Principles

The main goal is to get rid of the cancer. This can happen with one type of treatment (such as surgery) or a mix of treatments, such as surgery and chemotherapy (medicine that destroys cancer cells) and radiation therapy.

If it isn't possible to remove the cancer, doctors will try to shrink it, make you more comfortable, and lessen your symptoms to help you feel better.

Treating cancer is complex, and doctors and other healthcare professionals work together as a team.

Doctors decide on the best treatment for the cancer based on:

- The chance of a cure
- The chance of the longest, most comfortable life
- How well the treatment will lessen symptoms
- Side effects of treatment

Treatment protocols are standard methods developed by doctors to treat certain types of cancer. These plans have been tested carefully in research studies called clinical trials.

How do doctors tell if the treatment is working?

Doctors will check to see how well your treatment is working to fight cancer. Doctors may do scans (such as CT scans) to see if the tumor has shrunk.

If treatment works on the cancer, one may have:

- Remission—the cancer disappears completely
- A partial response—the tumor shrinks to less than half its previous size, which can give fewer symptoms and lengthen life expectancy
- Relapse—your cancer completely disappears but returns later

Curing cancer requires eliminating all cancer cells. The major modalities of therapy are –

- Surgery (for local and local-regional disease)
- Radiation therapy (for local and local-regional disease)
- Chemotherapy (for systemic disease)

Surgery

Surgery is the oldest form of effective cancer therapy. It may be used alone or in combination with other modalities. The size, type, and location of the primary tumor may determine operability and outcome. The presence of metastases may preclude an aggressive surgical approach to the primary tumor.

Radiation Therapy

Radiation therapy can cure many cancers, particularly those that are localized or that can be completely encompassed within the radiation field.

Radiation therapy plus surgery (for head and neck, laryngeal, or uterine cancer) or combined with chemotherapy and surgery (for sarcomas or breast, esophageal, lung, or rectal cancers) improves cure rates and allows for more limited surgery as compared with traditional surgical resection.

Radiation therapy can provide significant palliation when cure is not possible:

- For brain tumors: Prolongs patient functioning and prevents neurologic complications
- For cancers that compress the spinal cord: Prevents progression of neurologic deficits
- For superior vena cava syndromes: Relieves venous obstruction
- For painful bone lesions: Usually relieves symptoms

Radiation cannot destroy malignant cells without destroying some normal cells as well. Therefore, the risk to normal tissue must be weighed against the potential gain in treating the malignant cells.

Side effects of radiation therapy

- Feeling weak and tired
- Mouth sores
- Skin problems, such as redness, itching, and peeling
- Pain while swallowing

- Swelling in the lungs
- Nausea and / or vomiting
- Frequent urge to urinate or painful urination
- Bruising easily

Radiation therapy can damage normal tissue and gives you a higher chance of developing other cancers in the future. The risk depends on your age and where in your body you get radiation therapy.

Chemotherapy

The ideal chemotherapeutic drug would target and destroy only cancer cells. Only a few such drugs exist.

The most common routes of administration are IV for cytotoxic drugs and oral for targeted drugs. Frequent dosing for extended periods may necessitate subcutaneously implanted venous access devices (central or peripheral), multilumen external catheters, or peripherally inserted central catheters.

Cytotoxic drugs

Traditional cytotoxic chemotherapy, which damages cell DNA, kills many normal cells in addition to cancer cells.

Antimetabolites, such as 5-fluorouracil and methotrexate, are cell cycle–specific and have no linear dose-response relationship.

In contrast, other chemotherapeutic drugs (eg, alkylating agents) have a linear dose-response relationship, producing more tumor killing as well as more toxicity at higher doses. At their highest doses, they may cause bone marrow aplasia, necessitating bone marrow/stem cell transplantation to restore bone marrow function.

Single-drug chemotherapy may cure selected cancers (eg, choriocarcinoma, hairy cell leukemia). More commonly, multidrug regimens incorporating drugs with different mechanisms of action and different toxicities are used to increase the tumor cell kill, reduce dose-related toxicity, and decrease the probability of drug resistance. These regimens can provide significant cure rates (eg, in acute leukemia, testicular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and, less commonly, solid tumors such as small cell lung cancer and nasopharyngeal cancer).

Multidrug regimens typically are given as repetitive cycles of a fixed combination of drugs. The interval between cycles should be the shortest one that allows for recovery of normal tissue.

Continuous infusion may increase cell kill with some cell cycle–specific drugs (eg, 5-fluorouracil).

Hormonal therapy

Hormonal therapy uses hormone agonists or antagonists to influence the course of cancer. It may be used alone or in combination with other treatment modalities.

Hormonal therapy is particularly useful in prostate cancer, which grows in response to androgens.

Other cancers with hormone receptors on their cells (eg, breast, endometrium) can often be palliated by hormone antagonist therapy or hormone ablation.

Hormonal agents may block the secretion of pituitary hormones (luteinizing hormone-releasing hormone agonists), block the androgen (bicalutamide, enzalutamide) or estrogen receptor (tamoxifen), suppress the conversion of androgens to estrogens by aromatase (letrozole), or inhibit the synthesis of adrenal androgens (abiraterone).

All hormonal blockers cause symptoms related to hormone deficiency, such as hot flashes, and the androgen antagonists also induce a metabolic syndrome that increases the risk of diabetes and heart disease.

Use of prednisone, a glucocorticosteroid, is also considered hormonal therapy. It is frequently used to treat tumors derived from the immune system (lymphomas, lymphocytic leukemias, multiple myeloma).

Common side effects of chemotherapy

Chemotherapy has a reputation for unpleasant and sometimes dangerous side effects. New chemotherapy drugs are often less bothersome than older ones. And doctors now have better treatments for some side effects.

The most common side effects are:

- Nausea or vomiting
- Feeling less hungry than usual

- Weight loss
- Feeling weak and tired
- Diarrhea (frequent, loose, or watery poop)
- Loss of hair
- Mouth or nose sores

Chemotherapy often affects healthy blood-forming cells in the bone marrow. This can lower the number of blood cells, which can cause:

- Low blood count (anemia), if the red blood cell count is lowered
- Serious infections, if white cell count is lowered
- Bleeding, if the platelet count is lowered

Anemia can cause:

- Weakness
- Feeling dizzy
- Trouble breathing or chest pain

Infections from low white cell count can cause:

- Fever

Low platelet count can cause:

- Bruising easily
- Bleeding from nose, gums, or rectum

Chemotherapy can also affect other organs besides the bone marrow and cause other medical problems:

- Damage to lungs, heart, or liver
- Infertility (trouble getting pregnant)
- Sometimes a higher chance of getting another cancer such as leukemia

Combination Cancer Therapy

Combination cancer therapy is when doctors treat cancer with more than one type of treatment. The combination may be a mix of surgery, radiation therapy (uses high energy to shrink cancer tumors and destroy cancer cells), and chemotherapy (medicines to destroy cancer cells).

- Doctors may give several types of chemotherapy medicine at once (combination chemotherapy)—each medicine works differently to destroy cancer cells, so they destroy more cancer cells together
- Doctors may also treat cancer with several types of treatment—for example, both chemotherapy and surgery
- Doctors decide whether to use single or combination therapy depending on your stage and type of cancer

Why do doctors use combination cancer therapy?

- Some cancers can’t be treated with just surgery or radiation therapy
- Surgery or radiation therapy can treat a tumor in one part of body, while chemotherapy treats cancer cells that have spread to other parts of body
- Radiation therapy or chemotherapy can shrink the tumor before surgery, so less of it has to be cut out
- After surgery, radiation therapy and chemotherapy can help destroy cancer cells that a surgeon couldn't remove
- Combination chemotherapy can help lengthen life and lessen severity of symptoms

Respiratory Disorders

Disorders that affect the lungs and airways are called lung, respiratory, or pulmonary disorders.

Among the most common symptoms of lung disorders are –

- Cough
- Shortness of breath (dyspnea)
- Wheezing

Cough

Cough is a sudden, forceful expulsion of air from the lungs. The function of a cough is to clear material from the airways and to protect the lungs from particles that have been inhaled.

A cough may be characterized as dry (unproductive) or productive, bringing up blood or sputum (also called phlegm).

Sputum is a mixture of mucus, debris, and cells expelled by the lungs. It may be clear, yellow, green, or streaked with blood.

Cough may be very distressing and interfere with sleep.

Causes of Cough

Cough occurs when the airways are irritated. Likely causes of cough depend on whether the cough has lasted less than 3 weeks (acute) or 3 weeks or longer (chronic).

Common causes

For acute cough, the most common causes are –

- An upper respiratory infection (URI), including acute bronchitis
- Postnasal drip (drainage of secretions from the nose down the throat, or pharynx)
- A flare-up of chronic obstructive pulmonary disease (COPD)
- Pneumonia

For chronic cough, the most common causes are –

- Chronic bronchitis

- Postnasal drip
- Airway irritation that remains after a respiratory infection resolves (also known as post-infectious cough)
- Gastroesophageal reflux

Less common causes

For acute cough, less common causes include –

- A blood clot in the lungs (pulmonary embolism)
- Heart failure
- A foreign object (such as a piece of food) that has been inhaled (aspirated)

For chronic cough, less common causes include –

- Use of blood pressure drugs called angiotensin-converting enzyme (ACE) inhibitors
- Lung cancer
- Tuberculosis
- Fungal infections of the lungs

Asthma may cause cough. Rarely, the main symptom of asthma is cough rather than wheezing.

Evaluation of Cough

Not every cough requires immediate evaluation by a doctor.

Warning signs

In people with a cough, certain symptoms and characteristics are cause for concern. They include –

- Shortness of breath
- Coughing up blood
- Weight loss
- Fever that lasts longer than about 1 week
- Risk factors for tuberculosis, such as being exposed to tuberculosis, having HIV infection, or taking corticosteroids or other drugs that suppress the immune system
- Risk factors for HIV infection, such as high-risk sexual activities or use of street drugs by injection

Treatment of Cough

The best way to treat cough is to treat the underlying disorder. For example, antibiotics can be used for pneumonia, and inhalers containing drugs that widen airways (bronchodilators) or corticosteroids can be used for COPD or asthma.

Generally, because coughing plays an important role in bringing up sputum and clearing the airways, a cough should not be suppressed. However, if the cough is severe, interferes with sleep, or has certain causes, various treatments may be tried.

There are two basic approaches to people who are coughing -

- Cough suppressants (antitussive therapy), which reduce the urge to cough
- Expectorants, which are meant to thin the mucus blocking the airways to the lungs and make mucus easier to cough up

Cough suppressants

Cough suppressants include the following –

- Opioids
- Dextromethorphan

All opioids suppress cough because they reduce the responsiveness of the cough center in the brain. Codeine is the opioid used most often for cough.

Codeine and other opioid cough suppressants may cause nausea, vomiting, and constipation and may be addictive. They can also cause drowsiness, particularly when a person is taking other drugs that reduce concentration (such as alcohol, sedatives, sleep aids, antidepressants, or certain antihistamines).

Thus, opioids are not always safe, and doctors usually reserve them for special situations, such as cough that persists despite other treatments and that interferes with sleep.

Dextromethorphan is related to codeine but is technically not an opioid. It also suppresses the cough center in the brain.

Dextromethorphan is the active ingredient in many over-the-counter (OTC) and prescription cough preparations. It is not addictive and, when used correctly, causes little drowsiness.

However, it is frequently abused by people, particularly adolescents, because in high doses, it causes euphoria.

Overdose causes hallucinations, agitation, and sometimes coma. Overdose is particularly dangerous for people who are taking drugs for depression called serotonin reuptake inhibitors e.g. fluoxetine.

Expectorants

Some doctors recommend expectorants (sometimes called mucolytics) to help loosen mucus by making bronchial secretions thinner and easier to cough up. The most commonly used expectorants are OTC preparations that contain guaifenesin. Doctors may prescribe a saturated solution of potassium iodide to loosen mucus.

Also, inhaling a saline (salt) solution or inhaling acetylcysteine (for up to a few days) sometimes helps thin excessively thick and troublesome mucus.

Other treatments

Steam inhalation (for example, using a vaporizer) is commonly thought to reduce cough. Other topical treatments, such as cough drops, are also popular, but there is no convincing evidence that these other treatments are effective.

Decongestants (such as phenylephrine) that relieve a stuffy nose are only useful for relieving a cough that is caused by postnasal drip.

Acute Bronchitis

Bronchitis is inflammation of the windpipe (trachea) and the airways that branch off the trachea (bronchi) caused by infection.

- Acute bronchitis is usually caused by viral infections.
- Symptoms of the common cold that are followed by a cough usually indicate acute bronchitis.
- The diagnosis is made based primarily on symptoms.
- Most treatments, such as drugs to reduce fever and cough, are used to make the person more comfortable until the episode ends.
- Antibiotics are usually not needed.

Bronchitis can be either –

- Acute
- Chronic

Symptoms of acute bronchitis usually last from a few days to a few weeks.

Bronchitis that lasts longer, sometimes for months or years, is usually classified as chronic bronchitis.

(When chronic bronchitis occurs together with a decrease in the rate of airflow from the lungs when the person breathes out (expiratory airflow), it is considered a defining characteristic of chronic obstructive pulmonary disease (COPD). Only acute bronchitis is discussed here.)

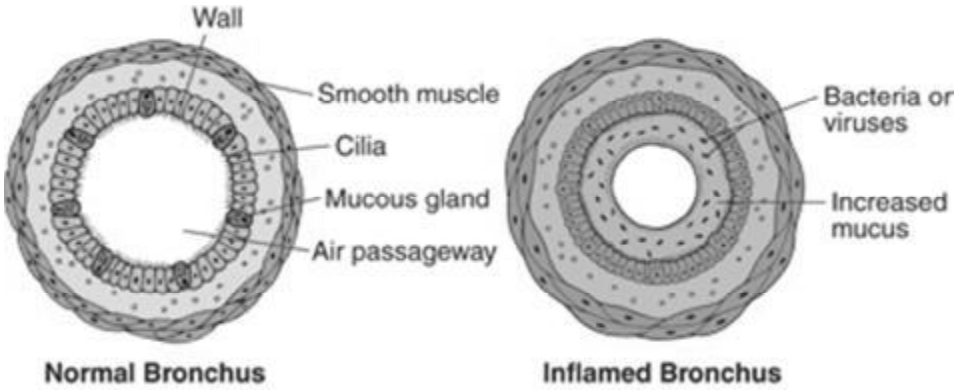
Causes

Acute bronchitis is caused by infection due to –

- Viruses (most common)
- Bacteria

Understanding Bronchitis

In bronchitis, areas of the bronchial wall become inflamed and swollen, and mucus increases. As a result, the air passageway is narrowed.



Viral bronchitis may be caused by a number of common viruses, including the influenza virus. Even after a viral infection has cleared up, the irritation it causes can continue to cause symptoms for weeks.

Bacterial bronchitis occasionally follows a viral upper respiratory infection. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* infection (which causes whooping cough) are among the bacteria that cause acute bronchitis. Bacterial causes of acute bronchitis are more likely when many people are affected (an outbreak).

Symptoms

Infectious bronchitis generally begins with the symptoms of a common cold: runny nose, sore throat, fatigue, and chilliness. Back and muscle aches together with a slight fever (100° to 101° F, or 37.5° to 38° Celsius [C]) may be present, particularly if the infection is due to influenza. The onset of cough (usually dry at first) signals the beginning of acute bronchitis.

With viral bronchitis, small amounts of white mucus are often coughed up. This mucus often changes from white to green or yellow. The color change does not mean there is a bacterial infection. Color change means only that cells associated with inflammation have moved into the airway and are coloring the sputum.

When bronchitis is severe, fever may be slightly higher at 101° to 102° F (38° to 39° C) and may last for 3 to 5 days, but higher fevers are unusual unless bronchitis is caused by influenza.

Cough is the last symptom to subside and often takes 2 to 3 weeks or even longer to do so. Viruses can damage the epithelial cells lining the bronchi, and the body needs time to repair the damage.

Treatment

Adults may take aspirin, acetaminophen, or ibuprofen to relieve symptoms like fever and general feelings of illness, but children should take only acetaminophen or ibuprofen, not aspirin, because children taking aspirin are at higher risk for Reye syndrome.

People with acute bronchitis, especially those who have a fever, should drink plenty of fluid.

Antibiotics are not used to treat bronchitis except for people whose infection is caused by bacteria (for example, during an outbreak). When an antibiotic is used, a drug such as azithromycin or clarithromycin is most often given.

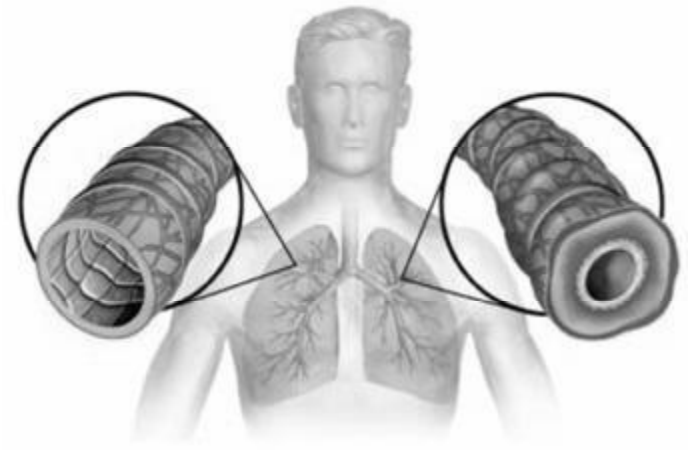
Antibiotics do not help people with viral bronchitis. Treatment with an antiviral drug for influenza such as oseltamivir or zanamivir may help speed recovery from influenza (whether or not it causes acute bronchitis) if given within 48 hours of the onset of symptoms.

Cough medicines can be used to suppress a dry, disturbing cough, particularly when it interferes with sleep. However, the degree of effectiveness of these drugs is not clear. Also, a cough that produces a lot of sputum usually should not be suppressed. Expectorants may help to thin secretions and make them easier to cough up.

Asthma

Asthma is a condition in which the airways narrow—usually reversibly—in response to certain stimuli.

- Coughing, wheezing, and shortness of breath that occur in response to specific triggers are the most common symptoms.
- Doctors confirm the diagnosis of asthma by doing breathing (pulmonary function) tests.
- To prevent attacks, people should avoid substances that trigger asthma and should take drugs that help keep airways open.
- During an asthma attack, people need to take a drug that quickly opens the airways.



Narrowing of the airways

Although asthma is one of the most common chronic diseases of childhood, adults can also develop asthma, even at an old age. Asthma occurs more frequently in boys before puberty and in girls after puberty.

Asthma can eventually resolve in children. However, sometimes asthma that appears to resolve recurs years later.

The most important characteristic of asthma is narrowing of the airways that can be reversed. The airways of the lungs (the bronchi) are basically tubes with muscular walls.

Cells lining the bronchi have microscopic structures, called receptors. These receptors sense the presence of specific substances and stimulate the underlying muscles to contract or relax, thus altering the flow of air.

There are many types of receptors, but two main types of receptors are important in asthma –

- Beta-adrenergic receptors respond to chemicals such as epinephrine and make the muscles relax, thereby widening (dilating) the airways and increasing airflow.

- Cholinergic receptors respond to a chemical called acetylcholine and make the muscles contract, thereby decreasing airflow.

Causes

The causes of asthma are unknown, but asthma likely results from complex interactions between many genes, environmental conditions, and nutrition.

Environmental conditions and circumstances around pregnancy, birth, and infancy have been associated with the development of asthma in childhood and later in adulthood.

Risk appears to be higher if a person's mother became pregnant at a young age or had poor nutrition during pregnancy. Risk may also be higher if someone is born prematurely, had a low weight at birth, or was not breastfed.

Environmental conditions such as exposures to household allergens (such as dust mites, cockroaches, and pet dander) and other environmental allergens have also been associated with the development of asthma in older children and adults.

Diets low in vitamins C and E and in omega–3 fatty acids have been also linked to asthma, as has obesity.

Narrowing of the airways is often caused by abnormal sensitivity of cholinergic receptors, which cause the muscles of the airways to contract when they should not. Certain cells in the airways, particularly mast cells, are thought to be responsible for initiating the response.

Mast cells throughout the bronchi release substances such as histamine and leukotrienes, which cause the following –

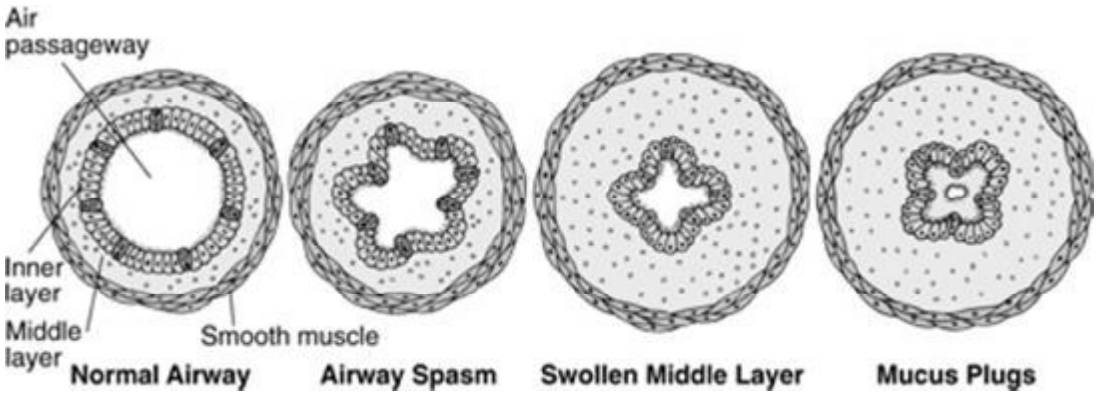
- Smooth muscle to contract
- Mucus secretion to increase

- Certain white blood cells to move to the area

Eosinophils, a type of white blood cell found in the airways of people with asthma, release additional substances, contributing to airway narrowing.

In an asthma attack, the smooth muscles of the bronchi contract, causing the bronchi to narrow (called bronchoconstriction).

The tissues lining the airways swell due to inflammation and mucus secretion into the airways. The top layer of the airway lining can become damaged and shed cells, further narrowing the airway.



How Airways Narrow

During an asthma attack, the smooth muscle layer goes into spasm, narrowing the airway. The middle layer swells because of inflammation, and excessive mucus is produced. In some segments of the airway, mucus forms plugs that nearly or completely block the airway.

A narrower airway requires the person to exert more effort to breathe. In asthma, the narrowing is reversible, meaning that with appropriate treatment or on their own, the muscular contractions of the airways stop, inflammation resolves so that the airways widen again, and airflow into and out of the lungs returns to normal.

Asthma triggers

In people who have asthma, the airways narrow in response to stimuli (triggers) that usually do not affect the airways in people without asthma. Such triggers include –

- Allergens e.g. dust mites, body secretions from cockroaches, particles from feathers, and animal dander
- Infections e.g. colds, bronchitis
- Irritants e.g. smoke from tobacco, marijuana, or cocaine; fumes, cold air; and stomach acid
- Exercise (called exercise-induced asthma)
- Stress and anxiety
- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)

Symptoms of an asthma attack

Asthma attacks occur most often in the early morning hours when the effects of protective drugs wear off and the body is least able to prevent airway narrowing.

An asthma attack may begin suddenly with wheezing, coughing, and shortness of breath. At other times, an asthma attack may come on slowly with gradually worsening symptoms.

The attack may be over in minutes, or it may last for hours or days.

During an asthma attack, shortness of breath may become severe, creating a feeling of severe anxiety. The person instinctively sits upright and leans forward, using the muscles in the neck and chest to help in breathing, but still struggles for air.

Sweating is a common reaction to the effort and anxiety. The heart rate usually quickens, and the person may feel a pounding in the chest.

Confusion, lethargy, and a blue skin color (cyanosis) are signs that the person's oxygen supply is severely limited, and emergency treatment is needed.

Status asthmaticus

The most severe form of asthma is called status asthmaticus. It is severe, intense, prolonged airway narrowing that is resistant to treatment. In status asthmaticus, the lungs are no longer able to provide the body with adequate oxygen or to remove carbon dioxide adequately.

Without oxygen, many organs begin to malfunction. The buildup of carbon dioxide leads to acidosis, an acidic state of the blood that affects the function of almost every organ. Blood pressure may fall to dangerously low levels. The airways are so narrowed that it is difficult to move air in and out of the lungs.

Treatment

- Anti-inflammatory drugs suppress the inflammation that narrows the airways. Anti-inflammatory drugs include corticosteroids (which can be inhaled, taken by mouth, or given intravenously), leukotriene modifiers, and mast cell stabilizers.

- Bronchodilators help to relax and widen (dilate) the airways. Bronchodilators include beta-adrenergic drugs (both those for quick relief of symptoms and those for long-term control), anticholinergics, and methylxanthines.

Beta-adrenergic Drugs

Short-acting beta-adrenergic drugs

Short-acting beta-adrenergic drugs are usually the best drugs for relieving asthma attacks. They also are used to prevent exercise-induced asthma. These drugs are referred to as bronchodilators because they stimulate beta-adrenergic receptors to widen (dilate) the airways.

Bronchodilators that act on all beta-adrenergic receptors throughout the body (such as epinephrine) cause side effects such as rapid heartbeat, restlessness, headache, and muscle tremors.

Bronchodilators (such as salbutamol) that act mainly on $beta_2$-adrenergic receptors, which are found primarily on cells in the lungs, have less effect on other organs and thus cause fewer side effects.

Most short-acting beta-adrenergic drugs, especially the inhaled ones, act within minutes, but the effects last only 2 to 6 hours.

Taking inhaled beta-adrenergic drugs

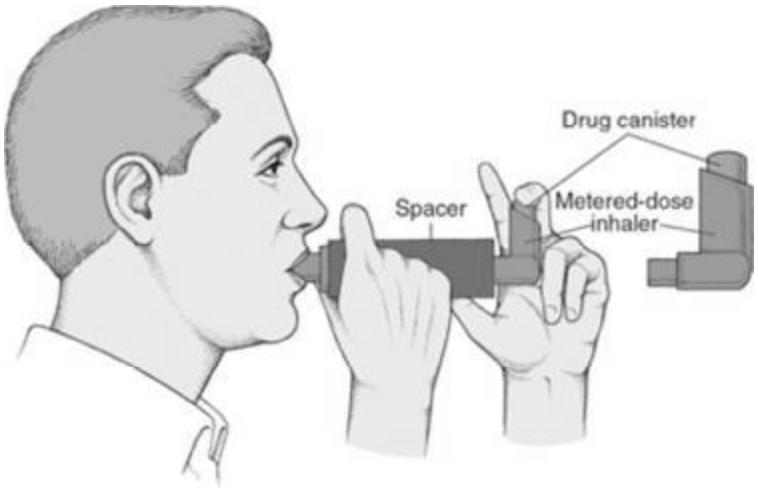
Metered-dose inhalers (handheld cartridges containing gas under pressure) are the most commonly used method for giving inhaled beta-adrenergic drugs. The pressure turns the drug into a fine spray containing a measured dose of drug.

Inhalation deposits the drug directly in the airways, so that it acts quickly, but the drug may not reach airways that are severely narrowed. For people who have difficulty using a metered-dose inhaler, spacers or holding chambers can be used. These devices increase the amount of drug delivered to the lungs.

With any type of inhaler, proper technique is vital. If the device is not used properly, the drug will not reach the airways.

How to Use a Metered-Dose Inhaler

- Shake the inhaler after removing the cap.
- Exhale fully for 1 or 2 seconds.
- Put the inhaler in your mouth or 1 to 2 inches from it and start to breathe in slowly, like sipping hot soup.
- While starting to breathe in, press the top of the inhaler.
- Breathe in slowly until your lungs are full. (This should take about 5 or 6 seconds.)
- Hold your breath for 10 seconds (or as long as you can).
- Breathe out and, if a second dose is required, repeat the procedure after 1 minute.
- If you find it difficult to coordinate breathing using this method, a spacer can be used.



- Immunomodulators, drugs that directly alter the immune system are sometimes used for people with severe asthma, but most people do not need immunomodulators. These drugs block substances in the body that cause inflammation.

  Omalizumab is a drug that is an antibody directed against a group of other antibodies called immunoglobulin E (IgE). Omalizumab is used in people with asthma who also have severe allergies and high levels of IgE in their blood. Omalizumab prevents IgE from binding to mast cells and thus prevents the release of inflammatory chemicals that can narrow the airways. It can decrease requirements for oral corticosteroids and help relieve symptoms. The drug is injected subcutaneously every 2 to 4 weeks.

Mepolizumab and reslizumab are antibodies that target molecules that cause airway inflammation (interleukins). They are used in the treatment of people with severe asthma triggered by allergens. Mepolizumab reduces the number of asthma attacks, decreases asthma symptoms, and reduces the need for corticosteroids. Mepolizumab is injected subcutaneously every 4 weeks. Reslizumab reduces the number of asthma attacks and decreases asthma symptoms. It is given intravenously every 4 weeks.

- Allergen desensitization through the use of allergy shots may help prevent attacks in people whose asthma is triggered by allergies. A doctor-supervised desensitization program may also be used for people whose asthma is triggered by aspirin or NSAIDs.

- Drugs, such as inhaled or oral corticosteroids, leukotriene modifiers, methylxanthines, antihistamines, or mast cell stabilizers are used to prevent attacks in most people with asthma. A minority of people with asthma have severe disease that remains uncontrolled, causing repeated attacks despite treatment with a combination of therapies. These people may benefit from treatment with immunomodulator drugs that block substances that cause allergic inflammation.

Leukotriene Modifiers

Leukotriene modifiers, such as montelukast and zafirlukast also help control asthma. They are anti-inflammatory drugs that prevent the action or synthesis of leukotrienes.

Leukotrienes are chemicals made by the body that cause bronchoconstriction. These drugs, which are taken by mouth, are used more to prevent asthma attacks than to treat them.

Mast Cell Stabilizers

Mast cell stabilizers, which are inhaled, include cromolyn and nedocromil. These drugs are thought to inhibit the release of inflammatory chemicals from mast cells and make the airways less likely to narrow. Thus, they are also anti-inflammatory drugs.

They are useful for preventing but not treating an attack. Mast cell stabilizers may be helpful for children who have asthma and for people who develop asthma due to exercise. These drugs are very safe and must be taken regularly even when a person is free of symptoms.

Corticosteroids

Corticosteroids block the body's inflammatory response and are exceptionally effective at reducing asthma symptoms. They are the most potent form of anti-inflammatory drugs and have been an important part of asthma treatment for decades.

Corticosteroids can be taken in several different forms. Often, inhaled versions are best because they deliver the drug directly to the airways and minimize the amount sent throughout the body. The inhaled form is used to prevent attacks and improve lung function.

Inhaled corticosteroids come in several strengths and are generally used twice a day. People should rinse their mouth after use to decrease the likelihood that a fungal infection of the mouth (thrush) develops.

Oral or injected corticosteroids may be used in high doses to relieve a severe asthma attack and are generally continued for 1 to 2 weeks.

Methylxanthines

Theophylline, a methylxanthine, is another drug that causes bronchodilation. It is now used less frequently than in the past. Theophylline is usually taken by mouth.

Oral theophylline comes in many forms, from short-acting tablets and syrups to longer-acting sustained release capsules and tablets. Theophylline is used mainly for prevention of asthma.

When first taking theophylline, a person who has asthma may feel slightly jittery and may develop headaches. These side effects usually disappear as the body adjusts to the drug. Larger doses may cause a rapid heartbeat, nausea, or palpitations and too much drug may cause life-threatening abnormal heart rhythms or seizures.

A person may also experience insomnia, agitation, vomiting, and seizures. Occurrence of these side effects is one of the reasons that theophylline is used less often than other drugs.

Pneumonia

Pneumonia is acute inflammation of the lungs caused by infection. Initial diagnosis is usually based on chest x-ray and clinical findings. Causes, symptoms, treatment, preventive measures, and prognosis differ depending on whether the infection is bacterial, mycobacterial, viral, fungal, or parasitic; whether it is acquired in the community, hospital, or other health care–associated location; and whether it develops in a patient who is immunocompetent or immunocompromised.

The most common cause of pneumonia in adults > 30 yr is bacterial infection.

Streptococcus pneumoniae is the most common pathogen in all age groups, settings, and geographic regions. However, pathogens of every sort, from viruses to parasites, can cause pneumonia.

The airways and lungs are constantly exposed to pathogens in the external environment; the upper airways and oropharynx in particular are colonized with so-called normal flora. Microaspiration of these pathogens from the upper respiratory tract is a regular occurrence, but these pathogens are readily dealt with by lung host defense mechanisms.

Pneumonia develops when -

- Defense mechanisms are compromised
- Macroaspiration leads to a large inoculum of bacteria that overwhelms normal host defenses
- A particularly virulent pathogen is introduced

Occasionally, infection develops when pathogens reach the lungs via the bloodstream or by contiguous spread from the chest wall or mediastinum.

Upper airway defenses include salivary IgA, proteases, and lysozymes; growth inhibitors produced by normal flora; and fibronectin, which coats the mucosa and inhibits adherence.

Nonspecific lower airway defenses include cough, mucociliary clearance, and airway angulation preventing infection in airspaces. Specific lower airway defenses include various pathogen-specific immune mechanisms, including IgA and IgG opsonization, antimicrobial peptides, anti-inflammatory effects of surfactant, phagocytosis by alveolar macrophages, and T-cell–mediated immune responses. These mechanisms protect most people against infection.

Numerous conditions alter the normal flora (eg, systemic illness, undernutrition, hospital or nursing home exposure, antibiotic exposure) or impair these defenses (eg, altered mental status, cigarette smoking, nasogastric or endotracheal intubation). Pathogens that then reach airspaces can multiply and cause pneumonia.

Pneumonias can be categorized as –

- Community-acquired
- Hospital-acquired (including ventilator-acquired and postoperative pneumonia)
- Health care–associated (including nursing home-acquired pneumonia)
- Occurring in immunocompromised patients, including patients with HIV infection
- Aspiration pneumonia, which occurs when large volumes of upper airway or gastric secretions enter into the lungs

These categorizations allow treatment to be selected empirically.

Community-acquired pneumonia develops in people with limited or no contact with medical institutions or settings. The most commonly identified pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, atypical bacteria (ie, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella* sp), and viruses.

Symptoms and signs are fever, cough, sputum production, pleuritic chest pain, dyspnea, tachypnea, and tachycardia.

Diagnosis is based on clinical presentation and chest x-ray.

Treatment is with empirically chosen antibiotics. Prognosis is excellent for relatively young or healthy patients, but many pneumonias, especially when caused by *S. pneumoniae*, Legionella, Staphylococcus aureus, or influenza virus, are serious or even fatal in older, sicker patients.

Causes

S. pneumoniae, *H. influenzae*, *C. pneumoniae*, and *M. pneumoniae* are the most common bacterial causes. Pneumonias caused by chlamydia and mycoplasma are often clinically indistinguishable from other pneumonias.

C. pneumoniae accounts for 2 to 5% of community-acquired pneumonia and is the 2nd most common cause of lung infections in healthy people aged 5 to 35 yr. *C. pneumoniae* is commonly responsible for outbreaks of respiratory infection within families, in college dormitories, and in military training camps. It causes a relatively benign form of pneumonia that infrequently

requires hospitalization. *Chlamydia psittaci* pneumonia (psittacosis) is rare and occurs in patients who own or are often exposed to birds.

P. aeruginosa is an especially common cause of pneumonia in patients with cystic fibrosis, neutropenia, advanced AIDS, and/or bronchiectasis.
Common viral agents include respiratory syncytial virus (RSV), adenovirus, influenza viruses, metapneumovirus, and parainfluenza viruses. Bacterial superinfection can make distinguishing viral from bacterial infection difficult.

Adenovirus, Epstein-Barr virus, and coxsackievirus are common viruses that rarely cause pneumonia. Seasonal influenza can rarely cause a direct viral pneumonia but often predisposes to the development of a serious secondary bacterial pneumonia.

Varicella virus and hantavirus cause lung infection as part of adult chickenpox and hantavirus pulmonary syndrome. A coronavirus causes severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).

Common fungal pathogens include *Histoplasma capsulatum* (histoplasmosis) and *Coccidioides immitis* (coccidioidomycosis). Less common fungal pathogens include *Blastomyces dermatitidis* (blastomycosis) and *Paracoccidioides braziliensis* (paracoccidioidomycosis). *Pneumocystis jirovecii* commonly causes pneumonia in patients who have HIV infection or are immunosuppressed.

In children, the most common causes depend on age-

- < 5 yr: Most often viruses; among bacteria, *S. pneumoniae*, *S. aureus*, and *S. pyogenes*, are common
- ≥ 5 yr: Most often the bacteria *S. pneumoniae*, *M. pneumoniae*, or *Chlamydia pneumoniae*

S. pneumoniae and MRSA can cause necrotizing pneumonia.

Signs

Signs include fever, tachypnea, tachycardia, crackles, bronchial breath sounds, egophony (E to A change—said to occur when, during auscultation, a patient says the letter “E” and the examiner hears the letter “A”), and dullness to percussion.

Signs of pleural effusion may also be present.

Nasal flaring, use of accessory muscles, and cyanosis are common among infants.

Fever is frequently absent in the elderly.

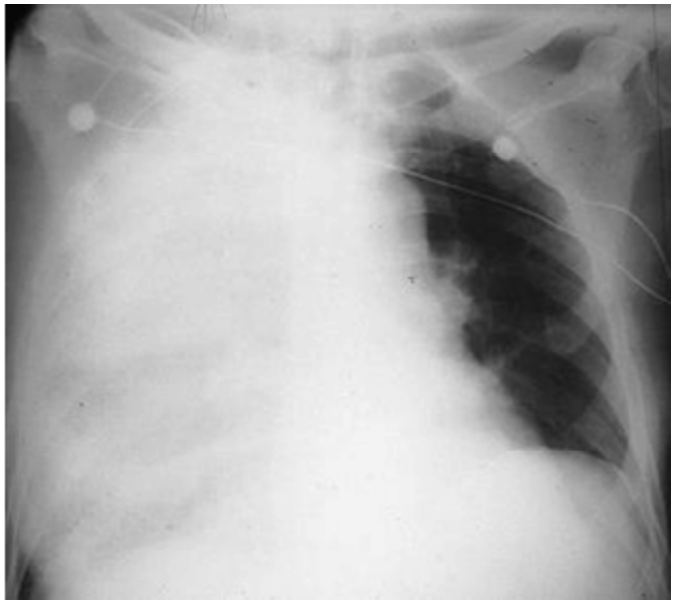
Symptoms and signs were previously thought to differ by type of pathogen. For example, factors thought to suggest viral pneumonia included gradual onset, preceding URI symptoms, diffuse findings on auscultation, and absence of a toxic appearance.

Pathogen identification

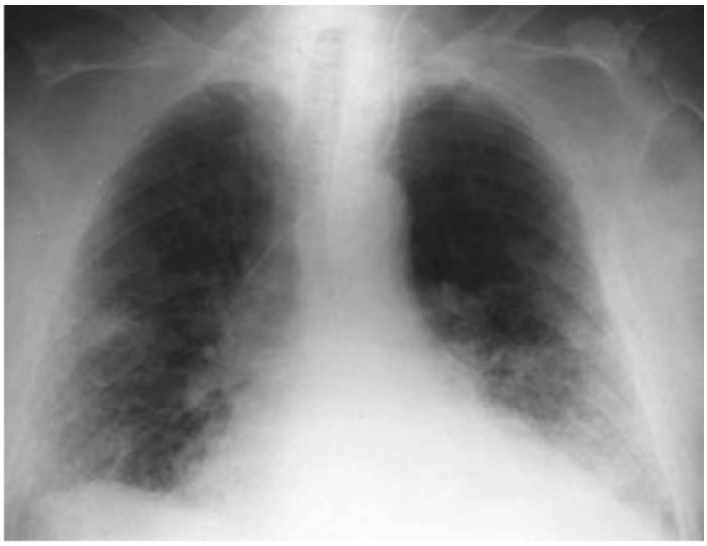
Identification of the pathogen can be useful to direct therapy and verify bacterial susceptibilities to antibiotics. However, because of the limitations of current diagnostic tests and the success of empiric antibiotic treatment, experts recommend limiting attempts at microbiologic identification (eg, cultures, specific antigen testing) unless patients are at high risk or have complications (eg, severe pneumonia, immunocompromise, asplenia, failure to respond to empiric therapy).

Chest x-ray findings generally cannot distinguish one type of infection from another, although the following findings are suggestive:

- Multilobar infiltrates suggest *S. pneumoniae* or *Legionella pneumophila* infection.
- Interstitial pneumonia (on chest x-ray, appearing as increased interstitial markings, subpleural reticular opacities that increase from the apex to the bases of the lungs, and peripheral honeycombing) suggests viral or mycoplasmal etiology.
- Cavitating pneumonia suggests *S. aureus* or a fungal or mycobacterial etiology.



Multilobar Pneumonia



Interstitial Opacities

Blood cultures, which are often obtained in patients hospitalized for pneumonia, can identify causative bacterial pathogens if bacteremia is present. About 12% of all patients hospitalized with pneumonia have bacteremia; *S. pneumoniae* accounts for two thirds of these cases.

Treatment

- Antibiotics
- Antivirals for influenza or varicella
- Supportive measures

Antimicrobials

Antibiotic therapy is the mainstay of treatment for community-acquired pneumonia. Appropriate treatment involves starting empiric antibiotics as soon as possible, preferably ≤8 h after presentation. Because organisms are difficult to identify, the empiric antibiotic regimen is selected based on likely pathogens and severity of illness.

If a pathogen is subsequently identified, the results of antibiotic susceptibility testing can help guide any changes in antibiotic therapy.

For children, treatment depends on age, previous vaccinations, and whether treatment is outpatient or inpatient. For outpatient treatment, treatments are dictated by age-

- < 5 yr: Amoxicillin or amoxicillin/clavulanate is usually the drug of choice. If epidemiology suggests an atypical pathogen as the cause and clinical findings are compatible, a macrolide (eg, azithromycin or clarithromycin) can be used instead. Some experts suggest not using antibiotics if clinical features strongly suggest viral pneumonia.
- ≥ 5 yr: Amoxicillin or (particularly if an atypical pathogen cannot be excluded) amoxicillin plus a macrolide. Amoxicillin/clavulanate is an alternative. If the cause appears to be an atypical pathogen, a macrolide alone can be used.

For children treated as inpatients, antibiotic therapy tends to be more broad-spectrum and depends on the child's previous vaccinations –

- Fully immunized (against *S. pneumoniae* and *H. influenzae*type b): Ampicillin or penicillin G (alternatives are ceftriaxone or cefotaxime). If MRSA is suspected, vancomycin or clindamycin is added. If an atypical pathogen cannot be excluded, a macrolide is added.

- Not fully immunized: Ceftriaxone or cefotaxime (alternative is levofloxacin). If MRSA is suspected, vancomycin or clindamycin is added. If an atypical pathogen cannot be excluded, a macrolide is added.

With empiric treatment, 90% of patients with bacterial pneumonia improve. Improvement is manifested by decreased cough and dyspnea, defervescence, relief of chest pain, and decline in WBC count.

Failure to improve should trigger suspicion of
- An unusual organism
- Resistance to the antimicrobial used for treatment
- Empyema
- Coinfection or superinfection with a 2nd infectious agent
- An obstructive endobronchial lesion
- Immunosuppression
- Metastatic focus of infection with reseeding (in the case of pneumococcal infection)
- Nonadherence to treatment (in the case of outpatients)

Antiviral therapy may be indicated for select viral pneumonias. Ribavirin is not used routinely for RSV pneumonia in children or adults, but may be used in occasional high-risk children age < 24 mo.

Oseltamivir 75 mg po bid or zanamivir 10 mg inhaled bid started within 48 h of symptom onset and given for 5 days reduces the duration and severity of symptoms in patients who develop

influenza infection. In patients hospitalized with confirmed influenza infection, observational studies suggest benefit even 48 h after symptom onset.

Acyclovir 5 to 10 mg/kg IV q 8 h for adults or 250 to 500 mg/m^2 body surface area IV q 8 h for children is recommended for varicella lung infections. Though pure viral pneumonia does occur, superimposed bacterial infections are common and require antibiotics directed against *S. pneumoniae*, *H. influenzae*, and *S. aureus*.

Follow-up x-rays should be obtained 6 wk after treatment in patients > 35; persistence of an infiltrate at ≥ 6 wk raises suspicions of TB or an underlying, possibly malignant endobronchial lesion.

Management of Community-Acquired Pneumonia in Adults

Group	Likely Organisms	Empiric Treatment
I. Outpatients—no modifying factors present†	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, respiratory viruses, miscellaneous organisms (eg, *Legionella* sp, *Mycobacterium tuberculosis*, endemic fungi)	Macrolide (azithromycin 500 mg po once, then 250 mg once/day; clarithromycin 250 to 500 mg po bid; or extended-release clarithromycin 1 g once/day) *or* Doxycycline 100 mg po bid (if allergic to macrolide)
II. Outpatients—modifying factors present†	*S. pneumoniae*, including antibiotic-resistant forms; *M. pneumoniae*; *C. pneumoniae*; mixed infection (bacteria + atypical pathogen or virus); *H. influenzae*; enteric gram-negative organisms; respiratory viruses; miscellaneous organisms (eg, *Moraxella catarrhalis, Legionella* sp, anaerobes [aspiration], *M. tuberculosis*, endemic fungi)	Beta-lactam (cefpodoxime 200 mg po q 12 h; cefuroxime 500 mg po q 12 h; amoxicillin 1 g q 8 h; amoxicillin/clavulanate 875/125 mg q 12 h) *plus* Macrolide po *or* Antipneumococcal fluoroquinolone po or IV (alone; eg, moxifloxacin [400 mg po/IV q 24 h], gemifloxacin [320 mg po/IV q 24 h], levofloxacin [750 mg po/IV q 24 h])
III. Inpatient—not in ICU	*S. pneumoniae*, *H. influenzae*; *M. pneumoniae*; *C. pneumoniae*; mixed infection (bacteria + atypical pathogen or virus); respiratory viruses; *Legionella* sp,	Azithromycin 500 mg IV q 24 h *plus* Beta-lactam IV (cefotaxime 1 to 2 g q 8 to 12 h; ceftriaxone 1 g q 24 h)

Group	Likely Organisms	Empiric Treatment
	miscellaneous organisms (eg, *M. tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)	*or* Antipneumococcal fluoroquinolone po or IV (alone)
IVA. ICU patient—no *Pseudomonas* risk factors	*S. pneumoniae*, including antibiotic-resistant forms; *Legionella* sp; *H. influenzae*; enteric gram-negative organisms,;*Staphylococcus aureus*; *M. pneumoniae*; respiratory viruses miscellaneous organisms (eg, *C. pneumoniae*, *M. tuberculosis*, endemic fungi)	Beta-lactam IV (cefotaxime 1 to 2 g IV q 8 to 12 h; ceftriaxone 1 g IV q 24 h) *plus either* Antipneumococcal fluoroquinolone IV *or* Azithromycin 500 mg IV q 24 h
IVB. ICU patient—*Pseudomonas*risk factors present	Same as those for category IVA (above) plus *Pseudomonas* sp	Antipseudomonal beta-lactam[‡]or aztreonam (if allergic to or intolerant of beta-lactams) 1 to 2 g q 8 h *plus either* Ciprofloxacin 400 mg IV q 12 h or levofloxacin 750 mg po or IV q 24 h Alternatively: Antipseudomonal beta-lactam[‡] *plus* An aminoglycoside *plus either* Ciprofloxacin 400 mg IV q 12 h or levofloxacin 750 mg po or IV q 24 h

*These guidelines do not apply to patients with immunosuppression, influenza, aspiration pneumonia, or health care–associated pneumonia.

[†]Modifying factors:

- *Increased risk of antibiotic-resistant organisms:* Age > 65, alcoholism, antibiotic within 3 mo, exposure to child in day care center, multiple coexisting illnesses.
- *Increased risk of enteric gram-negative organisms:*Antibiotic use within 3 mo, cardiopulmonary disease (including COPD and heart failure), multiple coexisting illnesses.
- *Increased risk of Pseudomonas aeruginosa:*Broad-spectrum antibiotics > 7 days in past month, corticosteroid use, undernutrition, structural pulmonary disease.

[‡]Antipseudomonal beta-lactams =cefepime 1 to 2 g IV q 12 h, imipenem 500 mg IV q 6 h, meropenem 500 mg to 1 g IV q 8 h, piperacillin/tazobactam 3.375 g IV q 4 h.

Supportive care

Supportive care includes fluids, antipyretics, analgesics, and, for patients with hypoxemia, oxygen. Prophylaxis against thromboembolic disease and early mobilization improve outcomes for patients hospitalized with pneumonia.

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia (HAP) develops at least 48 h after hospital admission. The most common pathogens are gram-negative bacilli and *Staphylococcus aureus*; antibiotic-resistant organisms are an important concern.

Symptoms and signs include malaise, fever, chills, rigor, cough, dyspnea, and chest pain, but in ventilated patients, pneumonia usually manifests as worsening oxygenation and increased tracheal secretions.

Diagnosis is suspected on the basis of clinical presentation and chest x-ray and is confirmed by blood culture or bronchoscopic sampling of the lower respiratory tract.

Treatment is with antibiotics. Overall prognosis is poor, due in part to comorbidities.

Risk factors

Endotracheal intubation with mechanical ventilation poses the greatest overall risk of hospital-acquired pneumonia; ventilator-associated pneumonia constitutes > 85% of all cases, with pneumonia occurring in 9 to 27% of mechanically ventilated patients. The highest risk of VAP occurs during the first 10 days after intubation.

Endotracheal intubation breaches airway defenses, impairs cough and mucociliary clearance, and facilitates microaspiration of bacteria-laden secretions that pool above the inflated endotracheal tube cuff. In addition, bacteria form a biofilm on and within the endotracheal tube that protects them from antibiotics and host defenses.

In nonintubated patients, risk factors include previous antibiotic treatment, high gastric pH (due to stress ulcer prophylaxis or therapy with H2 blockers or proton pump inhibitors), and coexisting cardiac, pulmonary, hepatic, or renal insufficiency.

Major risk factors for postoperative pneumonia are age > 70, abdominal or thoracic surgery, and functional debilitation.

Pathogens

Pathogens and antibiotic resistance patterns vary significantly among institutions and can vary within institutions over short periods (eg, month to month). In general, the most important pathogens are *Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus*, and methicillin-resistant *S. aureus* (MRSA).

Other important pathogens include enteric gram-negative bacteria (mainly *Enterobacter*sp, *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Proteus* sp, and *Acinetobacter* sp). Methicillin-sensitive *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are most commonly implicated when pneumonia develops within 4 to 7 days of hospitalization, whereas *P. aeruginosa*, MRSA, and enteric gram-negative organisms become more common with increasing duration of intubation or hospitalization.

Prior intravenous antibiotic treatment (within the previous 90 days) greatly increases the likelihood of antibiotic-resistant organisms, particularly MRSA and *Pseudomonas* infection in VAP and HAP.

Other risk factors for antibiotic-resistant organisms specific to VAP include –

- Septic shock at time of VAP
- ARDS preceding VAP
- Five or more days of hospitalization prior to the occurrence of VAP
- Acute renal replacement therapy prior to VAP onset

High-dose corticosteroids increase the risk of *Legionella* and *Pseudomonas* infections.

Chronic suppurative lung diseases such as cystic fibrosis and bronchiectasis increase the risk of Gram-negative pathogens, including antibiotic-resistant strains.

Symptoms and Signs

Symptoms and signs of hospital-acquired pneumonia in nonintubated patients are generally the same as those for community-acquired pneumonia and include malaise, fever, chills, rigor, cough, dyspnea, and chest pain.

Pneumonia in critically ill, mechanically ventilated patients more typically causes fever and increased respiratory rate or heart rate or changes in respiratory parameters, such as an increase in purulent secretions or worsening hypoxemia.

Treatment

If hospital-associated pneumonia is suspected, treatment is with antibiotics that are chosen empirically based on –

- Local sensitivity patterns
- Patient risk factors for antibiotic-resistant pathogens

Empiric therapy for HAP/VAP without risk factors for antibiotic-resistant organisms and high mortality (mechanical ventilation for pneumonia or septic shock), in an institution where MRSA incidence is < 20% (of *S. aureus* isolates) and *P. aeruginosa* resistance is < 10% for commonly used empiric antipseudomonal antibiotics, could include any one of the following –

- Piperacillin/tazobactam
- Cefepime
- Levofloxacin
- Imipenem
- Meropenem

In treatment settings where MRSA rates are > 20%, vancomycin or linezolid should be added.

In patients who are at high risk for mortality or who have risk factors for antibiotic-resistant organisms, or in the absence of reliable local antibiograms, recommendations include triple therapy using 2 drugs with activity against *Pseudomonas* and 1 drug with activity against MRSA:

- An antipseudomonal cephalosporin (cefepime or ceftazidime) *or* an antipseudomonal carbapenem (imipenem, meropenem) *or* a beta-lactam/beta-lactamase inhibitor (piperacillin/tazobactam)
- An antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) *or* an aminoglycoside (amikacin, gentamicin, tobramycin)
- Linezolid or vancomycin

Pneumonia in Immunocompromised Patients

Pneumonia in immunocompromised patients is often caused by unusual pathogens but may also be caused by the same pathogens as those that cause community-acquired pneumonia.

Symptoms and signs depend on the pathogen and on the conditions compromising the immune system.

Diagnosis is based on blood cultures and bronchoscopic sampling of respiratory secretions, sometimes with quantitative cultures.

Treatment depends on the immune system defect and the pathogen.

The potential pathogens in patients with compromised immune system defenses are legion; they include those that cause community-acquired pneumonia as well as unusual pathogens. Likely pathogens depend on the type of defect in immune system defenses.

However, respiratory symptoms and changes on chest x-rays in immunocompromised patients may be due to various processes other than infection, such as pulmonary hemorrhage, pulmonary edema, radiation injury, pulmonary toxicity due to cytotoxic drugs, and tumor infiltrates.

Pneumonia in Immunocompromised Patients

Immune System Defect	Disorders Or Therapy Associated With Defect*	Likely Pathogens
Defective PMNs		
Neutropenia	Acute leukemia, aplastic anemia, cancer chemotherapy	Gram-negative bacteria *Staphylococcus aureus* *Aspergillus*sp *Candida*sp
Defective chemotaxis	Diabetes mellitus	*S. aureus* Gram-negative aerobes
Defective intracellular killing	Chronic granulomatous disease	*S. aureus*
Defective alternative pathway	Sickle cell disease	*Streptococcus pneumoniae* *Haemophilus influenzae*
C5 deficiency	Congenital disorder	*S. pneumoniae* *S. aureus* Gram-negative bacteria

Immune System Defect	Disorders Or Therapy Associated With Defect*	Likely Pathogens
Cell-mediated immunity		
T-cell deficiency or dysfunction	Hodgkin lymphoma, cancer chemotherapy, corticosteroid therapy	Mycobacteria Viruses (eg, herpes simplex virus, cytomegalovirus) *Strongyloides* sp Opportunistic fungi (eg, *Aspergillus*, *Mucor*, *Cryptococcus* spp) *Nocardia* sp *Toxoplasma*sp
	AIDS	*Pneumocystis jirovecii* *Toxoplasma*sp Cytomegalovirus Herpes simplex virus Opportunistic fungi (eg, *Aspergillus*, *Mucor*, *Cryptococcus* spp) Mycobacteria
Humoral immunodeficiency		
B-cell deficiency or dysfunction	Multiple myeloma, agammaglobulinemia	*S. pneumoniae* *H. influenzae* *Neisseria meningitidis*
	Selective deficiency: IgA, IgG, IgM	*S. pneumoniae* *H. influenzae*
	Hypogammaglobulinemia	*P. jirovecii* Cytomegalovirus *S. pneumoniae* *H. influenzae*

PMN = polymorphonuclear leukocytes

Symptoms and Signs

Symptoms may include malaise, chills, fever, rigor, cough, dyspnea, and chest pain. However, immunocompromised patients may have no fever or respiratory signs and are less likely to have purulent sputum if they are neutropenic. In some patients, the only sign is fever.

Pathogen identification

Likely pathogens can often be predicted based on symptoms, x-ray changes, and the type of immunodeficiency. In patients with acute symptoms, the differential diagnosis includes bacterial infection, hemorrhage, pulmonary edema, a leukocyte agglutinin reaction to transfusion of blood products, and pulmonary emboli.

An indolent time course is more suggestive of a fungal or mycobacterial infection, an opportunistic viral infection, *P. jirovecii* pneumonia, tumor, a cytotoxic drug reaction, or radiation injury.

X-rays showing localized consolidation usually indicate an infection involving bacteria, mycobacteria, fungi, or *Nocardia* sp. A diffuse interstitial pattern is more likely to represent a viral infection, *P. jirovecii* pneumonia, drug or radiation injury, or pulmonary edema. Diffuse nodular lesions suggest mycobacteria, *Nocardia* sp, fungi, or tumor. Cavitary disease suggests mycobacteria, *Nocardia* sp, fungi, or bacteria, particularly *S. aureus*.

In organ or bone marrow transplantation recipients with bilateral interstitial pneumonia, the usual cause is cytomegalovirus, or the disease is idiopathic.

A pleural-based consolidation is usually Aspergillus infection.

In patients with AIDS, bilateral pneumonia is usually P. jirovecii pneumonia. About 30% of patients with HIV infection have *P. jirovecii* pneumonia as the initial AIDS-defining diagnosis, and > 80% of AIDS patients have this infection at some time if prophylaxis is not given. Patients with HIV infection become vulnerable to *P. jirovecii* pneumonia when the CD4+ T lymphocyte count is <200/μL.

Treatment

The antimicrobial therapy depends on the immune system defect and the risk factors for specific pathogens.

In patients with neutropenia, empiric treatment depends on the immune system defect, x-ray findings, and severity of illness. Generally, broad-spectrum antibiotics that are effective against gram-negative bacilli, *Staphylococcus aureus*, and anaerobes are needed, as for hospital-acquired pneumonia.

If patients with conditions other than HIV infection do not improve with 5 days of antibiotic therapy, antifungal therapy is frequently added empirically.

Laboratory Parameters Analyzed for Clinical Trials

The laboratory tests are ordered for the following purposes –

- Diagnosis of the disease condition
- Monitoring progression of disease
- Monitoring effectiveness of treatment
- Identifying complications of treatment
- Screening population for diseases

Most commonly ordered lab tests for Clinical trials are –

- CBC (Complete Blood Count)
- BMP (Basic Metabolic Panel)
- CMP (Comprehensive Metabolic Panel)

Complete blood count (CBC)

CBC may be ordered with or without differential leukocyte count.

Peripheral venous blood is collected in a tube containing the anticoagulant EDTA and should be thoroughly mixed.

Nowadays, whole blood analyzer is used to carry out CBC.

Red blood cell data reported is as below –

- Total red blood cell count (RBC count)
- Hemoglobin (Hgb)
- Hematocrit (Hct)
- Mean corpuscular volume (MCV)
- Red blood cell distribution width (RDW)

White blood cell data –

- Total white blood cell (leukocyte) count (WBC count)
- A differential white blood cell count may also be ordered

Platelet Count (PLT)

Red Blood Cell Count is the count of the number of circulating red blood cells in $1mm^3$ of peripheral venous blood.

Hematocrit is a measure of the percentage of the total blood volume that is made up by the red blood cells.

Normal Hct in adult males is 40-54% and in adult females 34-51%.

Hct is calculated from the RBC and MCV using the following formula –

Hematocrit % = RBC (cells/liter) x MCV (liter/cell)

Mean Corpuscular Volume is a measure of the average volume, or size, of an RBC.

The MCV is important in classifying anemias viz.

- Normal MCV = normocytic anemia
- Decreased MCV = microcytic anemia
- Increased MCV = macrocytic anemia

White Blood Cell Count is a count of the total WBC, or leukocyte, count in $1mm^3$ of peripheral blood.

A decrease in the number of WBCs is called Leukopenia. An increase in the number of WBCs is known as Leukocytosis.

Types of leukocytes include –

- Neutrophils (or Polymorphonuclear leukocytes)
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Platelet count is a count of the number of platelets (thrombocytes) per cubic milliliter of blood.

A decreased number of platelets is called Thrombocytopenia and an increased number of platelets is called Thrombocytosis.

CBC as reported by Lab

Component	Value	Flag	Low	High	Units
WBC	9.4		4.0	10.0	K/UL
RBC	4.81		3.60	5.50	M/UL
HGB	13.7		12.0	16.0	GM/DL
HCT	41.1		34.0	51.0	%
MCV	85.4		85	95	FL
MCH	28.6		28.0	32.0	PG
MCHC	33.4		32.0	36.0	GM/DL
RDW	14.3		11.0	15.0	%
PLT CNT	220		150	400	K/UL
DIFF TYPE AUTOMATED					
LYMPH # 3.6			1.0	4.0	K/MM3
MONO # 0.6			0.0	1.0	K/MM3
GRAN # 5.1			2.0	7.0	K/MM3
EO # 0.0			0.0	0.7	K/MM3
BASO # 0.0			0.0	0.2	K/MM3
LYMPH 39			20	45	%
MONO 6			0	10	%
GRAN 55			45	70	%
EO 0			0	7	%
BASO 0			0	2	%

Basic Metabolic Panel

These tests assess the electrolytes and kidney function. They include –

- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Carbon Dioxide Content (CO2)
- Blood Urea Nitrogen (BUN)
- Serum Creatinine (Cr)
- Serum glucose (Glu)
- Total Calcium (Calcium)

Sodium is the major cation in the extracellular space where serum levels of approximately 140mmol/L exist.

Sodium salts are major determinants of extracellular osmotic activity (osmolality).

Increased serum sodium level is called Hypernatremia, while a decreased serum sodium level is called Hyponatremia.

Potassium is the major intracellular cation with levels of ~ 4 mmol/L found in serum.

Elevated serum potassium level is called Hyperkalemia and a decreased serum potassium level is known as Hypokalemia.

Blood Urea Nitrogen

The BUN measures the amount of urea nitrogen in the blood.

Urea is formed in the liver as the end product of protein metabolism and is transported to the kidneys for excretion.

Nearly all renal diseases can cause an inadequate excretion of urea, which causes the blood concentration to rise above normal.

The BUN is interpreted in conjunction with the creatinine test – these tests are referred to as "renal function tests".

The creatinine test measures the amount of creatinine in the blood.

Creatinine is a catabolic product of creatine phosphate used in skeletal muscle contraction.

Creatinine, as with blood urea nitrogen, is excreted entirely by the kidneys and blood levels are therefore proportional to renal excretory function

Uric Acid

Uric acid is formed from breakdown of nucleic acids and excreted as a waste product by kidneys. It is increased in kidney disease, but most often used to diagnosis gout (pain in joints, mainly big toe, due to precipitated uric acid crystals)

It is also increased in increased cell destruction, such as after massive radiation or chemotherapy.

Plasma glucose levels may be indicative of diabetes mellitus. They should be evaluated in relation to a patient's meal i.e. postprandial vs fasting.

The criteria for the diagnosis of diabetes are –

- Fasting Plasma Glucose ≥126 mg/dL
- 2 hour Post-Prandial Glucose ≥200 mg/dl
- Random Plasma Glucose >200 mg/dL in the presence of symptoms

BMP as reported by Lab

Component	value	flag	low	high	units
Sodium	142		136	144	mm/l
Potassium	3.9		3.3	5.1	mm/l
Chloride	107		98	108	mm/l
Co2	27		20	32	mm/l
Bun	10		7	22	mg/dl
Creatinine	0.80		0.7	1.5	mg/dl

Complete Metabolic Panel

This involves more extensive laboratory evaluation of organ dysfunction and includes assessment of:

- Sodium
- Potassium
- Chloride
- Carbon Dioxide Content
- Albumin
- Total Bilirubin
- Total Calcium
- Glucose
- Alkaline Phosphatase
- Total Protein
- Aspartate Aminotransferase
- Blood Urea Nitrogen
- Creatinine

Total Protein

Albumin and globulin constitute most of the protein within the body and are measured in the total protein test.

Albumin comprises ~ 60% of the total protein within the extracellular portion of the blood.

Albumin's major effect within the blood is –

- to maintain colloid osmotic pressure
- to transport many important blood constituents e.g. drugs, hormones, enzymes

Albumin is synthesized in the liver and therefore is a measure of hepatic function.

Alkaline phosphatase is an enzyme present in a number of tissues, including liver, bone, kidney, intestine, and placenta; each of which contains distinct isoenzyme forms.

The two major circulating alkaline phosphatase isoenzymes are bone and liver.

Elevation in serum alkaline phosphatase is most commonly a reflection of liver or bone disorders.

Levels of alkaline phosphatase are increased in both extrahepatic and intrahepatic obstructive biliary disease.

The total serum bilirubin level is the sum of the conjugated (direct) and unconjugated (indirect) bilirubin.

Normally the unconjugated bilirubin makes up 70-85% of the total bilirubin

Bilirubin metabolism begins with the breakdown of red blood cells in the reticuloendothelial system in the spleen and bilirubin metabolism continues in the liver.

Elevation in total bilirubin reflects any aberrations in bilirubin metabolism or increased hemolysis.

Aspartate Aminotransferase (AST formerly called SGOT)

AST is an enzyme that is present in hepatocytes and myocytes (both skeletal muscle and cardiac muscle).

Elevations in AST are most commonly a reflection of hepatocellular injury but they may also be elevated in myocardial or skeletal muscle injury.

Alanine Aminotransferase (ALT; formerly called SGPT)

ALT levels may be increased up to 10x in cirrhosis, infections or tumors and up to 100x in viral or toxic hepatitis.

Lipid Metabolism Tests

Cholesterol is present in all tissues. It serves as the skeleton for many hormones.

The recommended total cholesterol level should be less than 200 mg/dL in adults.

Low Density Lipoprotein (LDL) is also called as "bad" cholesterol and HDL is known as "good" cholesterol

Triglycerides are the main storage form of lipids, comprising 95% of fat tissue.

Hypertriglyceridemia – having high blood levels of triglycerides – may increase risk of heart attack.

CMP from a patient with congestive heart failure

Component	value	flag	Range	units
Glucose	112	H	[70 – 100]	mg/dl
Blood Urea Nitrogen	39	H	[7 - 22]	mg/dl
Creatinine	1.6	H	[0.7 - 1.5]	mg/dl
Calcium	8.9		[8.5 - 10.5]	mg/dl
Sodium	132	L	[136 - 146]	mmol/L
Potassium	4.0		[3.5 - 5.3]	mmol/L
Chloride	93	L	[98 - 108]	mmol/L
Carbon Dioxide	23		[20 - 32]	mmol/L
Albumin	3.1	L	[3.6 - 5.0]	gm/dl

A different set of tests are necessary for investigating infectious diseases. These laboratory tests include –

- Detection Methods
  - Microscopy
  - Culture
  - Antigen test
  -
- Identification Methods
  - PCR
  - Serology

- Antimicrobial susceptibility

Microscopy

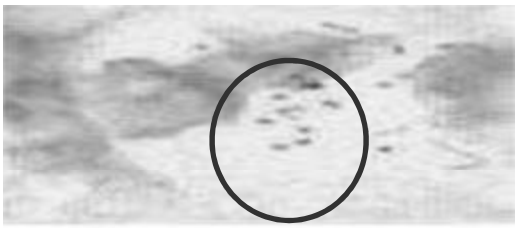
It involves direct examination of a specimen with or without use of stains to detect the presence of organisms

Pros:

- Quick and easy
- Preliminary results

Cons:

- Not specific



Gram negative diplococci

Culture

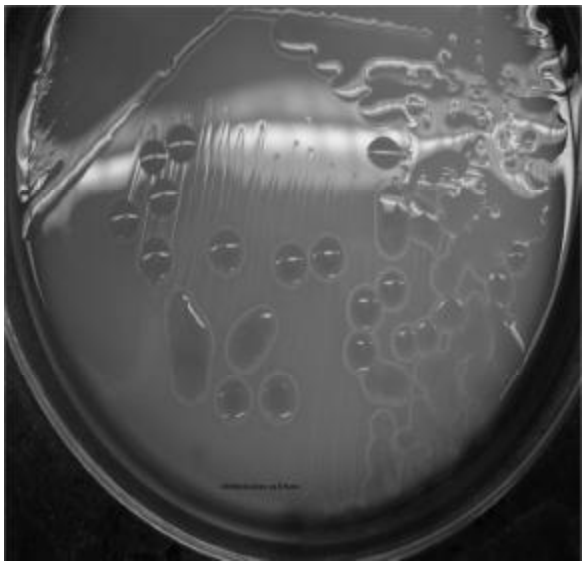
It is the process of growing and propagating organisms in a media that is conducive for their growth.

Pros:

- Confirm the organism
- Reproduce the organism and use for additional testing

Cons:

- Delay in confirmation
- Require viable organism
- Difficult for fastidious organisms



S. pneumoniae on blood agar plate

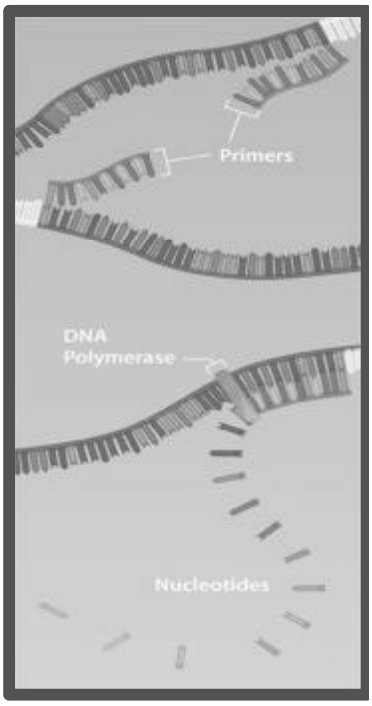
Antigen Test

These tests detect the presence of antigen/s in the given sample.

Technique	Principle
Agglutination	Known antiserum causes bacteria or other particulate antigens to clump together or agglutinate
Complement fixation	Known antiserum mixed with the test antigen and complement is added. Sheep red blood cells and hemolysins are then added. Positive test: no hemolysis, negative test: hemolysis
Enzyme-linked immunosorbant assay (ELISA); Enzyme immunoassay (EIA)	A rapid test where an antibody or antigen is linked to an enzyme as a means of detecting a match between the antibody and antigen.
Fluorescent antibody	Fluorescent dye is attached to known antibodies. When the fluorescent antibody reacts with the antigen, the antigen will fluoresce when viewed with a fluorescent microscope.

Identification Methods

Polymerase Chain Reaction (PCR)



It is a method used to amplify a specific region of a DNA strand.

Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase, an enzyme originally isolated from the thermophilic bacterium *Thermus aquaticus*. This DNA polymerase enzymatically assembles a new DNA strand from free nucleotides, the building blocks of DNA.

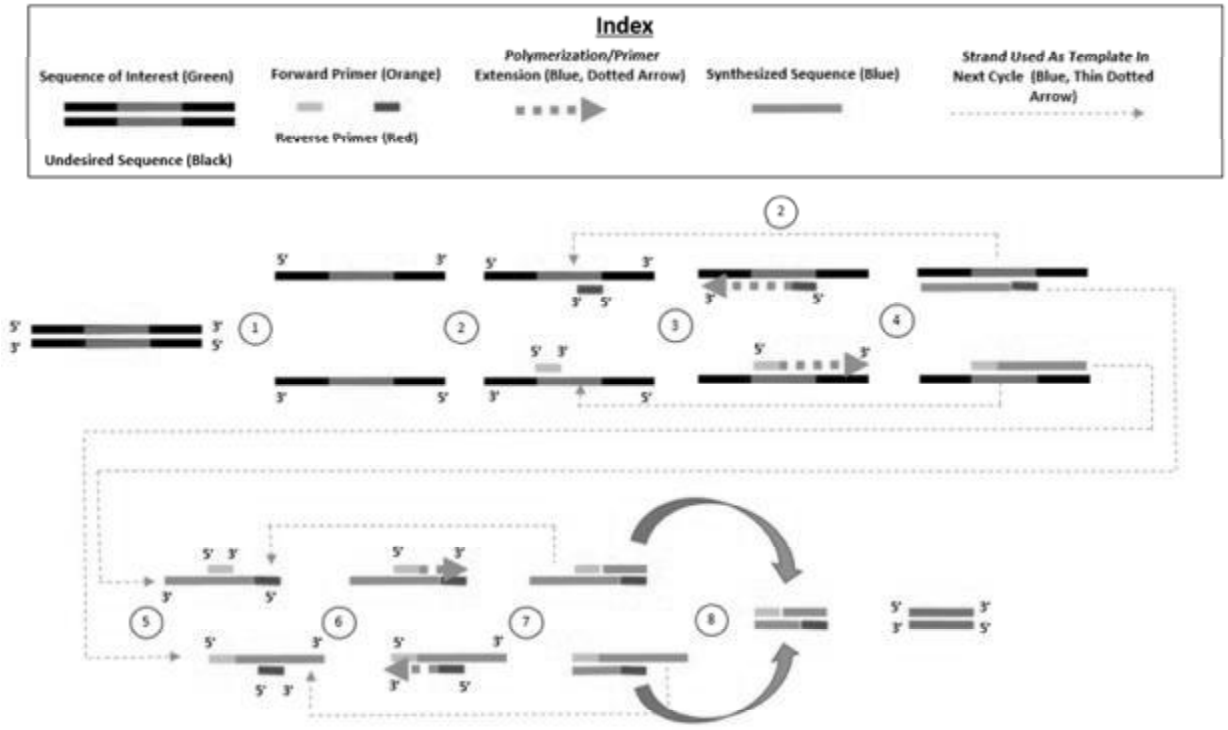
PCR allows for rapid and highly specific diagnosis of infectious diseases, including those caused by bacteria or viruses. PCR also permits identification of non-cultivatable or slow-growing microorganisms such as mycobacteria, anaerobic bacteria, or viruses from tissue culture assays and animal models.

Pros:

- Simple process, eliminates tedious work, results available within a day
- Does not require a viable organism as only a strand of DNA is needed,
- Sensitive test

Cons:

- Sensitive – pick up environmental contaminants



1. The DNA double helix is melted apart at T> 90°C and its strands separate.
2. The temperature is decreased to slightly below the T_m of both the primers being used. Both primers bind to the available strands. These primers are supplied in excess to insure that the strands do not only come back and reanneal to one another.
3. Polymerization (extension) occurs via DNA Polymerase in the 5' to 3' direction on each strand.
4. Incorporated additional nucleotides give rise to new strands that extend past the sequence of interest.
5. The previously polymerized strands act as template for the other primer (if forward primer bound first, reverse primer now binds and vice versa).
6. Polymerization occurs via DNA Polymerase in the 5' to 3' direction on each strand, this time ending at the end of the sequence of interest.
7. Incorporated additional nucleotides give rise to new strands that only encode the sequence of interest.
8. The synthesized strands encoding the sequence of interest anneal to one another to form the end product.

Serology

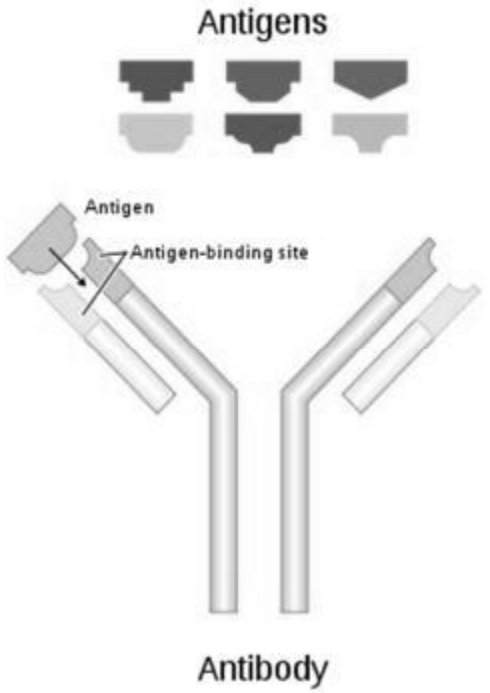
Serology is the study of blood serum, with emphasis on testing of antibodies in the serum.

Antigen is a substance which stimulates the body to produce antibody; usually a 'foreign' substance.

Antibody is a protein molecule produced by the body's immune system in response to a specific antigen.

The antibody combines with the antigen and disables it. It is also called Immunoglobulins (*e.g.* IgM, IgG, IgE , IgA).

It is referred to as anti-(name of antigen), *e.g.* anti-HCV, anti-HAV antibody.



Antibodies

There are different types of antibodies that are produced in response to different antigens.

- IgM is a type of antibody produced by the body, usually the first antibody to appear in response to a foreign substance exposure that eliminates the organism in the early stages of immunity before there is sufficient IgG.

- IgG: type of antibody that provides the majority of antibody-based immunity against invading organisms. The only antibody that crosses the placenta to provide immunity to the fetus.

- IgE is the type of antibody that is involved in the immediate type of allergic reactions e.g. anaphylaxis.

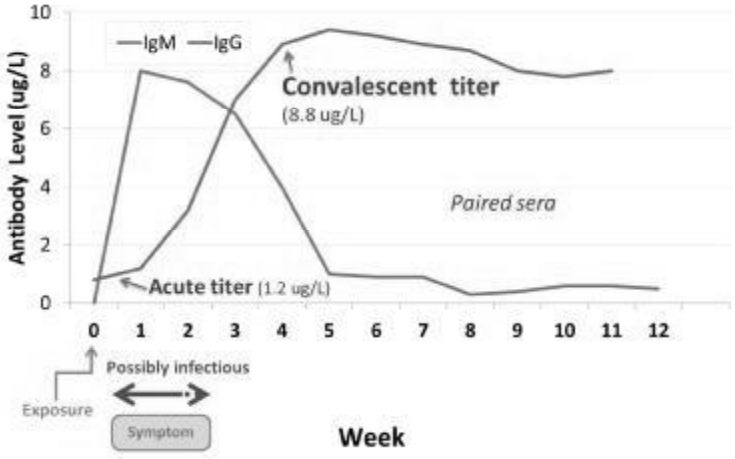
- IgA is an antibody that plays a crucial role in the immune function of mucous membranes. It provides local protection and is found in mucous secretions, including tears, saliva, sweat and secretions from the genitourinary tract, gastrointestinal tract, prostate and respiratory epithelium.

Titer is the term used to denote the amount of antibodies present in the blood usually as a result of infection.

Acute titer and Convalescent titer

At the acute stage of disease, serum is tested (acute phase) followed by another testing about 3 weeks later (convalescent phase). IgG levels are compared and a 4-fold increase between acute and convalescent samples usually indicate infection.

Antibody Response to Infection



Pros:

- Screening tool
- Readily available
- Indicates response to antigen (even if antigen is not detectable) – may indicate infection or immunity

Cons:

- Paired testing necessary for some diseases - may take a while to get results, impact on patient management
- Unable to differentiate between immunity and disease
- Sensitivity and specificity:
  - False-negative result: compromised immune system
  - False-positive result: liver disease, low disease prevalence

Antimicrobial susceptibility

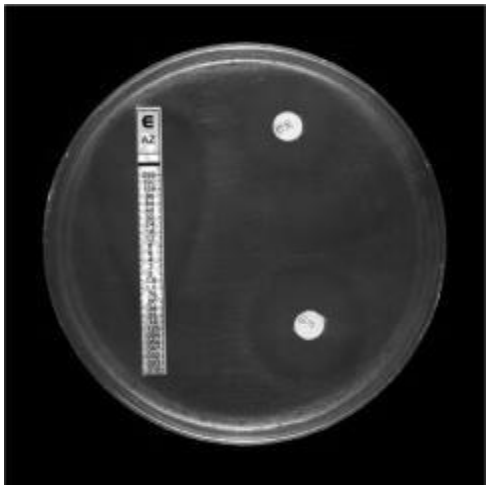
MIC (minimum inhibitory concentration)

It indicates the lowest concentration of antimicrobials that will inhibit the growth of organisms.

MICs are important to confirm resistance of organisms to an antimicrobial agent.

Methods:

- Disk diffusion test
- Broth dilution test



Disk diffusion test is a test of the antibiotic sensitivity of bacteria. It uses antibiotic discs to test the extent to which bacteria are affected by those antibiotics. In this test, wafers containing antibiotics are placed on an agar plate where bacteria have been placed, and the plate is left to incubate.

If an antibiotic stops the bacteria from growing or kills the bacteria, there will be an area around the wafer where the bacteria have not grown enough to be visible. This is called a zone of inhibition.

The size of this zone depends on how effective the antibiotic is at stopping the growth of the bacterium.

If the compound is effective against bacteria at a certain concentration, no colonies will grow where the concentration in the agar is greater than or equal to the effective concentration. This

is the zone of inhibition. In general, larger zones correlate with smaller minimum inhibitory concentration (MIC) of antibiotic for that bacteria.

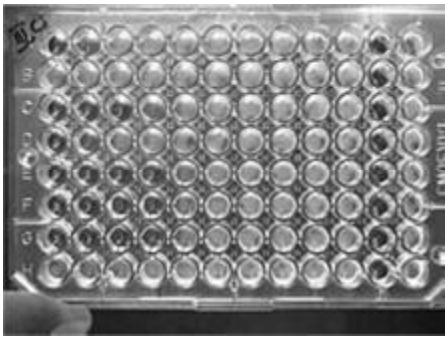
Broth dilution test is another method used to test the susceptibility of bacteria to antibiotics.

During testing, multiple microtiter plates are filled with a broth composed of Brucella and supplements of blood. Varying concentrations of the antibiotics and the bacteria to be tested are then added to the plate.

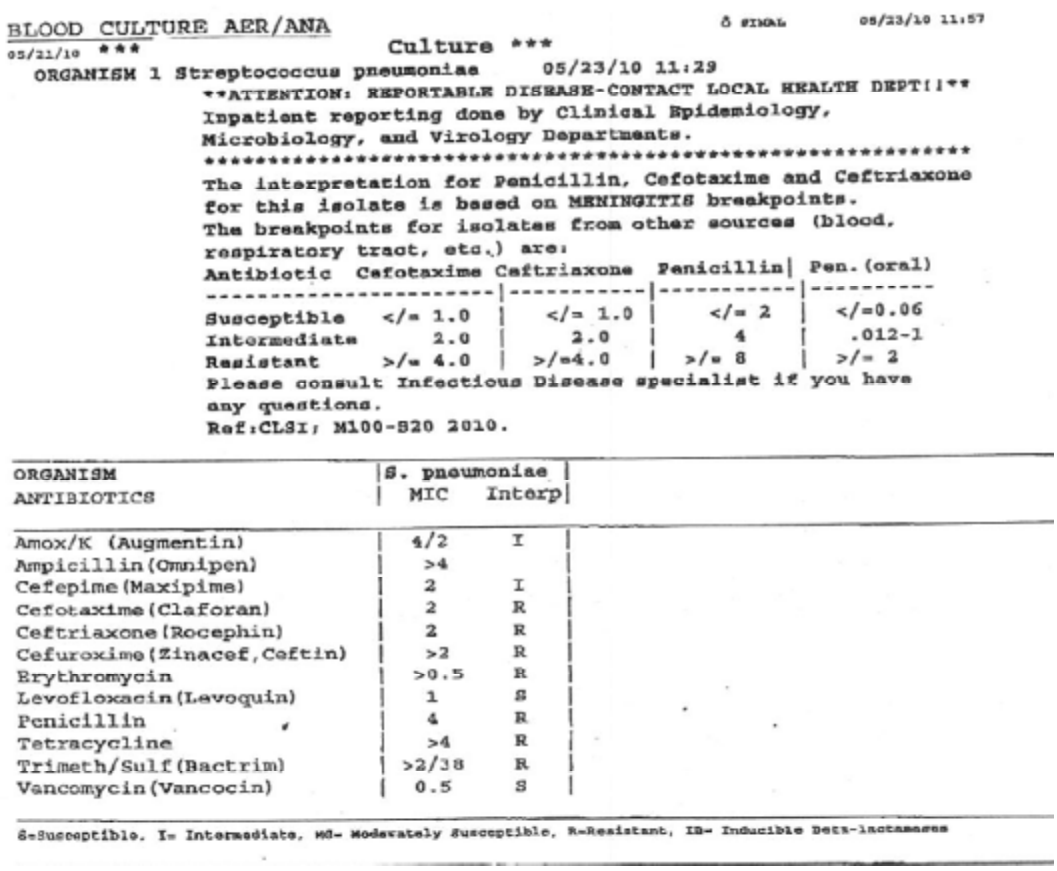
The plate is then placed into a non-CO2 incubator and heated at thirty-five degrees Celsius for sixteen to twenty hours. Following the allotted time, the plate is removed and checked for bacterial growth.

If the broth became cloudy or a layer of cells formed at the bottom, then bacterial growth has occurred.

The results of the broth microdilution method are reported in Minimum Inhibitory Concentration (MIC), or the lowest concentration of antibiotics that stopped bacterial growth.



A sample report of culture sensitivity report is given below.



BLOOD CULTURE AER/ANA — FINAL — 05/23/10 11:57

05/21/10 *** Culture ***

ORGANISM 1 Streptococcus pneumoniae 05/23/10 11:29

ATTENTION: REPORTABLE DISEASE-CONTACT LOCAL HEALTH DEPT!!
Inpatient reporting done by Clinical Epidemiology, Microbiology, and Virology Departments.

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The interpretation for Penicillin, Cefotaxime and Ceftriaxone for this isolate is based on MENINGITIS breakpoints.
The breakpoints for isolates from other sources (blood, respiratory tract, etc.) are:

Antibiotic	Cefotaxime	Ceftriaxone	Penicillin	Pen.(oral)
Susceptible	</= 1.0	</= 1.0	</= 2	</=0.06
Intermediate	2.0	2.0	4	.012-1
Resistant	>/= 4.0	>/=4.0	>/= 8	>/= 2

Please consult Infectious Disease specialist if you have any questions.
Ref:CLSI; M100-S20 2010.

ORGANISM / ANTIBIOTICS	S. pneumoniae MIC	Interp
Amox/K (Augmentin)	4/2	I
Ampicillin(Omnipen)	>4	
Cefepime(Maxipime)	2	I
Cefotaxime(Claforan)	2	R
Ceftriaxone(Rocephin)	2	R
Cefuroxime(Zinacef,Ceftin)	>2	R
Erythromycin	>0.5	R
Levofloxacin(Levoquin)	1	S
Penicillin	4	R
Tetracycline	>4	R
Trimeth/Sulf(Bactrim)	>2/38	R
Vancomycin(Vancocin)	0.5	S

S=Susceptible, I= Intermediate, MS= Moderately Susceptible, R=Resistant, IB= Inducible Beta-lactamases