Therapy of Dyslipidemias

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Therapy of Dyslipidemias

- **Hypercholesterolemia, elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL) and elevated lipoprotein(a) Lp(a) are linked to increased risk for coronary heart disease, peripheral vascular disease, and cerebrovascular disease (both morbidity and mortality).**
- **Hypertriglyceridemia is associated with the development of acute pancreatitis. VLDL also increase the risk of vascular diseases.**

Therapy of Dyslipidemias

- **Initial therapy of lipoprotein disorder is life-style modification with restricted intake of total and saturated fat and cholesterol, and a modest increase in unsaturated fat intake (specially mono-unsaturated fat), in addition to regular exercise, smoking cessation and weight reduction.**

Therapy of Dyslipidemias

- **A Statin is the drugs of choice for patients with hypercholesterolemia.**
- **Patients NOT responding to statin monotherapy may be treated with combination therapy for hypercholesterolemia, but should be monitored closely because of an increased risk for adverse effects and drug interactions.**

Therapy of Dyslipidemias

- **Hypertriglyceridemia usually responds well to niacin, and fibrates (gemfibrozil, fenofibrate).**
- **Low HDL-C needs life-style modifications such as smoking cessation, and exercise; and drug therapy with niacin and fibrates which can significantly increase HDL-cholesterol.**

Therapy of Dyslipidemias

- Lp(a) is formed from LDL and apolipoprotein (a).
- It is homologous with plasminogen but is NOT activated by tissue plasminogen activator.
- Its level is variable (nil to over 2000 nM/L).
- It may be found in atherosclerotic plaques and may contribute to coronary disease by inhibiting thrombolysis.
- It can be secondarily elevated in patients with severe nephrosis and some inflammatory states.
- Niacin reduces levels of Lp(a) in many patients.

Therapy of Dyslipidemias

- **Hypertriglyceridemia (diabetes mellitus, nephrotic syndrome, and chronic renal disease) is also associated with increased cardiovascular risk.**
- **VLDL carries about 10 - 15% of serum cholesterol and most of the triglycerides in the fasting state.**
- **VLDL is a precursor for LDL, and VLDL remnants may be atherogenic.**
- **It is a risk factor for developing acute pancreatitis.**
- **Chylomicrons are triglyceride-rich particles formed from dietary fat solubilized by bile salts.**

Secondary Causes of Lipoprotein Abnormalities

A. **Hypercholesterolemia:**

1) **Hypothyroidism.**
2) **Obstructive liver disease.**
3) **Nephrotic syndrome.**
4) **Anorexia nervosa.**
5) **Acute intermittent porphyria.**
6) **Drugs: progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, sirolimus, mirtazapine (Tetra-CA).**

Secondary Causes of Lipoprotein Abnormalities

B. Hypertriglyceridemia:

1. Obesity
2. Diabetes mellitus
3. Lipodystrophy
4. Glycogen storage disease
5. Ileal bypass surgery
6. Sepsis
7. Pregnancy
8. Acute hepatitis
9. Systemic lupus erythematous
10. Monoclonal gammopathy: multiple myeloma, lymphoma.

Secondary Causes of Lipoprotein Abnormalities

12. **Drugs:** Alcohol, estrogens, isotretinoin, thiazides β-blockers, glucocorticoids, bile-acid binding resins, asparaginase, interferons, azole antifungals, bexarotene, mirtazapine, anabolic steroids, sirolimus.

C. Low HDL:

- Malnutrition, **obesity**, sedentary life-style.
- **Drugs:** non-ISA β-blockers, anabolic steroids, probucol, isotretinoin, progestins.

Therapy of Dyslipidemias

Desired Outcomes:

- **The ultimate goals of therapy are to reduce the risk of MI, angina, heart failure, ischemic stroke, and peripheral arterial disease (carotid stenosis, abdominal aortic aneurysm, ..).**

Therapy of Dyslipidemias

Nonpharmacologic Therapy:

Therapeutic life-style modification should be implemented in all patients prior to considering drug therapy:

- **Reduced intakes of saturated fats, cholesterol and total fat.**
- **The use of dietary options to reduce LDL-C such as plant phytosterols and increased soluble fiber intake, in addition to, weight reduction and increased physical activity.**

Therapy of Dyslipidemias

- **Plant phytosterols are structurally similar to cholesterol, and compete for its intestinal absorption.**
- **They also reduce bile acid absorption, thus, cholesterol is degraded into bile acids.**
- **Thus, they have an LDL-lowering effect.**

Therapy of Dyslipidemias

Food sources of phytosterols:

1) Cereals (oat, wheat, brown rice).
2) Legumes (peas, beans, lentils).
3) Nuts and Seeds (peanuts, almonds, sunflower seeds, pumpkin seeds, sesame seeds).
4) Fruits and vegetables (broccoli, cauliflower, apples, avocados, tomato, blueberries).

Therapy of Dyslipidemias

- **Physical activity of moderate intensity 30 minutes per day for most days of the week.**
- **Patients with known CAD or at high risk should be evaluated before undertaking vigorous exercise.**
- **Weight reduction should be attempted in persons who are overweight.**

Therapy of Dyslipidemias

- **Patients should stop smoking and have their hypertension controlled.**
- **Weight control plus increased physical activity raises HDL and reduces non-HDL cholesterol.**
- **Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can result in useful adjunctive reductions in total and LDL cholesterol.**

Drugs Used in Hyperlipoproteinemias

- **Omega-3 fatty acids found in fish oils (eicosapentaenoic acid and docosahexaenoic acid), activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and can reduce triglycerides in VLDL in some patients.**
- **Fish oil causes also alterations in the synthesis of prostanoids → synthesis of vasodilator prostaglandins and inhibitors of platelet aggregation.**

Therapy of Dyslipidemias

Other effects of omega-3 fatty acids:

a) **changes in immune function and cellular proliferation.**
b) **antioxidative effects.**
c) **antiinflammatory actions.**
d) **antiarrhythmic activities.**

- **Potential complications: thrombocytopenia and bleeding disorders, especially with high doses (eicosapentaenoic acid 15 to 30 g/d).**

Therapy of Dyslipidemias

Pharmacologic Therapy:

- **Many effective lipid-lowering drugs exist, but none is useful for all lipoprotein disorders.**
- **In addition, all agents are associated with adverse effects and drug-drug interactions.**

Therapy of Dyslipidemias

Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia:

Type	Lipoprotein Elevation
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL
IV	VLDL
V	VLDL + Chylomicrons

Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	--
IIa	Statins Cholestyramine or colestipol Niacin	Niacin or bile acid resins (BAR) Statins or niacin Statins or BAR **Ezetimibe** Mipomersen, lomitapide
IIb	Statins Fibrates Niacin	BAR or Fibrates or niacin Statins or niacin or BAR[a] Statins or Fibrates **Ezetimibe**
III	Fibrates Niacin	Statins or niacin Statins or Fibrates **Ezetimibe**
IV	Fibrates Niacin	Niacin Fibrates
V	Fibrates Niacin	Niacin Fish oils

[a]BAR are not used as first-line therapy if triglycerides are elevated at baseline since hypertriglyceridemia may be worsen with BAR alone.

[b]Mipomersen and lomitapide are used in combinations with other lipid lowering therapy, in particular, statins for patients with familial hypercholestermia (homozygotes or heterzygotes) and in patient who cannot be managed adequately with maximally tolerated statin therapy.

Therapy of Dyslipidemias

- **Treatment of type I hyperlipoproteinemia (↑ Chylomicrons) is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides.**
- **Total daily fat intake should be reduced.**
- **Look for secondary causes of hypertriglyceridemia and treat them appropriately, if present.**

Therapy of Dyslipidemias

- **Type V hyperlipoproteinemia (↑ VLDL and chylomicrons) also requires reduction of total fat intake.**
- **In addition, drug therapy (fibrates and niacin) is indicated if the response to diet alone is inadequate.**
- **Omega-3 fatty acids may be useful in lipoprotein lipase (LPL) deficiency in some patients.**

Therapy of Dyslipidemias

- **Type III hyperlipoproteinemia may be treated with fibric acid derivatives or niacin.**

Niacin (Nicotinic Acid, Vitamin B_3)

- It is reduced in the body to the amide which is incorporated into NAD → energy metabolism.

Pharmacodynamics:

1. It inhibits VLDL secretion from the liver and thus LDL production.
- It reduces LDL, triglycerides and VLDL.
- Increased clearance of VLDL via the LPL pathway contributes to reduction of triglycerides.

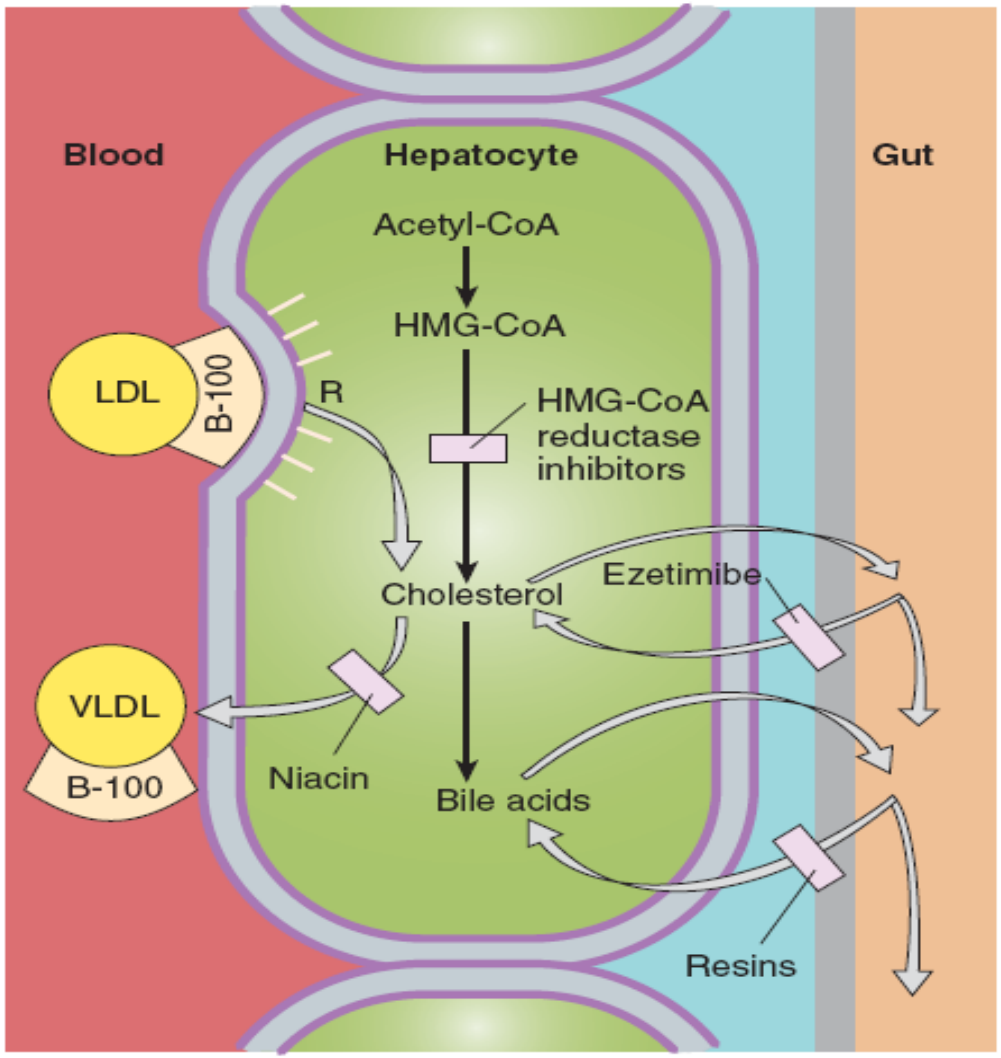


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

Niacin

2. It raises HDL cholesterol by decreasing its catabolism (most effective agent).
3. It reduces the level of $LP_{(a)}$.
4. It reduces fibrinogen levels.
5. It increases tissue plasminogen activator.

Niacin

- **The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia.**
- **It is also considered to be the first-line agent or an alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.**
- **Used for low HDL not responsive to life-style modification.**

Niacin

Adverse reactions:

1. **Cutaneous flushing and itching: prostaglandin-mediated and can be reduced by aspirin 325 mg given shortly before niacin ingestion.**
- **Laropiprant is a selective antagonist of the prostaglandin D receptor subtype 1 (DP1), which may mediate niacin-induced vasodilation, can be co-administred with extended-release (ER) niacin to lower flushing symptoms.**
2. **Acanthosis nigricans, darkening of the skin in skin-folds. (external marker of insulin resistance).**

Niacin

3. **Elevation liver function tests (more common with sustained-release preparations). It is contraindicated in patients with active liver disease.**
4. **Hyperuricemia, and hyperglycemia.**

- **Preexisting gout and diabetes may be exacerbated by niacin.**

5. **Increases risk of myopathy when given with statins.**

- **Concomitant alcohol and hot drinks may magnify flushing and pruritus with niacin and they should be avoided at the time of ingestion.**

Fibric Acid Derivatives

Mechanism of Action:

- They bind to the nuclear transcription factor receptor, peroxisome proliferator-activated receptor-α (PPAR-α), and up-regulate LPL, apo AI and apo AII, and down-regulate apo CIII, an inhibitor of lipolysis.

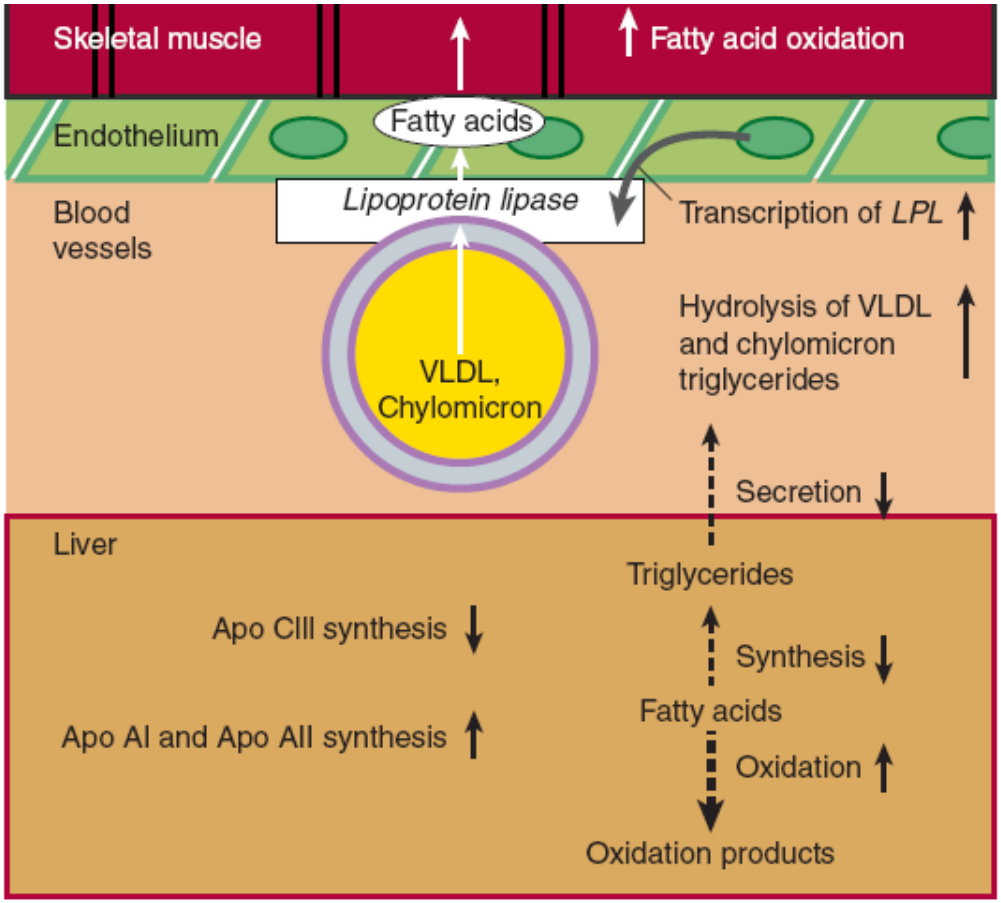


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

Fibric Acid Derivatives

- **A major effect is an increase in oxidation of fatty acids in liver and striated muscle. → →**

1. **Reduction of VLDL.**
2. **Modest decrease in LDL.**
3. **Elevation of HDL, partly due to lower triglyceride in plasma, resulting in reduction in the exchange of triglycerides into HDL in place of cholesteryl esters.**
4. **They may increase LDL in patients with hypertriglyceridemia as triglycerides are reduced.**

Fibric Acid Derivatives

Adverse effects:

1. **Gastrointestinal symptoms.**
2. **Skin rash.**
3. **Gallstones due to an increase in the lithogenicity of bile.**
4. **May potentiate the effects of oral anticoagulants and the (INR) should be monitored with this combination.**
5. **Reduce platelet activity→ potentiate actions of anticoagulants.**

Fibric Acid Derivatives

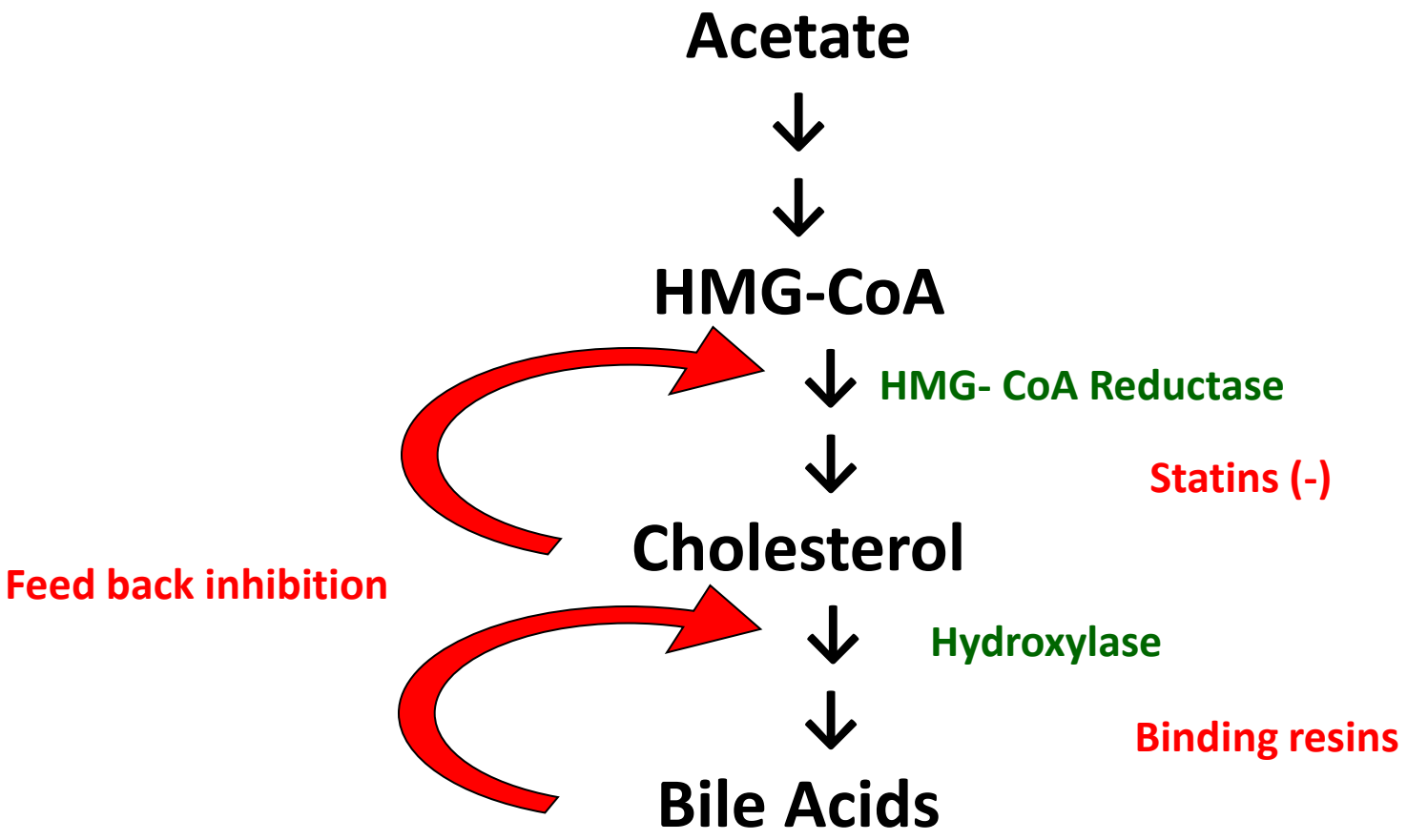
5. **A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine phosphokinase, especially in patients with renal insufficiency.**
6. **Hypokalemia and cardiac arrhythmias.**
7. **Elevation of liver enzymes (aminotransferases and alkaline phosphatase).**
8. **Reduce WBCs and hematocrit.**

- **Avoid in hepatic or renal dysfunction.**

Therapy of Dyslipidemias

- **Primary hypercholesterolemia (familial hypercholesterolemia, familial combined hyperlipidemia, and type IIa hyperlipoproteinemia) may be treated with bile acid resins (colestipol, cholestyramine, & colesevelam), HMG Co-A reductase inhibitors (statins), niacin or ezetimibe.**
- **Of these, statins are the first choice.**

Cholesterol Metabolism



Statins (HMG-CoA reductase inhibitors)

- **They inhibit the rate-limiting step in cholesterol biosynthesis, the 3-hydroxy- 3- glutaryl CoA reductase.**
- **The reduced cholesterol content of hepatocytes increase LDL receptor synthesis → an increase in catabolic rate of LDL and LDL precursors (VLDL remnants) from the blood, thus reducing LDL.**

Statins (HMG-CoA reductase inhibitors)

Other actions:

a) reduce oxidative stress.
b) reduce vascular inflammation.
c) stabilize atherosclerotic lesions.
d) improve the microcirculation.
e) inhibit proliferation of arterial wall smooth muscle and improve endothelial cell function.

Statins (HMG-CoA reductase inhibitors)

- **Available products include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and pitvastatin.**

Statins (HMG-CoA reductase inhibitors)

- **Combination therapy with bile acid sequestrants and statins is rational as LDL receptor numbers are increased, leading to greater degradation of LDL-C; inhibition of intracellular synthesis of cholesterol, and interruption of the enterohepatic recycling of bile acids.**
- **Combination therapy with a statin plus ezetimibe is also rational since ezetimibe inhibits cholesterol absorption through the gut.**

Statins (HMG-CoA reductase inhibitors)

Adverse effects:

1. **Elevation of serum alanine aminotransferase.**
2. **Serious muscle toxicity (myopathy), elevated serum CK, rhabdomyolysis , myoglobinuria , renal shutdown.**
3. **Teratogenicity: contraindicated in pregnancy (and lactation).**

Statins (HMG-CoA reductase inhibitors)

Drug interactions:

- **Myopathy increases in severity if coadministered with nicotinic acid, fibrates, ketoconazole, cyclosporine, erythromycin, verapamil, cimetidine, metronidazole, amiodarone, grapefruit juice and protease inhibitors (anti HIV).**

Bile Acid Binding Resins

- **Include cholestyramine, colestipol, and colesevelam.**
- **They exchange Cl^- for the negatively charged bile acids, thus, preventing the negative feedback on the hydroxylase → enhancing of cholesterol breakdown**
- **Reduction of hepatic cholesterol increases LDL receptors which accelerates cholesterol removal from plasma → Increased uptake of LDL and IDL from plasma.**

Bile Acid Binding Resins

- **Loss of bile acids also reduces fat and cholesterol absorption from GIT.**
- **In patients with combined hyperlipidemia (hypertriglyceridemia and hypercholesterolemia), VLDL may be increased during treatment with the resins.**
- **Thus, they are useful only for isolated increases in LDL.**

Bile Acid Binding Resins

Adverse effects:

1. **Gastrointestinal complaints of gritty taste, constipation, bloating, epigastric fullness, nausea, and flatulence, GIT obstruction.**
- **Patients may discontinue therapy because of these adverse effects.**
2. **Impaired absorption of fat-soluble vitamins A, D, E, and K.**
3. **Hypernatremia and Hyperchloremic metabolic acidosis.**

Bile Acid Binding Resins

Drug interaction:

- **Reduced bioavailability of many drugs such as coumarin anticoagulants, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron, ….**
- **Drug interactions may be avoided by spacing administration by 6 hours between the bile acid resin and other drugs.**

Bile Acid Binding Resins

- **Both the statins and the resins are NOT effective in patients lacking LDL receptors. (familial homozygous hypercholesterolemia).**
- **Severe forms of hypercholesterolemia (familial hypercholesterolemia, familial defective apolipoprotein B-100, severe polygenic hypercholesterolemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia (type III) may require more intensive combination therapy.**

Inhibitors of Intestinal Sterol Absorption

Ezetimibe:

- **It inhibits intestinal cholesterol and phytosterol absorption → reduces LDL.**
- **It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in bile.**
- **It could be used in combination therapy in Type IIb, synergistic with statins. [unlike BARs]**
- **Plasma concentration is increased when coadministered with fibrates and reduced when given with the resins.**
- **May produce reversible hepatic impairment.**
- **Myositis is rare.**

Therapy of Dyslipidemias

- **Combined hyperlipoproteinemia (type IIb) may be treated with statins, niacin, or gemfibrozil combinations to lower LDL cholesterol without elevating VLDL and triglycerides.**
- **Bile acid resins monotherapy may elevate VLDL and triglycerides, and should be avoided.**
- **Fibric acid (gemfibrozil, fenofibrate) monotherapy is effective in reducing VLDL, but may increase LDL.**

Therapy of Dyslipidemias

Low HDL Cholesterol (< 40 mg/dL ???):

- **It may be a consequence of insulin resistance, physical inactivity, type 2 diabetes, cigarette smoking, very high carbohydrate intake, and certain drugs (non-ISA beta blockers, anabolic steroids, probucol, isotretinoin, progestins).**
- **Weight reduction, increased physical activity, and smoking cessation should be emphasized.**
- **Niacin or fibric acid derivatives are the drugs of choice.**

Therapy of Dyslipidemias

Hypertriglyceridemia:

- **It is important to remember that lipoprotein pattern types I, III, IV, and V are associated with hypertriglyceridemia.**
- **High serum triglycerides should be treated by achieving desirable body weight, consumption of a low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol.**

Therapy of Dyslipidemias

Diabetic Dyslipidemia:

- **Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and minimal elevation of LDL.**
- **Most patients will require therapeutic life-style modification and drug therapy.**
- **When LDL-C is high, intensify glycemic control and add fibric acid derivatives or niacin, and intensify LDL-C-lowering therapy using statins.**

Therapy of Dyslipidemias, Special Considerations

The Elderly:

- **Changes in body composition, renal function, and other physiologic changes of aging may make older patients more susceptible to adverse effects of lipid-lowering drug therapy.**
- **They are more likely to have constipation (bile acid resins), skin and eye changes (niacin), gout (niacin), gallstones (fibric acid derivatives), and bone/joint disorders (fibric acid derivatives, statins).**
- **Therapy should be started with lower doses and titrated up slowly to minimize adverse effects.**

Therapy of Dyslipidemias, Special Considerations

Women:

- **HDL may be a more important predictor of disease in women.**
- **Cholesterol and triglyceride levels rise progressively throughout pregnancy.**
- **Drug therapy is NOT instituted and it should NOT be continued during pregnancy.**
- **Dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet.**
- **If their is a very high risk, a bile acid resin may considered.**
- **Statins are category X and are contraindicated.**
- **Ezetimibe might be an alternative (Category C drug).**

Therapy of Dyslipidemias, Special Considerations

Children:

- **Drug therapy in children is NOT recommended until the age of 8 years or older.**
- **Younger children are generally managed with therapeutic life-style changes until after the age of 2 years.**
- **Statins may be safe and are effective in children.**
- **Severe forms of hypercholesterolemia (familial hypercholesterolemia) may require more aggressive treatment.**

Mipomersen

- It is an antisense oligonucleotide that specifically binds to the apolipoprotein B-100 mRNA, blocking translation of the gene product.
- The reduction in production of apo B-100 results in reduced hepatic production of the atherogenic lipoproteins VLDL, IDL, LDL, and lipoprotein(a).
- It is indicated in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other lipid-lowering medications.
- It is hepatotoxic (hepatic steatosis), and its use is restricted.

Lomitapide

- **Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), which is responsible for absorbing dietary lipids and transferring triglycerides onto apolipoprotein B (apo-B) in the assembly of VLDL.**
- **Thus, transfer of lipid to apo-B is blocked, leading to apo-B destruction and inhibition of lipoprotein secretion.**
- **It also inhibits CYP3A4 and P-Glycoprotein.**
- **It is used for familial hypercholesterolemia.**

Adverse effects:

- **Elevation of serum aminotransferase.**
- **Increased hepatic fat (steatohepatitis) and hepatic fibrosis.**

Alirocumab

- **PCSK9 binds to LDLRs on hepatocytes → LDLR degradation, thus, elevating LDL-C blood levels.**
- **Alirocumab inhibits the binding of PCSK9 to LDLR → reduces LDL-C levels.**
- **Given by SC injection.**
- **Used as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia.**
- **Evolocumab is similar.**

Classification of Total-, LDL-, HDL-Cholesterol and Triglycerides in Adults

Total Cholesterol	
<200 mg/dL	Desirable
200-239 mg/dL	Borderline high
≥240 mg/dL	High
LDL Cholesterol	
<100 mg/dL	Optimal
100-129 mg/dL	Near or above optimal
130-159 mg/dL	Borderline high
160-189 mg/dL	High
≥190 mg/dL	Very high
HDL Cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High
Triglycerides	
<150 mg/dL	Normal
150-199 mg/dL	Borderline high
200-499 mg/dL	High
≥500 mg/dL	Very high

Cut Points for Total Cholesterol and LDL Concentrations in Children and Adolescents:

Category	Total Cholesterol, mg/dL	LDL Cholesterol, mg/dL
Acceptable	<170	<110
Borderline	170-199	110-129
Elevated	>200	>130

Lipoprotein Disorders

Disorder	Lipoproteins		Clinical signs
	Elevated	Phenotype	
Isolated Hypercholesterolemia			
Familial hypercholesterolemia (Hetero- and homo-zygous)	LDL	IIa	Usually develop xanthomas in adulthood and vascular disease at 30-50 years
Familial defective apo B100	LDL	IIa	
Polygenic hypercholesterolemia	LDL	IIa	Usually asymptomatic until vascular disease develops; no xanthomas

Isolated Hypertriglyceridemia			
Familial hypertriglyceridemia	VLDL	IV	Asymptomatic; maybe associated with increased risk of vascular disease
Familial LPL* deficiency	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitits, abdominal pain, hepatosplenomegaly
Familial apo CII deficiency	Chylomicrons, VLDL	I, V	May be asymptomatic; may be associated with pancreatitits, abdominal pain, hepatosplenomegaly

*LPL, lipoprotein lipase.

Hypertriglyceridemia and Hypercholesterolemia			
Combined hyperlipidemia	VLDL, LDL	IIb	Usually asymptomatic until vascular disease develops; familial form may also present as isolated high TG or an isolated high LDL cholesterol
Dysbetalipoproteinemia	VLDL, IDL; LDL normal	III	Usually asymptomatic until vascular disease develops; may have palmar or tuboeruptive xanthomas

Effects of Drug Therapy on Lipids and Lipoproteins

Drugs	Mechanism of action	Effects on lipids	Effects on Lipoproteins	Comments
Cholestyramine, colestipol and colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL	Problem with compliance; binds many co-administered acidic drugs
Niacin	↓ LDL and VLDL ↓ synthesis	↓ Triglyceride And ↓ cholesterol	↓ VLDL, ↓ LDL, ↑ HDL	Problems with patient acceptance; good in combination with bile acid resins; extended release niacin causes less flushing and is less hepatotoxic than sustained release

Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride and cholesterol	↓ VLDL, ↓LDL, ↑ HDL	Clofibrate causes cholesterol gall stones; modest LDL-lowering; raises HDL; gemfibrozil inhibits glucuronidation of simvastatin, lovastatin and atorvastatin
Lovastatin, Pravastatin, Simvastatin, Fluvastatin, Atorvastatin Rosuvastatin	↑ LDL catabolism; inhibit LDL synthesis	↓ Cholesterol	↓ LDL	Highly effective in heterozygous familial hypercholesterolemia and in combination with other agents

Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL	Few adverse effects; effects additive to other drugs
Mipomerson	Inhibitor of Apolipoprotein B-100	↓ Cholesterol	↓ LDL, non-HDL	Increase in transaminases, risk of hepatosteatosis and hepatotoxicity; must be given by SQ injection. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)

Lomitapide	Microsomal triglyceride transfer protein inhibitor	↓ Cholesterol	↓ LDL, non-HDL	Hepatotoxicity must be monitored. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)
Alirocumab, Evolocumab	PCSK9 inhibitor	↓ Cholesterol, ↓ Lpa	↓Cholesterol and LDL	Given by SQ injection, injection site pain, low risk of hepatoxicity

Therapy of Acute Coronary Syndromes

Therapy of Acute Coronary Syndromes

- The cause of an acute coronary syndrome (ACS) is the rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, and aggregation, and the activation of the clotting cascade.
- Ultimately, a clot forms composed of fibrin and platelets.
- It includes ST-segment elevation (STE) myocardial infarction (MI) [STE MI] and non–ST-segment elevation (NSTE) ACS.
- Acute coronary syndromes (ACS) include unstable angina (UA) and myocardial infarction (MI).

Therapy of Acute Coronary Syndromes

- **Early reperfusion therapy with primary percutaneous coronary intervention (PCI) of the infarct artery is recommended for patients presenting with ST-segment elevation myocardial infarction (STEMI) within 12 hours of symptom onset.**

Therapy of Acute Coronary Syndromes

- **In addition, all patients with STEMI and without contraindications should receive within the first day of hospitalization and preferably in the emergency department (ED):**

1. **Intranasal oxygen (if oxygen saturation is low).**
2. **Sublingual (SL) nitroglycerin (NTG).**
3. **Aspirin.**
4. **A $P2Y_{12}$ (ADP receptor) inhibitor (clopidogrel, prasugrel, or ticagrelor).**

Therapy of Acute Coronary Syndromes

5. **Anticoagulation with bivalirudin (direct thrombin inhibitor, leech), unfractionated heparin (UFH), enoxaparin, or fondaparinux.**
6. **A glycoprotein IIb/IIIa inhibitor (GPI) may be considered if UFH is selected as the anticoagulant for patients undergoing primary PCI.**
7. **A high-intensity statin should be administered prior to PCI.**

Therapy of Acute Coronary Syndromes

8. **Intravenous (IV) β-blockers and IV NTG should be administered cautiously in selected patients.**
9. **Oral β-blockers should be initiated within the first day in patients without contraindications.**
10. **An ACE inhibitor is recommended within the first 24 hours in patients with STEMI who have either an anterior wall MI or an LVEF ≤ 0.40 and no contraindications.**

Therapy of Acute Coronary Syndromes

11. **Morphine may be given to patients with refractory angina as an analgesic and a veno-dilator that lowers preload.**

- **It slows the absorption of oral antiplatelet agents due to decreased gastric motility.**

Therapy of Acute Coronary Syndromes

- **In the absence of contraindications, all patients with NSTE-ACS should be treated in the ED with:**

1. **Intranasal oxygen (if oxygen saturation is low).**
2. **SL NTG.**
3. **Aspirin.**
4. **An anticoagulant (UFH, enoxaparin, fondaparinux, or bivalirudin).**
5. **High-risk patients should proceed to early angiography, and may receive a GPI.**

Therapy of Acute Coronary Syndromes

6. **A $P2Y_{12}$ inhibitor should be administered to all patients.**
7. **A high-intensity statin should be administered prior to PCI.**
8. **IV β-blockers and IV NTG should be administered cautiously in selected patients.**
9. **Oral β-blockers should be initiated within the first day in patients without contraindications.**

Therapy of Acute Coronary Syndromes

Secondary prevention guidelines suggest that following MI from either STEMI or NSTE-ACS:

- **All patients, in the absence of contraindications, should receive indefinite treatment with aspirin, a β-blocker, a moderate-to-high intensity statin, and an angiotensin-converting enzyme (ACE) inhibitor for secondary prevention of death, stroke, or recurrent infarction.**

Therapy of Acute Coronary Syndromes

- **A $P2Y_{12}$ inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients treated medically (without PCI or thrombolytics).**
- **Clopidogrel should be continued for at least 14 days, and ideally 1 year, in patients with STEMI treated with fibrinolytics.**
- **An angiotensin II receptor blocker and an aldosterone antagonist may be given to selected patients.**

Therapy of Acute Coronary Syndromes

- **For all patients with ACS, treatment and control of modifiable risk factors such as hypertension (HTN), dyslipidemia, obesity, smoking, and diabetes mellitus (DM) are essential.**

Therapy of Acute Coronary Syndromes

Ventricular Remodeling Following an Acute MI:

- **Ventricular remodeling is a process that occurs in several cardiovascular conditions including HF and MI.**
- **It is characterized by: left ventricular (LV) dilation and reduced pumping function of the LV, leading to HF.**
- **Because HF represents one of the principal causes of morbidity and mortality following an MI, preventing ventricular remodeling is an important therapeutic goal.**
- **ACE-inhibitors, ARBs, β-blockers, and aldosterone antagonists can slow down or reverse ventricular remodeling through inhibition of the renin–angiotensin–aldosterone system and/or through improvement in hemodynamics (decreasing preload, afterload or neurohormonal activation).**

Therapy of Acute Coronary Syndromes

Desired Outcomes:

Short-term desired outcomes in a patient with ACS:

1. **Early reperfusion to the infarct artery to prevent infarct expansion (in MI), or prevent complete occlusion and MI (in UA).**
2. **Prevention of death and other MI complications.**
3. **Prevention of coronary artery re-occlusion.**
4. **Relief of ischemic chest discomfort.**
5. **Resolution of ST-segment and T-wave changes on the ECG.**

Therapy of Acute Coronary Syndromes

Long-term desired outcomes:

1. **Control of CV risk factors.**
2. **Prevention of re-infarction, stroke, and HF.**
3. **Improving the quality-of-life.**

Therapy of Acute Coronary Syndromes

- **General management measures for all STEMI, and high- and intermediate-risk NSTE-ACS patients also include:**

1. **Continuous multi-lead ECG monitoring for arrhythmias and ischemia.**
2. **Frequent measurement of vital signs.**
3. **Bed rest for 12 hours in hemodynamically stable patients.**
4. **Avoidance of the Valsalva maneuver (prescribe stool softeners routinely).**
5. **Pain relief.**

Therapy of Acute Coronary Syndromes

Antiplatelet Therapy in PCI and STEMI and NSTE-ACS:

- **All patients undergoing PCI with ACS should receive an initial dose of 162- or 325-mg of aspirin followed by a daily aspirin dose of 81 mg/day indefinitely.**
- **A $P2Y_{12}$ inhibitor antiplatelet (clopidogrel, prasugrel, ticagrelor, or IV cangrelor) should be administered as early as possible concomitantly with aspirin and then an oral $P2Y_{12}$ agent should ideally be continued for at least 12 months following PCI.**
- **Earlier discontinuation of the $P2Y_{12}$ inhibitor can be reasonable in patients at a high bleeding risk or with "overt bleeding".**

Therapy of Acute Coronary Syndromes

Fibrinolytic Therapy:

Administration of a fibrinolytic agent is indicated in patients:

1. **With STEMI who present within 12 hours of the onset of chest discomfort to a hospital NOT capable of primary PCI.**
2. **Who have at least a 1 mm STE in two or more contiguous ECG leads.**
3. **Who have no absolute contraindications to fibrinolytic therapy.**
4. **Who are NOT able to be transferred to undergo primary PCI within 120 minutes of medical contact.**

Therapy of Acute Coronary Syndromes

- **A door-to-needle time of less than 30 minutes from the time of hospital presentation until start of fibrinolytic therapy is recommended.**
- **A fibrin-specific agent (alteplase, reteplase, or tenecteplase) is preferred over a non–fibrin-specific agent (streptokinase).**
- **Fibrin-specific fibrinolytics open a greater percentage of arteries.**

Therapy of Acute Coronary Syndromes

- **The mortality benefit of fibrinolysis is highest with early administration and diminishes after 12 hours.**
- **The use of fibrinolytics between 12-24 hours after symptom onset should be limited to patients with ongoing ischemia.**

Therapy of Acute Coronary Syndromes

Adverse effects:

- **Intracranial hemorrhage (ICH) and major bleeding are the most serious.**
- **The risk of ICH is higher with fibrin-specific agents than with streptokinase.**
- **The risk of systemic bleeding other than ICH is higher with streptokinase than with other more fibrin-specific agents.**

Therapy of Acute Coronary Syndromes

- **Patients with contraindications for fibrinolysis should NOT receive fibrinolytic therapy, and should be transferred to a hospital capable of performing PCI.**
- **In patients who have a contraindication to fibrinolytics and PCI, or who do NOT have access to a facility that can perform PCI, treatment with an anticoagulant for up to 8 days is recommended.**

Absolute Contraindications to Fibrinolytic Therapy

1. Active internal bleeding.
2. Previous intracranial hemorrhage at any time; ischemic stroke within 3 months (except acute ischemic stroke within ~4 hours)
3. Known intracranial neoplasm.
4. Known structural cerebral vascular lesion (A-V malformation).
5. Suspected aortic dissection.
6. Significant closed head or facial trauma within 3 months.
7. Intracranial or intraspinal surgery within 2 months.
8. Severe uncontrolled hypertension (unresponsive to emergency therapy).
9. For streptokinase, prior treatment within the previous 6 months.

Therapy of Acute Coronary Syndromes

Anticoagulants:

- **For patients undergoing primary PCI: either UFH or bivalirudin should be used. Anticoagulation is discontinued immediately following the PCI procedures.**
- **Bivalirudin would be a preferred anticoagulant for patients with a history of heparin-induced thrombocytopenia undergoing PCI.**

Therapy of Acute Coronary Syndromes

- **For fibrinolysis: UFH, enoxaparin, or fondaparinux may be used.**
- **UFH is continued for 48 hours, and enoxaparin or fondaparinux are continued for the duration of hospitalization, up to 8 days.**
- **For patients who do not undergo reperfusion therapy: UFH for 48 hours, and enoxaparin or fondaparinux for the duration of hospitalization.**

Therapy of Acute Coronary Syndromes

β-Blockers:

- **β_1-Blockade reduces heart rate (HR), myocardial contractility, and blood pressure (BP), thus, decreasing myocardial oxygen demand.**
- **The reduction in HR prolongs diastole, thus improving ventricular filling and coronary artery perfusion.**
- **β-blockers reduce the risk for recurrent ischemia, reduce infarct size, reduce risk of re-infarction, and reduce the occurrence of ventricular arrhythmias in the hours and days following MI.**

Therapy of Acute Coronary Syndromes

- **Initiating IV followed by oral β-blockers early in the course of STEMI was associated with a lower risk of re-infarction or ventricular fibrillation, but an early risk of cardiogenic shock, especially in patients presenting with pulmonary congestion or systolic BP less than 120 mm Hg.**
- **Oral beta blockers are preferred over IV in the management of ACS.**

Therapy of Acute Coronary Syndromes

- Initiation of β-blockers, particularly when administered IV, should be limited to patients who present with HTN and/or have ongoing signs of myocardial ischemia and do NOT demonstrate any signs or symptoms of acute HF.
- Careful monitoring for signs of hypotension and HF should be performed following β-blocker initiation and prior to any dose titration.

Therapy of Acute Coronary Syndromes

- **The most serious adverse effects early in ACS are hypotension, acute HF, bradycardia, and heart block.**
- **β-blockers should be initiated before hospital discharge in most patients following treatment of acute HF.**
- **They should be continued for at least 3 years in patients with normal LV function, and indefinitely in patients with LV systolic dysfunction and LVEF ≤ 0.4.**

Therapy of Acute Coronary Syndromes

Statins:

- **A high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) should be administered to all patients without contraindications prior to PCI (regardless of prior lipid-lowering therapy) to reduce the frequency of peri-procedural MI following PCI.**
- **Required:**
- https://www.uptodate.com/contents/mechanisms-of-benefit-of-lipid-lowering-drugs-in-patients-with-coronary-heart-disease

Therapy of Acute Coronary Syndromes

Nitrates:

- **One SL NTG tablet should be administered every 5 minutes for up to 3 doses in order to relieve myocardial ischemia.**
- **If patients have been previously prescribed SL NTG, and ischemic chest discomfort persists for more than 5 minutes after the first dose, IV NTG can be initiated in all patients with an ACS who have persistent ischemia, HF, or uncontrolled high BP in the absence of contraindications.**

Therapy of Acute Coronary Syndromes

- **IV NTG should be continued for approximately 24 hours after ischemia is relieved.**
- **Nitrates promote the release of nitric oxide from the endothelium which results in venodilation, and vasodilation in large coronary arteries.**
- **Venodilation lowers preload and myocardial oxygen demand.**
- **Arterial vasodilation may lower BP, thus reducing myocardial oxygen demand.**

Therapy of Acute Coronary Syndromes

- Arterial vasodilation also relieves coronary artery vasospasm, dilating coronary arteries to improve myocardial blood flow and oxygenation.
- Nitrates have NO mortality benefit (IV or oral).
- The most significant adverse effects of nitrates are: tachycardia, flushing, headache, and hypotension.
- Nitrate administration is contraindicated in patients who have received oral phosphodiesterase-5 inhibitors (sildenafil and vardenafil) within the last 24 hours, and tadalafil within the last 48 hours.

Therapy of Acute Coronary Syndromes

Calcium Channel Blockers:

- **In the setting of STEMI, they are used for relief of ischemic symptoms only in patients who have certain contraindications to β-blockers.**
- **Agent that lowers HR (diltiazem or verapamil) are preferred unless the patient has LV systolic dysfunction, bradycardia, or heart block, when either amlodipine or felodipine may be used.**
- **Nifedipine should be avoided (→ reflex sympathetic stimulation, tachycardia, and worsened myocardial ischemia).**

Therapy of Acute Coronary Syndromes

Early Pharmacotherapy for NSTE-ACS:

- **In general, early pharmacotherapy of NSTE-ACS is similar to that of STEMI.**

Fibrinolytic Therapy:

- **Fibrinolytic therapy is NOT indicated in any patient with NSTE-ACS because it is associated with increased mortality.**

Therapy of Acute Coronary Syndromes

Anticoagulants:

- **All patients should receive UFH, enoxaparin, fondaparinux, or bivalirudin.**

Antiplatelet drugs:

- **Clopidogrel (300 or 600-mg loading dose followed by 75 mg daily) can be used in addition to low-dose aspirin.**
- **Low-dose aspirin is continued indefinitely.**

Therapy of Acute Coronary Syndromes

Glycoprotein IIb/IIIa Receptor Inhibitors:

- **For patients managed with conservative strategy but who experience recurrent ischemia (chest discomfort and ECG changes), HF, or arrhythmias after initial medical therapy necessitating a change in strategy to angiography and revascularization, a GPI may be added to aspirin and clopidogrel prior to the angiogram.**

Therapy of Acute Coronary Syndromes

Duration of Anticoagulant Therapy:

a) at least 48 hours for UFH,
b) until the patient is discharged from the hospital (or 8 days, whichever is shorter) for either enoxaparin or fondaparinux,
c) until the end of PCI or angiography procedure (or up to 72 hours following PCI) for bivalirudin.

Therapy of Acute Coronary Syndromes

Nitrates and β-Blockers:

- **Use is similar to that for STEMI.**

Calcium channel blockers:

- **Should NOT be administered to most patients with ACS.**
- **Indications for calcium channel blockers are similar to that of STEMI.**

Therapy of Acute Coronary Syndromes

Secondary Prevention Following MI:

The long-term goals following MI are to:

1. **Control modifiable CHD risk factors.**
2. **Prevent the development of systolic HF.**
3. **Prevent recurrent MI and stroke.**
4. **Prevent death, including sudden cardiac death.**
5. **Prevent stent thrombosis following PCI.**

Therapy of Acute Coronary Syndromes

- **Pharmacotherapy, which has been proven to decrease mortality, HF, re-infarction or stroke, and stent thrombosis, should be initiated prior to hospital discharge for secondary prevention.**
- **All patients, in the absence of contraindications, should receive indefinite treatment with aspirin, an ACE inhibitor, and a "high-intensity" statin for secondary prevention of death, stroke, or recurrent infarction.**

Therapy of Acute Coronary Syndromes

- **A β-blocker should be continued for at least 3 years in patients with normal LV function and indefinitely in patients with LVEF ≤ 0.4 or HF symptoms.**
- **It may be reasonable to continue a β-blocker indefinitely in patients without contraindications and with normal LVEF.**
- **β-blockers should be used in patients with a previous MI.**

Therapy of Acute Coronary Syndromes

- **A $P2Y_{12}$ inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided strategy of treatment.**
- **Clopidogrel should be continued for at least 14 days in patients with STEMI NOT undergoing PCI.**
- **All patients should be prescribed short-acting, SL NTG or NTG spray to relieve any anginal symptoms when necessary, and should be instructed on its use.**

Therapy of Acute Coronary Syndromes

- **ACE Inhibitors should be initiated in all patients following MI to reduce mortality, decrease re-infarction, and prevent the development of HF, because of their ability to prevent cardiac remodeling.**
- **They should be continued indefinitely.**
- **Hypotension should be avoided because coronary artery filling may be compromised.**
- **Adverse effects: hypotension, cough (30% of patients), acute renal failure, hyperkalemia, and angioedema.**
- **If patients cannot tolerate chronic ACE inhibitor therapy secondary to adverse effects, ARBs can be used (candesartan, valsartan, or losartan).**

Therapy of Acute Coronary Syndromes

- **Aldosterone plays an important role in HF and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, LV hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias.**
- **To reduce mortality, aldosterone antagonists (spironolactone or eplerenone), should be considered within the first 7 days following MI in all patients who are already receiving an ACE inhibitor (or ARB) and a β-blocker and have an LVEF ≤ 0.40 and either HF symptoms or DM.**
- **Spironolactone decreases all-cause mortality in patients with stable severe HF.**

Therapy of Acute Coronary Syndromes

- **All patients, regardless of low-density lipoprotein cholesterol level, should ideally be prescribed a high-intensity statin.**
- **Patients aged greater than 75 years may be prescribed a moderate-intensity statin as initial therapy because they are at higher risk of adverse drug effects.**
- **Other agents such as ezetimibe and PCSK9 inhibitors (alirocumab and evolocumab) can be used in patients already receiving statins for secondary prevention (preference given to ezetimibe).**

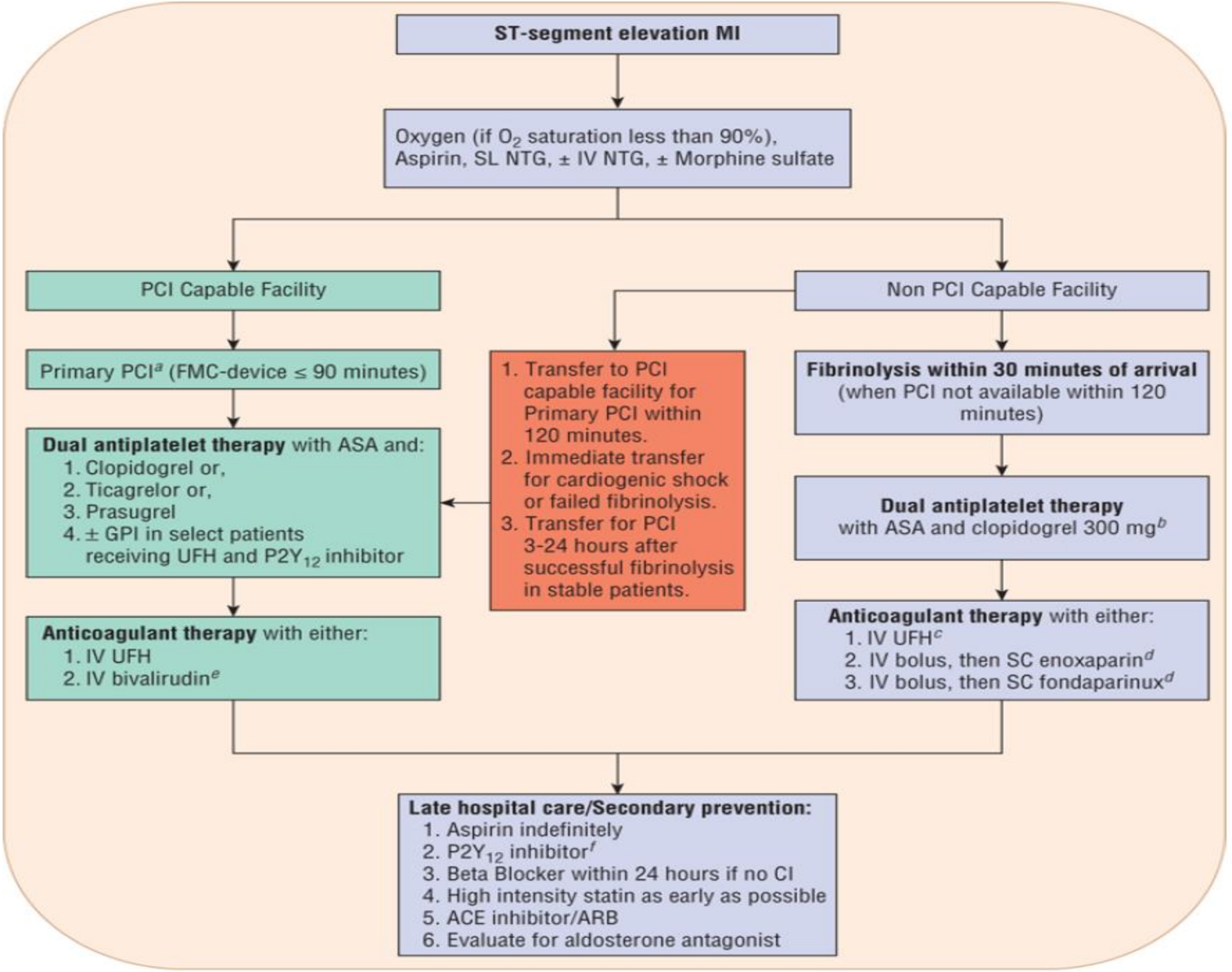
Therapy of Acute Coronary Syndromes

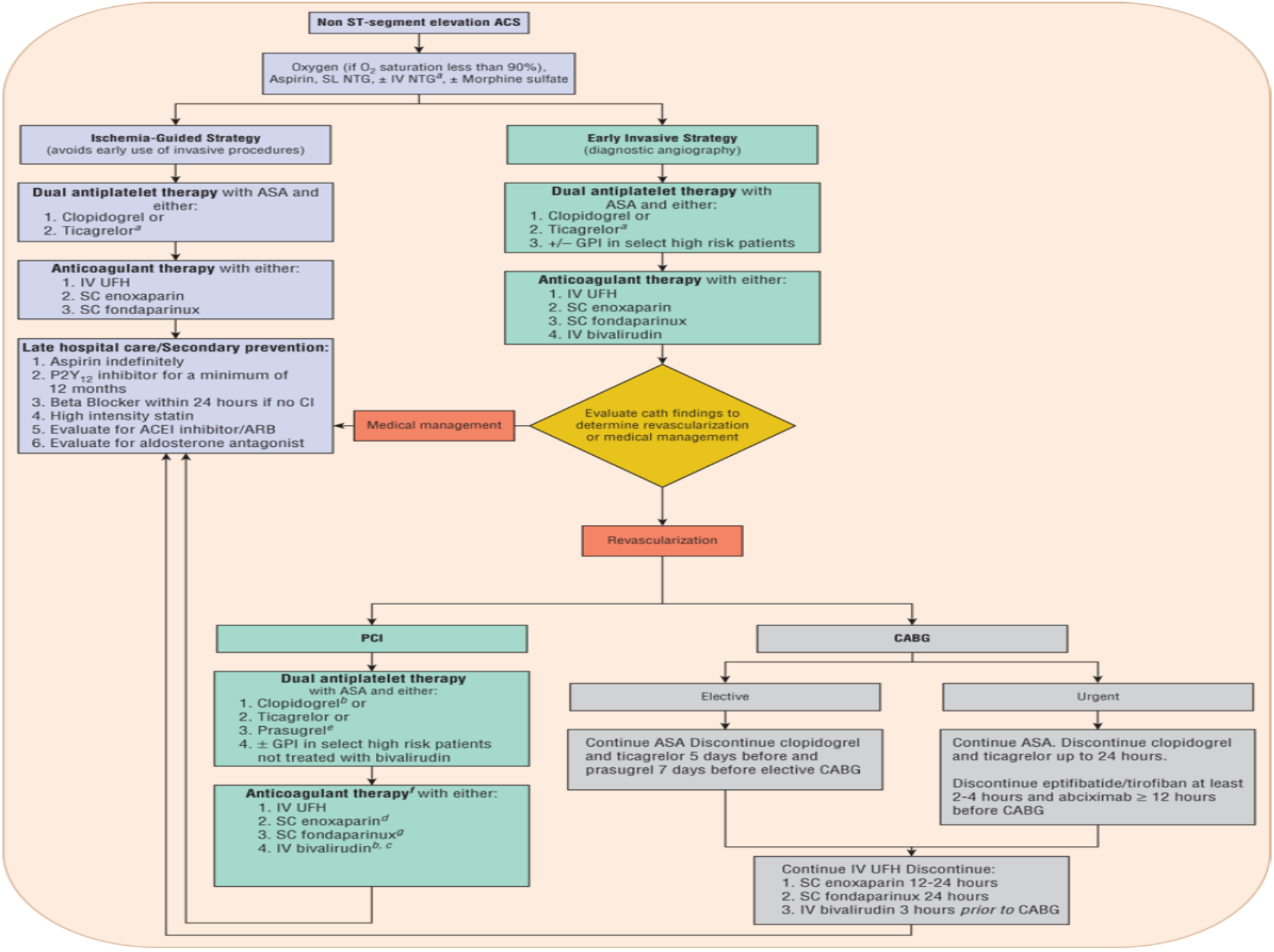
Other Modifiable Risk Factors:

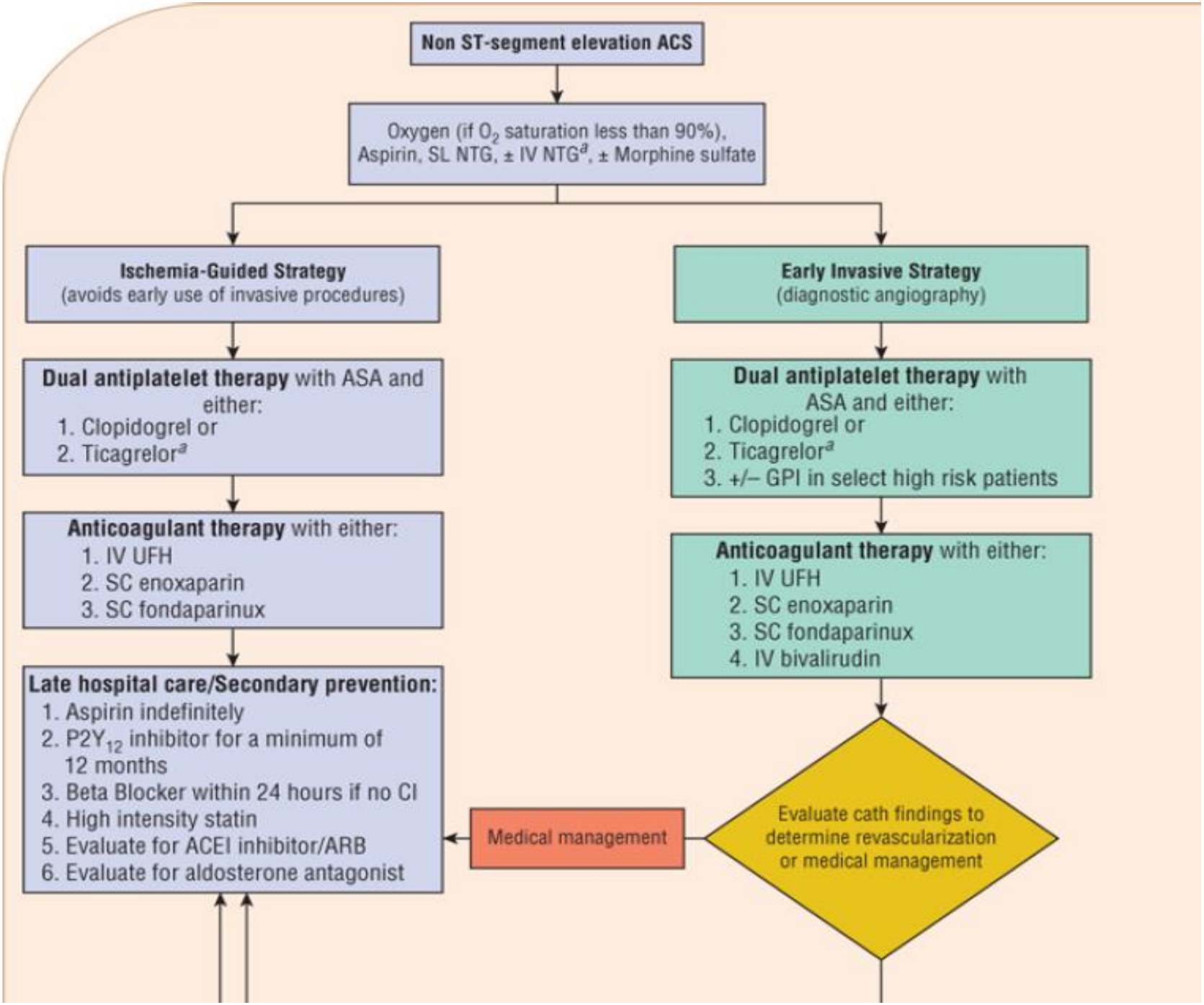
- **Smoking cessation, managing HTN, weight loss, exercise, and tight glucose control for patients with DM, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.**
- **Behavioral therapy aided with nicotine replacement alone or combined with bupropion (Antidepressant that decreases cravings for and withdrawal symptoms of nicotine) or varenicline (a partial agonist of the nicotinic acetylcholine receptor, used to treat smoking addiction), for smoking cessation should be considered in appropriate patients.**

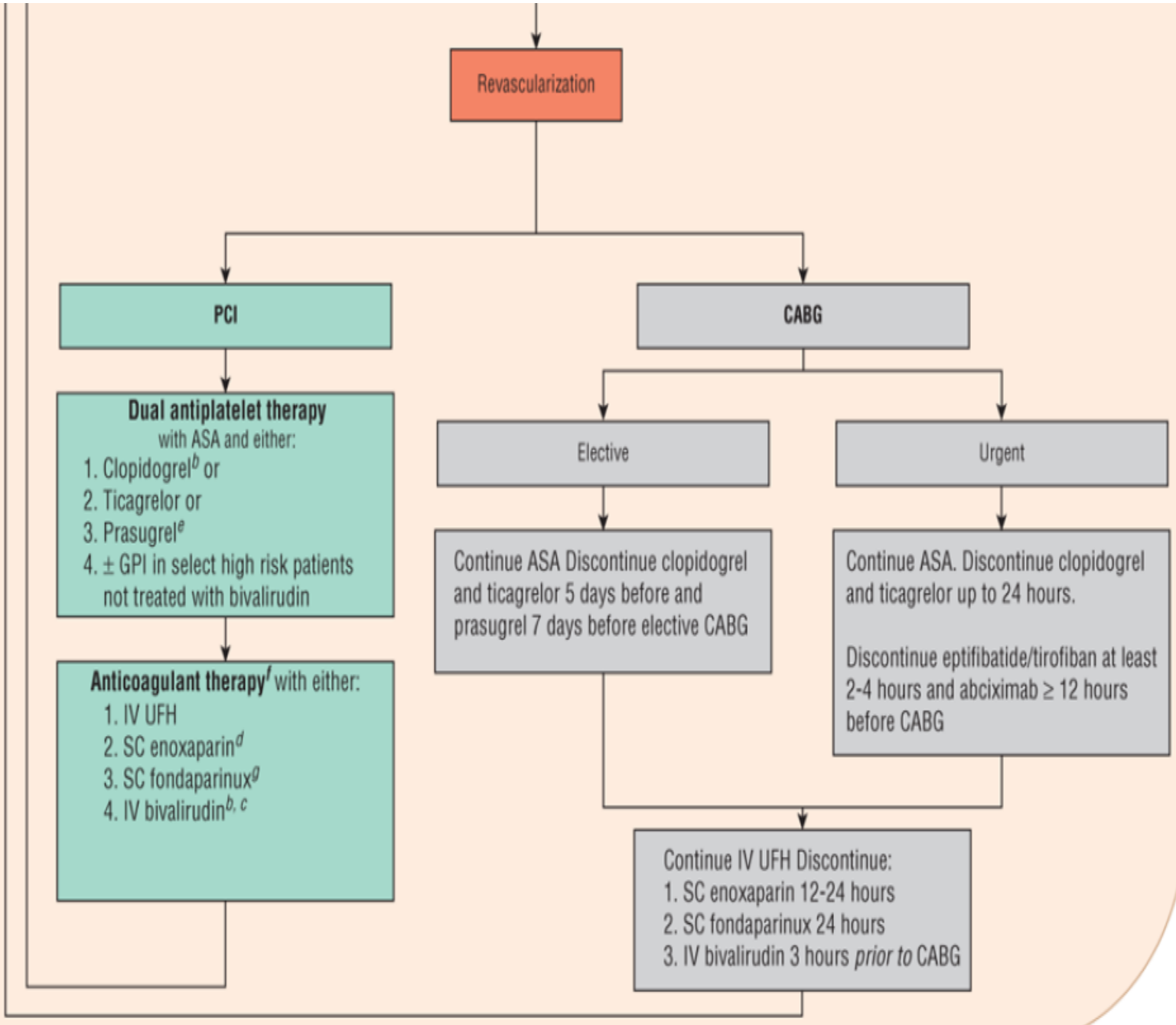
Therapy of Acute Coronary Syndromes

- **HTN should be strictly controlled according to published guidelines.**
- **Patients who are overweight should be educated on the importance of regular exercise, healthy eating habits, and reaching and maintaining an ideal weight.**
- **Moderate intensity aerobic exercise for at least 30 minutes, 7 days/wk (minimum 5 days/wk) is recommended.**
- **The goal body mass index is less than 25 kg/m^2.**
- **Blood glucose control is important, because DM is associated with 4-fold increase in mortality in these patients.**


ST-segment elevation MI
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG, ± Morphine sulfate
PCI Capable Facility
Non PCI Capable Facility
Primary PCI[a] (FMC-device ≤ 90 minutes)
1. Transfer to PCI capable facility for Primary PCI within 120 minutes.
2. Immediate transfer for cardiogenic shock or failed fibrinolysis.
3. Transfer for PCI 3-24 hours after successful fibrinolysis in stable patients.
Fibrinolysis within 30 minutes of arrival (when PCI not available within 120 minutes)
Dual antiplatelet therapy with ASA and:
1. Clopidogrel or,
2. Ticagrelor or,
3. Prasugrel
4. ± GPI in select patients receiving UFH and $P2Y_{12}$ inhibitor
Dual antiplatelet therapy with ASA and clopidogrel 300 mg[b]
Anticoagulant therapy with either:
1. IV UFH
2. IV bivalirudin[e]
Anticoagulant therapy with either:
1. IV UFH[c]
2. IV bolus, then SC enoxaparin[d]
3. IV bolus, then SC fondaparinux[d]
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor[f]
3. Beta Blocker within 24 hours if no CI
4. High intensity statin as early as possible
5. ACE inhibitor/ARB
6. Evaluate for aldosterone antagonist


Non ST-segment elevation ACS
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG[a], ± Morphine sulfate
Ischemia-Guided Strategy (avoids early use of invasive procedures)
Early Invasive Strategy (diagnostic angiography)
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
3. +/– GPI in select high risk patients
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
4. IV bivalirudin
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor for a minimum of 12 months
3. Beta Blocker within 24 hours if no CI
4. High intensity statin
5. Evaluate for ACEI inhibitor/ARB
6. Evaluate for aldosterone antagonist
Medical management
Evaluate cath findings to determine revascularization or medical management
Revascularization
PCI
CABG
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel[b] or
2. Ticagrelor or
3. Prasugrel[e]
4. ± GPI in select high risk patients not treated with bivalirudin
Anticoagulant therapy[f] with either:
1. IV UFH
2. SC enoxaparin[d]
3. SC fondaparinux[g]
4. IV bivalirudin[b, c]
Elective
Urgent
Continue ASA Discontinue clopidogrel and ticagrelor 5 days before and prasugrel 7 days before elective CABG
Continue ASA. Discontinue clopidogrel and ticagrelor up to 24 hours.
Discontinue eptifibatide/tirofiban at least 2-4 hours and abciximab ≥ 12 hours before CABG
Continue IV UFH Discontinue:
1. SC enoxaparin 12-24 hours
2. SC fondaparinux 24 hours
3. IV bivalirudin 3 hours *prior to* CABG


Non ST-segment elevation ACS
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG[a], ± Morphine sulfate
Ischemia-Guided Strategy
(avoids early use of invasive procedures)
Early Invasive Strategy
(diagnostic angiography)
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
3. +/– GPI in select high risk patients
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
4. IV bivalirudin
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor for a minimum of 12 months
3. Beta Blocker within 24 hours if no CI
4. High intensity statin
5. Evaluate for ACEI inhibitor/ARB
6. Evaluate for aldosterone antagonist
Medical management
Evaluate cath findings to determine revascularization or medical management


Revascularization
PCI
CABG
Dual antiplatelet therapy
with ASA and either:
1. Clopidogrel[b] or
2. Ticagrelor or
3. Prasugrel[e]
4. ± GPI in select high risk patients not treated with bivalirudin
Anticoagulant therapy[f] with either:
1. IV UFH
2. SC enoxaparin[d]
3. SC fondaparinux[g]
4. IV bivalirudin[b, c]
Elective
Urgent
Continue ASA Discontinue clopidogrel and ticagrelor 5 days before and prasugrel 7 days before elective CABG
Continue ASA. Discontinue clopidogrel and ticagrelor up to 24 hours.
Discontinue eptifibatide/tirofiban at least 2-4 hours and abciximab ≥ 12 hours before CABG
Continue IV UFH Discontinue:
1. SC enoxaparin 12-24 hours
2. SC fondaparinux 24 hours
3. IV bivalirudin 3 hours *prior to* CABG

Therapy of Chronic Heart Failure

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Chronic Heart Failure

- **Heart failure (HF) is a progressive clinical syndrome associated with impairment of the ability of the ventricle to fill with or eject blood.**
- **HF may be caused by an abnormality in systolic function, diastolic function, or both.**
- **The leading causes of HF are coronary artery disease and hypertension.**
- **The primary manifestations of the syndrome are dyspnea, fatigue, and fluid retention.**

Chronic Heart Failure

- **In heart failure with reduced ejection fraction (HFrEF) there is a decrease in cardiac output, resulting in activation of compensatory responses that attempt to maintain adequate cardiac output.**
- **These responses include: activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), resulting in vasoconstriction and sodium and water retention, ventricular hypertrophy and remodeling.**

Chronic Heart Failure

- **The compensatory mechanisms are responsible for the symptoms of HFrEF and contribute to disease progression.**
- **Norepinephrine (NE), angiotensin II, aldosterone, vasopressin, and numerous proinflammatory cytokines play an important role in ventricular remodeling and the subsequent progression of HF.**

Chronic Heart Failure

- **Pharmacotherapy targeted at antagonizing the neurohormonal activation has slowed the progression of HFrEF and improved survival.**
- **Heart failure with preserved ejection fraction (HFpEF) is primarily due to diastolic dysfunction of the heart (or disturbances in relaxation).**
- **It may be treated differently from HFrEF.**

Causes of Heart failure

Causes of systolic dysfunction (decreased contractility):

1) **Reduction in muscle mass (myocardial infarction).**
2) **Dilated cardiomyopathies.**
3) **Ventricular hypertrophy.**
4) **Pressure overload (systemic or pulmonary hypertension, aortic or pulmonary valve stenosis).**
5) **Volume overload (valvular regurgitation, shunts, high-output states).**

Causes of Heart failure

Causes of diastolic dysfunction (restriction in ventricular filling):

1) **Increased ventricular stiffness.**
2) **Ventricular hypertrophy (hypertrophic cardiomyopathy, others).**
3) **Infiltrative myocardial diseases (amyloidosis, sarcoidosis, endomyocardial fibrosis).**
4) **Myocardial ischemia and infarction.**
5) **Mitral or tricuspid valve stenosis.**
6) **Pericardial disease (pericarditis, pericardial tamponade).**

Factors Precipitating/Exacerbating Heart Failure

- **Cardiac events: myocardial ischemia and infarction, atrial fibrillation, uncontrolled HTN.**
- **Noncardiac events: pulmonary infections, pulmonary embolus, diabetes, worsening renal function, hypothyroidism, and hyperthyroidism.**
- **Nonadherence with prescribed HF medications or with dietary recommendations, such as sodium intake and fluid restriction.**

Factors Precipitating/Exacerbating Heart Failure

- **Drugs can precipitate or exacerbate HF by one or more of the following mechanisms:**

a) **Negative inotropic effects.**

b) **Direct cardiotoxicity.**

c) **Increased sodium and/or water retention:**

- **Nonsteroidal antiinflammatory drugs (NSAIDs) → volume retention, decreased renal function, and increased BP.**

Factors Precipitating/Exacerbating Heart Failure

Negative Inotropic Effect:

- **Antiarrhythmics (disopyramide, flecainide, propafenone).**
- **Beta-blockers (propranolol, metoprolol, carvedilol).**
- **Calcium channel blockers (verapamil, diltiazem).**

Cardiotoxicity:

Doxorubicin, epirubicin, daunomycin, ethanol, cyclophosphamide, trastuzumab, bevacizumab, mitoxantrone, ifosfamide, mitomycin, lapatinib, sunitinib, imatinib, amphetamines, cocaine.

Factors Precipitating/Exacerbating Heart Failure

Sodium and Water Retention:

NSAIDs, COX_2-inhibitors, rosiglitazone and pioglitazone, glucocorticoids, androgens and estrogens, high dose salicylates, high sodium-containing drugs (carbenicillin disodium, ticarcillin disodium)

Uncertain Mechanism:

Adalimumab, dronedarone, etanercept, infliximab.

Factors Precipitating/Exacerbating Heart Failure

- **Many of these precipitating factors are preventable.**
- **Medication history and discontinuation of medications known to exacerbate HF are part of therapy.**

Ventricular Hypertrophy and Remodeling

- **Left ventricular hypertrophy and remodeling are key elements in the pathogenesis of progressive myocardial failure.**
- **Ventricular remodeling is a broad term describing changes in both myocardial cells and extracellular matrix that result in changes in the size, shape, structure, and function of the heart.**
- **These progressive changes result in a change in shape of the left ventricle from an ellipse to a sphere.**

Ventricular Hypertrophy and Remodeling

- **The change in ventricular size and shape further depresses the mechanical performance of the heart, increases regurgitant flow through the mitral valve, and thus, sustains progression of remodeling.**
- **Ventricular hypertrophy and remodeling can follow any condition that causes myocardial injury.**
- **The onset of the remodeling process precedes the development of HF symptoms.**

Ventricular Hypertrophy and Remodeling

- **The progression of the remodeling process leads to reductions in myocardial systolic and/or diastolic function, which results in further myocardial injury, perpetuating the remodeling process and the decline in left ventricular performance.**
- **Angiotensin II, NE, endothelin, aldosterone, vasopressin, and numerous inflammatory cytokines, play an important role in initiating the signal transduction cascade responsible for ventricular remodeling.**

Ventricular Hypertrophy and Remodeling

- **The increased circulating and tissue concentrations of these mediators are also toxic to other organs and provide evidence that HF is a systemic as well as a cardiac disorder.**

Therapy of Chronic Heart Failure

Desired Outcomes:

- **The goals of therapy in management of chronic HF are to:**

1) **improve the patient's quality of life**
2) **relieve or reduce symptoms**
3) **prevent or minimize hospitalizations**
4) **slow progression of the disease**
5) **prolong survival.**

- **Prevention of HF by identification of risk factors for HF development and recognition of its progressive nature is thus, essential.**

Therapy of Chronic Heart Failure

- **The general principles used to guide the treatment of HFrEF are based on numerous large, randomized, double-blind, multicenter clinical trials.**
- **Until recently, NO such randomized trials had been performed in patients with HFpEF.**
- **The guidelines for the management of HFpEF are based primarily on studies in relatively small groups of patients and clinical experience.**

Therapy of Chronic Heart Failure

General Measures:

- **The complexity of the HF syndrome necessitates a comprehensive approach to management.**
- **This approach includes:**

a) **Accurate diagnosis.**

b) **Identification and treatment of risk factors.**

c) **Elimination or minimization of precipitating factors.**

d) **Appropriate pharmacologic and nonpharmacologic therapy.**

e) **Close monitoring and follow up.**

Therapy of Chronic Heart Failure

- **The first step in management of chronic HF is to determine the etiology and/or precipitating factors.**
- **Appropriate treatment of underlying disorders (hyperthyroidism, valvular heart disease, ..etc) may obviate the need for specific HF treatment.**
- **Revascularization or anti-ischemic therapy in patients with CHD may reduce HF symptoms.**
- **Drugs that aggravate HF should be discontinued if possible.**

Therapy of Chronic Heart Failure

- **Restriction of physical activity reduces cardiac workload and is recommended for all patients with acute congestive symptoms, until patient's symptoms have stabilized and excess fluid is removed.**
- **Exercise training may improve functional status & quality of life, and may reduce hospitalizations and death from cardiovascular causes.**

Therapy of Chronic Heart Failure

- **Restriction of dietary sodium and fluid intake is an important life-style intervention for both HFrEF and HFpEF, to allow use of lower and safer diuretic doses.**
- **In patients with hyponatremia (Na <130 mEq/L) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to 2 L/day from all sources.**
- **You should be careful with sodium and fluid restriction in patients with HFpEF, because excessive restriction can lead to hypotension, low-output state, and/or renal insufficiency.**

Therapy of Chronic Heart Failure

General Approach to Treatment:

- **The ACC/AHA treatment guidelines are organized around the four identified stages of HF.**

New York Heart Association Functional Classification

Functional classes:

A. **Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.**

B. **Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.**

C. **Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.**

D. **Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.**

Therapy of Chronic Heart Failure

Heart Failure with Preserved Ejection Fraction:

- **Less information on the treatment of HFpEF is available.**
- **Guidelines recommend treating co-morbid conditions by controlling HR and BP, alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial fibrillation.**

Treatment Approach of HFpEF

Symptom-targeted treatment	Rationale	Agent
Decrease pulmonary venous pressure	Reduce left ventricular volume	Diuretics, nitrates, salt restriction
Reduce myocardial oxygen demand	Reduce heart rate, control blood pressure	B-blockers, (verapamil, diltiazem), (ACEIs, ARB), other calcium channel blockers
Maintain atrial contraction	Restore sinus rhythm	Cardioversion of atrial fibrillation
Improve exercise tolerance		Use positive inotropic agents with caution

Disease-targeted treatment		
Prevent or treat myocardial ischemia		B-blockers, nitrates, (verapamil, diltiazem)
Prevent or regress ventricular hupertrophy		Antihypertensive therapy
Mechanism-targeted treatment		
Modify myocardial and extramyocardial mechanisms		Possibly (ACEIs, ARB), diuretics, spironolactone
Modify intracellular and extracellular mechanisms		Possibly (ACEIs, ARB), diuretics

Therapy of Chronic Heart Failure

Diuretics:

- **A loop or a thiazide diuretic should be considered for patients with volume overload.**
- **Caution is warranted NOT to lower preload excessively, which may reduce stroke volume and cardiac output.**
- **Aldosterone antagonists can be considered to reduce the risk of hospitalization in patients that do NOT have contraindications or who are NOT at risk of hyperkalemia development.**

Therapy of Chronic Heart Failure

ACE inhibitors:

- **ACE inhibitors should be considered in all patients who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.**
- **Angiotensin receptor blockers are alternatives in patients who are intolerant of ACE inhibitors.**

Therapy of Chronic Heart Failure

β-Blockers:

- **They should be considered in patients with one or more of the following conditions:**

a) **Myocardial infarction.**

b) **Hypertension.**

c) **Atrial fibrillation requiring ventricular rate control.**

Therapy of Chronic Heart Failure

Calcium channel blockers:

- **In patients with atrial fibrillation who are intolerant to or have NOT responded to a β-blocker; diltiazem or verapamil may be considered.**
- **A nondihydropyridine or dihydropyridine calcium channel blocker can be considered for angina and hypertension.**

Therapy of Chronic Heart Failure

Treatment of Stage A Heart Failure:

- **Patients in Stage A do NOT have structural heart disease or HF symptoms but are at high risk for developing HF because of the presence of risk factors.**
- **Risk factors (HTN, dyslipidemia, diabetes, obesity, metabolic syndrome, smoking, and coronary artery disease) identification and modification to prevent the development of structural heart disease and subsequent HF is important.**
- **Risk factors act synergistically to develop both HFrEF and HFpEF.**
- **ACE inhibitors (or ARBs) and statins are recommended for HF prevention in patients with multiple cardiovascular risk factors.**

Therapy of Chronic Heart Failure

Treatment of Stage B Heart Failure:

- **Patients in Stage B have structural heart disease (left ventricular hypertrophy, recent or old MI, valvular heart disease, or LVEF < 0.4), but do NOT have HF symptoms.**
- **Treatment aims at minimizing additional injury and preventing or slowing the remodeling process.**
- **In addition to management of risk factors, ACEIs (or ARBs) and β-blockers are important components of therapy, to prevent development of HF, whether or NOT they have had an MI.**
- **Patients with a previous MI and reduced LVEF should also receive an ACEI (or ARB), evidence-based β-blocker, and a statin.**

Therapy of Chronic Heart Failure

Treatment of Stage C HF:

- **Patients with structural heart disease and previous or current symptoms are classified as Stage C and can have HFrEF or HFpEF.**
- **In addition to management of risk factors, patients with HFrEF in Stage C should be treated with an ACEI (or ARB) and an evidence-based β-blocker.**
- **These drugs slow HF progression, reduce morbidity and mortality, and improve symptoms.**
- **Loop diuretics, aldosterone antagonists, and hydralazine–isosorbide dinitrate may be used in these patients.**

Therapy of Chronic Heart Failure

- Digoxin can be considered in selected patients, as can two newly approved medications, ivabradine and sacubitril/valsartan.
- **Nonpharmacologic therapy with devices such as an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) with a biventricular pacemaker is also indicated in certain patients with HFrEF in Stage C.**

Therapy of Chronic Heart Failure

Treatment of Stage D HFrEF:

- **Stage D HF is advanced, refractory, or end-stage HF.**
- **Patients should be referred to HF management programs to receive specialized therapies: mechanical circulatory support, continuous IV positive inotropic therapy, and cardiac transplantation in addition to standard treatments outlined in stages A-C.**
- **Restriction of sodium and fluid intake, high doses of diuretics, combination therapy with a loop and thiazide diuretic, or ultrafiltration to remove excess fluid may be required.**

Therapy of Chronic Heart Failure

- **Patients in Stage D may be less tolerant to ACE inhibitors (hypotension, worsening renal insufficiency) and β-blockers (worsening HF).**
- **Initiation of therapy with low doses, slow upward dose titration, and close monitoring for signs and symptoms of intolerance are essential.**

Therapy of Chronic Heart Failure

- **With a few exceptions, many of the drugs used to treat HFrEF are the same as those for treatment of HFpEF.**
- **The rationale for their use, and the dosing regimen may be different.**
- **β-blockers are recommended for the treatment of both HFrEF and HFpEF.**

a) **In HFpEF, β-blockers are used to decrease HR, prolong diastole, and modify hemodynamic response to exercise.**

b) **In HFrEF, β-blockers are used in the long term to improve the inotropic state and modify LV remodeling.**

Therapy of Chronic Heart Failure

- Diuretics also are used in the treatment of both HFrEF and HFpEF.
- The doses of diuretics used to treat HFpEF are much smaller than those used to treat HFrEF.
- Antagonists of the RAAS are useful in lowering BP and reducing LVH.
- Some drugs, are used to treat either HFrEF or HFpEF.
- Calcium channel blockers (diltiazem, amlodipine, and verapamil) may be useful in the treatment of HFpEF.
- They have little utility in the treatment of HFrEF.

Diuretics

- **Diuretic therapy and sodium restriction, are recommended in all patients with fluid retention.**
- **Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia.**

Benefits:

1. **Reduction of symptoms associated with fluid retention**
2. **Improvement of exercise tolerance and quality of life**
3. **Reduction of hospitalizations from HF.**
4. **Reduction of pulmonary and peripheral edema through reduction of preload.**

Diuretics

- **Diuretics do NOT prolong survival or alter disease progression.**
- **Over-diuresis leads to reduction in cardiac output, and renal hypoperfusion.**
- **Hypotension or worsening renal function (increased creatinine) may be indicative of volume depletion and necessitate a reduction in the diuretic dose.**
- **Diuretic therapy is usually initiated at low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight.**

Diuretics

- **Over-diuresis may produce hypotension with ACE inhibitor or β-blocker therapy.**
- **In patients with HFpEF, diuretic treatment should be initiated at low doses in order to avoid hypotension and fatigue.**
- **Hypotension can be a significant problem in the treatment of HFpEF because a small change in volume causes a large change in filling pressure and cardiac output.**

Diuretics

- **After the acute treatment of HFpEF has been completed, long-term treatment should include small - moderate oral doses of diuretics (furosemide 20-40 mg/day, chlorthalidone 25-100 mg, or hydrochlorothiazide 12.5-25 mg/day).**

Thiazide diuretics:

- **Thiazide or the thiazide-like diuretics (metolazone, indapamide) can be used in combination with loop diuretics to promote a very effective diuresis.**

Diuretics

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

Loop Diuretics:

- **Loop diuretics are usually necessary to restore and maintain euvolemia in HF.**
- **Probenecid or organic by-products of uremia can inhibit delivery of loop diuretics to their site of action and decrease effectiveness.**

Diuretics

- **Loop diuretics induce a prostaglandin-mediated increase in renal blood flow, which contributes to their natriuretic effect.**
- **Coadministration of NSAIDs, including COX-2 inhibitors, blocks the prostaglandin-mediated effect and can diminish diuretic efficacy.**
- **Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses are necessary to obtain adequate delivery of the drug to the site of action.**

ACE Inhibitors

- **ACE inhibitors are key component of therapy of patients with HFrEF.**
- **They decrease the production of angiotensin II and aldosterone.**
- **This decrease in angiotensin II and aldosterone attenuates ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, norepinephrine release, vasoconstriction, and sodium and water retention.**
- **Bradykinin is increased by ACE inhibitors along with the release of vasodilatory prostaglandins and histamine.**

ACE Inhibitors

- **The most common cause of HFrEF is ischemic heart disease, which results in loss of myocytes, followed by ventricular dilation and remodeling.**
- **Captopril, ramipril, and trandolapril all benefit post-MI patients whether therapy is initiated early or late after the infarct.**
- **ACE inhibitors may have favorable effects on concomitant disorders (HTN, previous MI).**
- **Chronic kidney disease is NOT an absolute contraindication to ACE inhibitor use in patients with reduced LVEF.**

ACE Inhibitors

- **Angiotensin-converting enzyme (ACE) inhibitors lower glomerular capillary pressure, decrease proteinuria, and may halt progressive glomerular injury and loss of renal function in experimental chronic renal failure (CRF).**
- **However, CRF is a heterogeneous disorder and it is difficult to predict which patients will benefit from ACEi therapy.**
- **They can cause of acute kidney injury in advanced CKD caused by intercurrent illness and infections.**

ACE Inhibitors

- **However, these patients should be monitored carefully for the development of worsening renal function and/or hyperkalemia.**
- **Current guidelines recommend that all patients with HFrEF, regardless of whether or NOT symptoms are present, should receive ACE inhibitors, unless there are contraindications.**
- **ACE inhibitors improve survival by 20% to 30% compared with placebo.**

Angiotensin II Receptor Blockers

- **Angiotensin II can be formed in a number of tissues, including the heart, through non-ACE-dependent pathways (chymase, cathepsin, and kallikrein).**
- **By blocking the angiotensin II receptor subtype, AT1, ARBs attenuate the effects of angiotensin II on ventricular remodeling, regardless of the site of origin of the hormone.**
- **These agents do NOT affect bradykinin, which is linked to ACEIs-induced cough and angioedema.**

Angiotensin II Receptor Blockers

- **ARBs include candesartan, losartan, or valsartan which can reduce mortality and hospitalizations and improve symptoms.**
- **ARBs are indicated in patients who are unable to tolerate cough produced by ACE inhibitors.**
- **The role of ARBs in the treatment of HFpEF is less clear.**

β-Blockers

- β-blockers reduce morbidity and mortality in patients with HFrEF.
- They should be used in all stable patients with HF and a reduced left ventricular EF in the absence of contraindications or a clear history of β-blocker intolerance.
- Patients should receive a β-blocker when their symptoms are mild or well-controlled with diuretic and ACE inhibitor therapy.
- They are also recommended for asymptomatic patients with a reduced left ventricular EF to decrease the risk of progression to HF.

β-Blockers

- **Three β-blockers have been shown to significantly reduce mortality compared with placebo: carvedilol, metoprolol succinate (CR/XL), and bisoprolol.**
- **They have been shown to decrease ventricular mass, improve the sphericity of the ventricle, and reduce systolic and diastolic volumes.**
- **These effects are collectively called reverse remodeling, which means return of the heart toward more normal size, shape, and function.**

β-Blockers

- ACE inhibitors should be started first in most patients.
- Initiating a β-blocker first may be of benefit for patients with evidence of excessive SNS activity (tachycardia), and for patients whose renal function or potassium concentrations preclude starting an ACE inhibitor (or ARB) at that time.
- However, the risk for decompensation during β-blocker initiation may be greater in the absence of preexisting ACE inhibitor therapy, and careful monitoring is essential.

β-Blockers

- **β-Blockers favorable effects include: antiarrhythmic effects, attenuating or reversing ventricular remodeling, decreasing myocyte death from catecholamine-induced necrosis or apoptosis, preventing fetal gene expression, improving left ventricular systolic function, decreasing HR and ventricular wall stress thereby reducing myocardial oxygen demand, and inhibiting plasma renin release.**
- **β-blockers should NOT be started in patients on IV inotropic support.**

β-Blockers

- **They should be started in very low doses with slow upward dose titration (not < 2 weeks), and close monitoring to minimize acute decompensation.**
- **Dose up-titration is a long and gradual process.**
- **Response to therapy may be delayed and HF symptoms may actually worsen during the initiation period.**
- **β-blockers are recommended as standard therapy for all patients with HFrEF, regardless of the severity of their symptoms.**

β-Blockers

- In patients with HFpEF, β-blockers may help to lower and maintain low pulmonary venous pressure by decreasing HR and increasing the duration of diastole.
- Tachycardia is poorly tolerated in patients with HFpEF because rapid HRs cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time, which can promote ischemia even in the absence of epicardial CAD.

β-Blockers

- **A rapid rate reduces diastolic filling time.**
- **However, excessive bradycardia can result in a fall of cardiac output despite an increase in LV filling.**

Aldosterone Antagonists

- **Spironolactone and eplerenone inhibit sodium reabsorption and potassium excretion, thus, they have potassium-sparing effects (and protons).**
- **Aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.**
- **They attenuate the systemic pro-inflammatory state, atherogenesis, and oxidative stress caused by aldosterone.**
- ~~**They may attenuate aldosterone-induced calcium excretion and reductions in bone mineral density and protect against fractures in HF. (*****)**~~

Aldosterone Antagonists

- **Spironolactone reduces mortality by 30% and eplerenone by 15% in HFrEF.**
- **The most common adverse effects of spironolactone are gynecomastia and hyperkalemia, while that of eplerenone is hyperkalemia.**
- **There are NO clear guidelines on aldosterone antagonist use for patients with HFpEF.**
- **It may be reasonable to add an aldosterone antagonist if plasma natriuretic peptide levels are elevated.**

Aldosterone Antagonists

Factors contributing to the high incidence of Hyperkalemia with aldosterone antagonists:

1) **The initiation of aldosterone antagonists in patients with impaired renal function or high serum K^+.**
2) **The failure to decrease or stop potassium supplements when starting aldosterone antagonists.**
3) **Diabetes mellitus.**
4) **High potassium intake with food.**
5) **Concomitant use of ACE inhibitors /ARBs and NSAIDs.**

Aldosterone Antagonists

Strategies for reducing the risk for hyperkalemia with aldosterone antagonists:

1. **Avoid starting aldosterone antagonists in patients with any of the following:**

a) **Serum creatinine concentration >2.0 mg/dL in women or >2.5 mg/dL in men or a CrCL <30 mL/min.**

b) **Recent worsening of renal function.**

c) **Serum K^+ >5 mEq/L.**

d) **History of severe hyperkalemia.**

Aldosterone Antagonists

2. **Start with low doses (12.5 mg/day for spironolactone and 25 mg/day for eplerenone) especially in the elderly, patients with diabetes, or a CrCL <50 mL/min.**
3. **Decrease or discontinue potassium supplements when starting an aldosterone antagonist.**
4. **Avoid concomitant use of NSAIDs or COX-2 inhibitors.**
5. **Avoid concomitant use of high-dose ACE inhibitors or ARBs.**

Aldosterone Antagonists

6. **Monitor serum K^+ and renal function within 3 days and 1 week after the initiation or dose titration of an aldosterone antagonist or any other medication that could affect potassium.**
7. **Thereafter, K^+ and renal function should be monitored monthly for the first 3 months, and then every 3 months.**
8. **If K^+ exceeds 5.5 mg/dL at any point during therapy, discontinue any potassium supplementation or, in the absence of potassium supplements, reduce or stop aldosterone antagonist therapy.**

Aldosterone Antagonists

9. **Counsel patients to:**

a) **Limit intake of high potassium-containing foods and salt substitutes.**

b) **Avoid the use of over-the-counter NSAIDs.**

c) **Temporarily discontinue aldosterone antagonist therapy if diarrhea develops or diuretic therapy is interrupted.**

Drug Therapies for Selected Patients with HFrEF

Nitrates and Hydralazine:

- **Nitrates and hydralazine are combined in the treatment of HFrEF because of their complementary hemodynamic actions.**
- **Nitrates cause venodilation and decrease preload.**
- **Hydralazine is a direct-acting arterial vasodilator causing a decrease in afterload.**

Drug Therapies for Selected Patients with HFrEF

- **Hydralazine and ISDN reduce all-cause mortality.**
- **By serving as a nitric oxide donor, nitrates increase nitric oxide bioavailability.**
- **Nitric oxide attenuates myocardial remodeling and may play a protective role in HF.**
- **Hydralazine reduces oxidative stress.**
- **The combination requires frequent dosing three times daily.**

Drug Therapies for Selected Patients with HFrEF

- **In the absence of another indication for nitrate therapy (angina), nitrates provide limited benefits to patients with HFpEF.**

Drug Therapies for Selected Patients with HFrEF

ARB/Neprilysin Inhibitor (fixed dose combination):

- **The natriuretic peptides ANP and BNP cause vasodilation, natriuresis, and diuresis.**
- **They inhibit renin secretion, aldosterone production and attenuate ventricular hypertrophy and fibrosis.**
- **Neprilysin is a zinc-dependent metalloprotease that breaks down the natriuretic peptides ANP & BNP bradykinin and other peptides.**
- **Neprilysin is also involved in the clearance of amyloid-β from the brain and CSF.**

Drug Therapies for Selected Patients with HFrEF

- **Valsartan/sacubitril can be used for the treatment of patients with HFrEF.**
- **Sacubitril is prodrug, which inhibits the action of neprilysin.**
- **Natriuretic pepetides are beneficial because they cause vasodilation, increased glomerular filtration, natriuresis, and diuresis.**
- **The combination reduces mortality and hospitalizations in patients with HFrEF.**

Drug Therapies for Selected Patients with HFrEF

Adverse Effects:

- **Hypotension, dizziness, hyperkalemia, worsening renal function, and cough – most common.**
- **Angioedema.**

Drug interactions:

1. **Should not be used concurrently with ACE inhibitors or ARBs. ACEIs should be discontinued 36 hours prior to initiating sacubitril/valsartan.**
2. **Should be avoided with aliskiren (direct renin inhibitor).**

Drug Therapies for Selected Patients with HFrEF

Sacubitril/valsartan contraindications:

1. **Patients with history of angioedema**
2. **Pregnancy**
3. **Severe hepatic impairment.**
4. **Diabetes mellitus**

Drug Therapies for Selected Patients with HFrEF

Ivabradine:

- Ivabradine blocks the I_f current in the SA node that is responsible for controlling the heart rate.
- By blocking this current, ivabradine slows the spontaneous depolarization of the sinus node resulting in a dose-dependent slowing of the heart rate.
- Ivabradine's effects are specific to the I_f current and it does not affect BP, myocardial contractility, or AV conduction.

Drug Therapies for Selected Patients with HFrEF

- **Used for patients with HFrEF in sinus rhythm with a heart rate ≥ 70 beats/min that are receiving maximally tolerated treatment with β-blockers or have contraindications to β-blockers.**
- **Ivabradine is extensively metabolized by intestinal and hepatic CYP3A4.**
- **Co-administration with CYP3A4 inhibitors (itraconazole, macrolide antibiotics, HIV protease inhibitors, verapamil, diltiazem, grapefruit juice) is contraindicated because of the large increase in exposure and potential for bradycardia.**

Drug Therapies for Selected Patients with HFrEF

- **Use with CYP3A inducers (St. John's wort, rifampin, phenytoin) should be avoided.**
- **Because QT interval prolongation can be increased by slower heart rates, ivabradine should be used cautiously, if at all, with other agents known to prolong the QT interval.**

Adverse Effects:

1. **Bradycardia in ~ 10% of patients.**
2. **Effects on vision primarily manifesting as phosphenes (transient brightness in portions of the visual field).**
3. **Atrial fibrillation.**

Drug Therapies for Selected Patients with HFrEF

Digoxin:

- **It has a positive inotropic effect on the heart.**
- **It improves cardiac function, quality of life, exercise tolerance, and HF symptoms in patients with HFrEF (decreases morbidity)**
- **No apparent benefit of digoxin on hospitalizations or mortality.**
- **It is not a first line agent in HF.**
- **It helps control of ventricular response in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective, especially during exercise.**
- **There is NO established role for digoxin in HFpEF when patients are in normal sinus rhythm, but may be of benefit in patients with concomitant HFpEF and atrial fibrillation.**

Drug Therapies for Selected Patients with HFrEF

Calcium Channel Blockers:

- They can provide symptom-targeted treatment in patients with HFpEF by decreasing HR.
- They may be used to treat concomitant HTN and CAD.
- They provide both short- and long-term improvement in exercise capacity in patients with HFpEF.
- Verapamil and diltiazem are the most effective because they lower heart rate in addition to lowering BP.
- They should be avoided in patients with HFrEF.

Drug Monitoring

ACE inhibitors:

Adverse Effect:

- **Angioedema, cough, hyperkalemia, hypotension, renal dysfunction**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or increase in dose.**

Comments:

- **Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy.**

Drug Monitoring

ARBs:

Adverse Effect:

- **Hyperkalemia, hypotension, renal dysfunction**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or increase in dose.**

Comments:

- **Contraindicated in patients with bilateral renal artery stenosis or pregnancy.**
- **Use with caution in patients with a history of ACE inhibitor-associated angioedema.**

Drug Monitoring

Sacubitril/valsartan:

Adverse Effect:

- **Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction.**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or dose increase.**

Comments:

- **Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy.**
- **Start with a low dose and double the dose every 2-4 weeks as tolerated based on BP, serum potassium, and renal function.**

Drug Monitoring

Aldosterone antagonists:

Adverse Effect:

- **Gynecomastia, breast tenderness, menstrual irregularities (spironolactone), hyperkalemia, worsening renal function**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline.**
- **Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months.**

Comments:

- **Change to eplerenone if gynecomastia develops with spironolactone.**

Drug Monitoring

β-blockers:

Adverse Effect:

- **Bradycardia, heart block, bronchospasm, hypotension, worsening HF.**

Monitoring Parameters:

- **BP, HR, ECG, signs and symptoms of worsening HF, blood glucose**

Comments:

- **Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms.**
- **Patients may feel worse before they improve.**

Drug Monitoring

Digoxin:

Adverse Effect:

- **GI and CNS adverse effects, brady- and tachyarrhythmias**

Monitoring Parameters:

- **electrolytes, BUN, creatinine, ECG, serum digoxin concentration.**

Comments:

- **Target serum digoxin concentration 0.5-0.9 ng/mL.**

Drug Monitoring

Ivabradine:

Adverse Effect:

- **Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field).**

Monitoring Parameters:

- **BP, HR, ECG.**

Comments:

- **Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50-60 b/m.**
- **Only use for patients in sinus rhythm.**

Drug Monitoring

Diuretics (thiazide and loop diuretics):

Adverse Effect:

- **Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, renal dysfunction, thirst.**

Monitoring Parameters:

- **BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, jugular venous distension.**

Comments:

- **Dose should be adjusted based on volume status, renal function, electrolytes, and BP.**
- **Reassess these parameters 1-2 weeks after dose changes.**

Drug Monitoring

Hydralazine:

Adverse Effect:

- **Hypotension, headache, rash, arthralgia, lupus, tachycardia.**

Monitoring Parameters:

- **BP, HR.**

Nitrates:

Adverse Effect:

- **Hypotension, headache, lightheadedness.**

Monitoring Parameters:

- **BP, HR.**

Therapy of Hypertension

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Therapy of Hypertension

Classification:

1. **Essential or primary hypertension:**

- **Most common (~ 90% of patients).**
- **Unknown etiology.**
- **Can NOT be cured, but it can be controlled.**

2. **Secondary hypertension:**

- **A small percentage of patients (< 10% of patients).**
- **Specific cause.**
- **Can be relieved or potentially cured.**

Secondary Hypertension

Secondary Hypertension:

- **A co-morbid disease or a drug is responsible for elevating BP.**

Causes:

1. **Chronic kidney disease**
2. **Cushing's syndrome**
3. **Coarctation of the aorta**
4. **Obstructive sleep apnea**
5. **Primary hyperparathyroidism**
6. **Pheochromocytoma**
7. **Primary aldosteronism**

Secondary Hypertension

8. Renovascular disease.
9. Thyroid disease (both hypo- and hyper-thyrodism)
10. Drugs:

a) Amphetamines.

b) Antivascular endothelial growth factor agents (Bevacizumab, ranibizumab and aflibercept). May increase vascular tone due to inhibition of VEGF-mediated vasodilation.

c) Corticosteroids.

d) Calcineurin inhibitors (cyclosporine, tacrolimus).

Secondary Hypertension

e) Decongestants (pseudoephedrine, phenylephrine)

f) Ergot alkaloids (bromocriptine, methysergide, dihydroergotamine).

g) Erythropoiesis-stimulating agents (erythropoietin, darbepoetin). May increase response to circulating vasoconstrictors.

h) Estrogen-containing oral contraceptives.

i) Nonsteroidal anti-inflammatory drugs.

j) β-blocker withdrawal.

k) Tryamine-containing foods.

Secondary Hypertension

l) **Street drugs and other products: Cocaine and cocaine withdrawal; Ephedra alkaloids (Ma huang), "herbal ecstasy" ; Nicotine and withdrawal, anabolic steroids, narcotic withdrawal, ergot-containing herbal products; St. John's wort.**

m) **Food substances: Sodium, Alcohol drinking (by increasing levels of endothelin and angiotensin II), Licorice (aldosterone-like action).**

n) **Others…**

Secondary Hypertension

- **When a secondary cause is identified, removing the offending agent or treating/correcting the underlying co-morbid condition should be the first step in management.**

Classification of Hypertension

- **2020 International Society of Hypertension Global Hypertension Practice Guidelines**

https://www.ahajournals.org/doi/epub/10.1161/HYPERTENSIONAHA.120.15026

Table 1 Blood pressure classification in the ACC/AHA and ESC/ESH guidelines

ACC/AHA				ESC/ESH			
Category	SBP		DBP	Category	SBP		DBP
Normal	< 120	and	< 80	Optimal	< 120	and	< 80
Elevated	120–129	and	< 80	Normal	120–129	and/or	80–84
Stage 1 hypertension	130–139	or	80–89	High-normal	130–139	and/or	85–89
Stage 2 hypertension	≥ 140	or	≥ 90	Grade 1 hypertension	140–159	and/or	90–99
				Grade 2 hypertension	160–179	and/or	100–109
				Grade 3 hypertension	≥ 180	and/or	≥ 110
				Isolated systolic hypertension	≥ 140	and	< 90

Reference:

New American (JNC8) and European Hypertension Guidelines, Reconciling the Differences. Cardiol Ther (2019) 8:157–166. https://doi.org/10.1007/s40119-019-0144-3

Classification of Hypertension

- **Hypertensive crises are clinical situations where there are extreme BP elevations, typically greater than 180/120 mm Hg.**
- **They are categorized as either:**

1. **Hypertensive emergency: extreme BP elevations that are accompanied by acute or progressing end-organ damage.**
2. **Hypertensive urgency: extreme BP elevations without acute or progressing end-organ injury.**

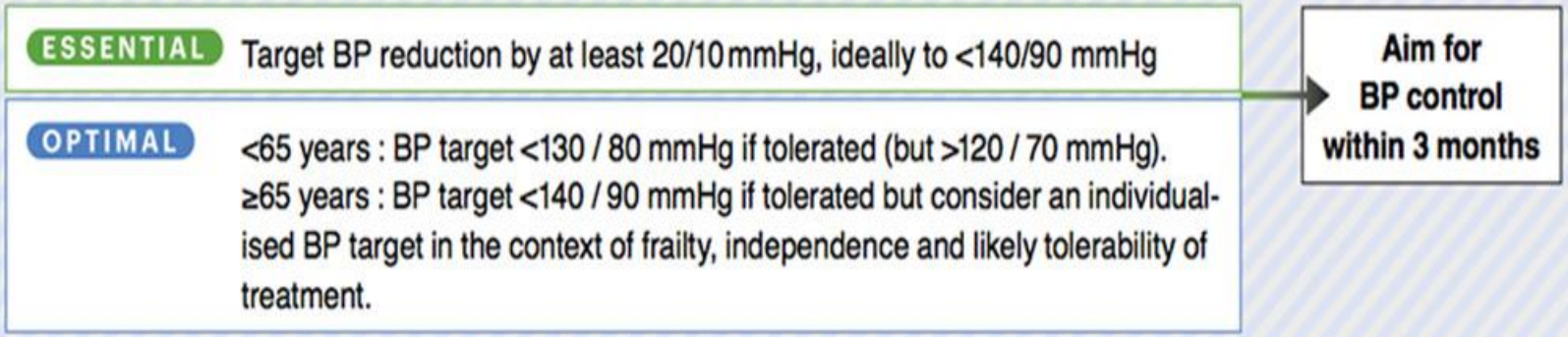
Therapy of Hypertension

Overall Goal of Treatment:

- **The overall goal of treating hypertension is to reduce associated morbidity and mortality from cardiovascular (CV) events (coronary events, cerebrovascular events, heart failure, kidney disease).**
- **Therefore, the specific selection of antihypertensive drug therapy should be based on evidence demonstrating CV event reduction.**

Therapy of Hypertension

- **Guidelines recommend a goal BP of < 130/80 mm Hg for the management of hypertension in most patients. (American guidelines).**



Reference is in slide 8

Therapy of Hypertension

- **Treating patients to lower BP goals may lead to hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure.**
- **BP control rates are poor. The main reason is "Clinical Inertia" which is defined as a clinic visit at which NO therapeutic move was made to lower BP in a patient with uncontrolled hypertension.**
- **During visits, treatment can be initiated, titrated, and/or changed.**

Therapy of Hypertension

General Approach to Treatment:

- **Most patients should be placed on both life-style modifications and drug therapy concurrently after the diagnosis of hypertension.**
- **Life-style modification alone is appropriate for most patients with pre-hypertension.**
- **Life-style modifications alone may NOT adequately lower BP in hypertensive patients.**

Therapy of Hypertension

- **Patients with additional CV risk factors or those with hypertension-associated complications need antihypertensive drug therapy in addition to life-style modifications.**
- **The choice of initial antihypertensive drug therapy depends on the degree of BP elevation and presence of compelling indication.**

Therapy of Hypertension

1. **Most patients with stage 1 hypertension should be initially treated with a first-line drug or the combination of two.**

- **Monotherapy: ACEi, ARB, CCB or a thiazide diuretic.**
- **Two-drug combination: ACEi or ARB + CCB or thiazide diuretic.**

Therapy of Hypertension

2. **For patients with stage 2 hypertension, combination drug therapy is recommended, using preferably two first-line antihypertensive drugs.**

- **ACEi or ARB + CCB.**
- **ACEi or ARB + thiazide.**

Therapy of Hypertension

Non-pharmacologic Therapy:

- **All patients with pre-hypertension and hypertension should follow life-style modifications.**
- **Life-style modifications should never be used as a replacement for antihypertensive drug therapy.**
- **They can provide small-to-moderate reductions in SBP.**
- **Strict adherence with life-style modification can decrease the progression to hypertension in patients with pre-hypertension.**

Life-style Modifications

Modification	Recommendation
Weight loss	Maintain normal body weight (body mass index, 18.5-24.9 kg/m^2), reduce wt gradually
Diet	A diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, (1.5 g/day sodium, or 3.8 g/day sodium chloride)
Aerobic physical activity	3 to 4 sessions/wk, lasting an average of 40 min/session, and involving moderate- to vigorous-intensity physical activity
Moderation of alcohol intake	Limit consumption to ≤2 drink equivalents per day in men and ≤1 drink equivalent per day in women and lighter-weight persons

Therapy of Hypertension

Pharmacotherapy:

- **An ACE-inhibitor, an angiotensin II receptor blocker (ARB), a calcium channel blocker (CCB), or a thiazide diuretic are preferred first-line antihypertensive agents for most patients.**
- **They should be used to treat the majority of patients with hypertension because of evidence demonstrating cardiovascular event reduction.**

Therapy of Hypertension

- **β-Blocker therapy should be reserved to either treat a specific compelling indication or used in combination with one or more of the first-line antihypertensive agents for patients without a compelling indication.**
- **A β-blocker can be used as a first-line antihypertensive agent when an ACEi, ARB, CCB, or thiazide can NOT be used as the first-line agent.**

Therapy of Hypertension

- **Alternative antihypertensive drug classes may be used in select patients after first-line agents:**
  Loop diuretics, potassium sparing diuretics, β-blockers, α_1-blockers, central α_2-agonists, direct renin inhibitors, and direct arterial vasodilator (hydralazine).

Therapy of Hypertension

Patients with Compelling Indications:

- **Compelling indications represent specific co-morbid conditions where evidence supports using specific antihypertensive classes to treat both the compelling indication and hypertension.**
- **In these cases, drug therapy consists of drug combination.**

Therapy of Hypertension

Heart Failure with Reduced Ejection Fraction:

- **Systolic heart failure associated with decreased cardiac output.**
- **The following are indicated: An ACEi or ARB plus diuretic therapy, followed by the addition of a β-blocker (bisoprolol, carvedilol, or metoprolol) and possibly an aldosterone receptor antagonist.**
- **An ACEi or ARB should be started with low doses, especially in patients with acute exacerbation.**

Therapy of Hypertension

- **Heart failure induces a compensatory high-renin condition, and starting an ACEi or ARB can cause a profound first-dose effect and possible orthostatic hypotension.**
- **Diuretics provide symptomatic relief of edema.**
- **Loop diuretics are often needed, especially for patients with more advanced heart failure and/or CKD.**

Therapy of Hypertension

- **A β-Blocker must be started in very low doses, much lower than that used to treat hypertension, and titrated slowly to higher doses based on tolerability.**
- **Bisoprolol, carvedilol, and sustained-release metoprolol are the only β-blockers proven to be beneficial.**
- **The addition of an aldosterone antagonist (spironolactone or eplerenone) can reduce cardiovascular morbidity and mortality.**

Therapy of Hypertension

Post-Myocardial Infarction:

- **β-Blockers (without intrinsic sympathomimetic activity) and ACEi or ARB are first choice to decrease cardiac adrenergic stimulation.**
- **They reduce the risk of a subsequent MI or sudden cardiac death.**
- **ACEi treatment improves cardiac remodeling and cardiac function and reduces cardiovascular events post-MI.**
- **β-blockers should be used first.**

Therapy of Hypertension

Coronary Artery Disease:

- **Chronic stable angina and acute coronary syndrome (unstable angina and acute MI) are the most common hypertension-associated complications.**
- **β-Blocker therapy is a standard of care for treating these conditions in patients with hypertension.**
- **They are first-line therapy in chronic stable angina and have the ability to reduce BP and improve ischemic symptoms by decreasing myocardial oxygen consumption and demand.**

Therapy of Hypertension

- **Long-acting CCBs (the non-dihydropyridines diltiazem and verapamil) are alternatives to β-blockers.**
- **Dihydropyridine CCBs are considered as add-on therapy in chronic stable angina for patients with ischemic symptoms.**
- **For acute coronary syndromes (ST-elevation MI and unstable angina/non-ST-segment MI), first-line therapy should consist of a β-blocker and ACEi or ARB.**

Therapy of Hypertension

- **Once ischemic symptoms are controlled with β-blocker and/or CCB therapy, other antihypertensive drugs (ACEi or ARB) can be added to provide additional cardiovascular risk reduction.**
- **Thiazides can be added thereafter to provide additional BP lowering and to further reduce cardiovascular risk, but they do NOT provide anti-ischemic effects.**

Therapy of Hypertension

Diabetes Mellitus:

- **The primary cause of mortality in diabetes is cardiovascular disease, and hypertension management is a very important risk reduction strategy.**
- **ACEi or an ARB have been shown to reduce CV events in patients with diabetes.**
- **These agents provide nephro-protection due to vasodilation in the efferent arteriole.**

Therapy of Hypertension

- **CCBs are the most appropriate add-on agents for BP control for patients with diabetes.**
- **A thiazide (?), used in low doses, is recommended add-on therapy to lower BP and provide additional cardiovascular risk reduction.**

Therapy of Hypertension

- β-Blockers (especially non-selective) can mask the signs and symptoms of hypoglycemia in patients with tightly controlled diabetes because most of the symptoms of hypoglycemia (tremor, tachycardia, and palpitations) are mediated through the sympathetic nervous system.
- Sweating, a sympathetic-cholinergic function, still occurs during a hypoglycemic episode despite β-blocker therapy.
- Patients may have a delay in hypoglycemia recovery time because compensatory recovery mechanisms need catecholamine input which is antagonized by β-blockers.
- Unopposed α-receptor stimulation during the acute hypoglycemic recovery phase (due to endogenous epinephrine release intended to reverse hypoglycemia) may result in acutely elevated BP due to vasoconstriction.
- Despite these potential problems, β-blockers (selective) can be used for patients with diabetes.

Therapy of Hypertension

Chronic Kidney Disease (CKD):

- **ACEi or ARB therapy reduces intraglomerular pressure, which slows progression of CKD in diabetics and nondiabetics.**
- **Patients may experience a rapid and profound drop in BP or acute kidney failure when given an ACEi or ARB, especially in patients with bilateral renal artery stenosis or a solitary functioning kidney with stenosis.**
- **Start with low dose and measure serum creatinine soon after starting the drug to minimize this risk.**

Therapy of Hypertension

Recurrent Stroke Prevention:

- **Ischemic stroke and transient ischemic attack are complications of hypertension.**
- **A thiazide is a reasonable choice.**
- **It can be combined with an ACEi or an ARB.**
- **Antihypertensive drug therapy should only be implemented after the patient has stabilized following an acute cerebrovascular event.**

Therapy of Hypertension

Alternative Drug Treatments:

- **Include: direct renin inhibitors, α-blockers, central α_2-agonists, adrenergic inhibitors, and arterial vasodilators.**
- **These agents are effective in lowering BP, but they may NOT reduce morbidity and mortality in hypertension, or have poor tolerability and adverse effects that significantly limit their use.**
- **Alternative agents may be used for patients with resistant hypertension, or as add-on therapy with multiple other first-line antihypertensive agents.**

Therapy of Hypertension

Hypertension in elderly patients:

- **Hypertension may present as isolated systolic hypertension in the elderly.**
- **This population is at high risk for hypertension-associated complications.**
- **Many elderly patients with hypertension are either NOT treated, or treated but NOT controlled.**
- **Thiazides and long-acting dihydropyridine CCBs reduce cardiovascular morbidity and mortality in these patients.**

Therapy of Hypertension

- Elderly patients are more sensitive to volume depletion and sympathetic inhibition than younger patients → orthostatic hypotension.
- This can increase the risk of falls due to the associated dizziness.
- Centrally acting agents and α_1-blockers should be avoided because they are frequently associated with dizziness and orthostatic hypotension.

Therapy of Hypertension

- **A thiazide, ACEi, or ARB provide significant benefits and can safely be used in the elderly, at smaller-than-usual initial doses.**
- **To minimize risks, dosage should be titrated over a longer period of time.**
- **Standard SBP goals of <140 mm Hg should be considered for elderly patients.**

Therapy of Hypertension

Patients at Risk of Orthostatic Hypotension:

- **The risk of orthostatic hypotension is increased in older patients, those with isolated systolic hypertension, those with long-standing diabetes, severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and on concomitant venodilators (α-blockers, mixed α-/β-blockers, nitrates, and phosphodiesterase inhibitors).**
- **Antihypertensive agents should be started in low doses, especially a thiazide, ACEi or ARB.**

Therapy of Hypertension

Hypertension in Children and Adolescents:

- Hypertensive children often have a family history of high BP, and many are overweight predisposing them to insulin resistance and associated cardiovascular disease.
- Secondary hypertension is more common in children and adolescents, thus, we need to find the cause.
- Kidney disease (pyelonephritis, glomerulonephritis) is the most common cause of secondary hypertension in children.
- Coarctation of the aorta can also produce secondary hypertension.

Therapy of Hypertension

- **Medical or surgical management of the underlying disorder usually normalizes BP.**
- **Weight loss is the cornerstone of therapy.**
- **An ACEi, ARB, β-blocker, CCB, and thiazide are all acceptable choices in children.**
- **Like adults, selection of initial agents should be based on the presence of compelling indications or concurrent conditions that may warrant their use (ACEi or ARB for diabetics or CKD).**

Therapy of Hypertension

Pulmonary Disease:

- **Nonselective β-Blockers should be avoided in hypertensive patients with reactive airway disease (asthma or COPD) due to a fear of inducing bronchospasm.**

Peripheral Arterial Disease:

- **β-Blockers decrease peripheral blood flow secondary to unopposed stimulation of α_1-receptors that results in vasoconstriction, and should be avoided.**
- **β-blocker with α_1-blocking properties (carvedilol) can be used.**

Monitoring of Therapy

Ongoing monitoring, in all patients treated with antihypertensive drugs, is required to assess:

1) **The desired effects of antihypertensive therapy (BP goal).**
2) **Drug adverse effects.**
3) **Disease progression.**

Monitoring of Therapy

Monitoring of antihypertensive therapy

Class	Parameters
Aldosterone antagonists	BP; BUN/serum creatinine; serum potassium
ACEis & ARBs	BP; BUN/serum creatinine; serum potassium
Calcium channel blockers	BP; heart rate
Thiazides	BP; BUN/serum creatinine; serum electrolytes (potassium, magnesium, sodium); uric acid, glucose.
β-Blockers	BP; heart rate

Adherence and Persistence

- Poor adherence is frequent.
- Only 50% of patients with newly diagnosed hypertension are continuing treatment at 1 year.
- Identification of nonadherence should be followed up with appropriate patient education, counseling, and intervention.
- Once-daily regimens are preferred in most patients to improve adherence.

Resistant Hypertension

- **Failure to achieve goal BP with the use of three or more antihypertensive drugs indicates resistant hypertension.**
- **It affects ~ 12% of patients.**
- **Pseudo-resistance should also be ruled out by assuring adherence with prescribed therapy.**

Causes of Resistant Hypertension

1. Improper BP measurement.
2. Volume overload:
- Excess sodium intake.
- Volume retention from kidney disease.
- Inadequate diuretic therapy.
3. Drug-induced (2◦) (mentioned before)
4. Other causes:
- Nonadherence.
- Inadequate antihypertensive doses.
5. Associated conditions:
- Obesity, excess alcohol intake, obstructive sleep apnea.

Hypertensive Urgencies and Emergencies

- **Hypertensive urgencies and emergencies (hypertensive crises) are characterized by very elevated BP (> 180/120 mm Hg).**
- **The difference is that emergencies are associated with acute or immediately progressing end-organ injury.**
- **Urgencies are NOT associated with acute or immediately progressing end-organ injury.**

Hypertensive Urgencies and Emergencies

- **Acute end-organ injury include encephalopathy, intracranial hemorrhage, retinopathy, nephropathy, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, and eclampsia or severe hypertension during pregnancy.**

Hypertensive Urgency

- **A common error with hypertensive urgency is aggressive antihypertensive therapy.**
- **Hypertensive urgencies are ideally managed by adjusting maintenance therapy:**

1) **adding a new antihypertensive.**
2) **increasing the dose of a present medication.**

- **This provides a more gradual reduction in BP.**

Hypertensive Urgency

- **Very rapid reductions in BP to goal values should NOT be attempted because autoregulation of blood flow in patients with hypertension occurs at a much higher range of pressure than in normotensive persons.**
- **The risks of reducing BP too rapidly include cerebrovascular accidents, MI, and acute renal failure.**

Hypertensive Urgency

- **Hypertensive urgency requires BP reductions with oral antihypertensive agents to stage 1 over a period of several hours to days.**
- **All patients with hypertensive urgency should be reevaluated within, and NOT later than, 7 days (preferably after 1 to 3 days).**

Hypertensive Urgency

- Administration of a short-acting oral antihypertensive (captopril, clonidine, labetalol) followed by careful observation for several hours to assure a gradual reduction in BP is an option.
- For patients with hypertensive rebound following withdrawal of clonidine, 0.1-0.2 mg can be given initially, followed by 0.05-0.1 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg clonidine has been administered.

Hypertensive Urgency

- **A single dose may be all that is necessary.**
- **Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.**
- **Oral or sublingual immediate-release nifedipine is dangerous, should never be used for hypertensive urgencies due to risk of causing severe adverse events (MI, stroke).**

Hypertensive Emergency

- Hypertensive emergencies require immediate BP reduction to limit new or progressing end-organ damage.
- They require parenteral therapy, at least initially.
- Do NOT lower BP to < 140/90 mm Hg.
- The initial target is a reduction in MAP of up to 25% within minutes to hours. [MAP = {SBP + 2 (DBP)}/ 3]
- When the patient is stable, DBP can be reduced to 100 - 110 mm Hg within the next 2 - 6 hours.

Hypertensive Emergency

- **Precipitous drops in BP may lead to end-organ ischemia or infarction.**
- **If patients tolerate this reduction well, additional gradual reductions toward goal BP values can be attempted after 24 to 48 hours.**
- **The exception to this guideline is for patients with an acute ischemic stroke where maintaining an elevated BP is needed for a longer period of time.**

AHA/ASA Recommendations for BP Management in Acute Ischemic Stroke

1. Patients eligible for treatment with intravenous thrombolytics or other acute reperfusion intervention and SBP >185 mm Hg or DBP >110 mm Hg should have BP lowered before the intervention. A persistent SBP of >185 mm Hg or a DBP >110 mm Hg is a contraindication to intravenous thrombolytic therapy. After reperfusion therapy, keep SBP <180 mm Hg and DBP <105 mm Hg for at least 24 hours.
2. Patients who have other medical indications for aggressive treatment of BP should be treated.
3. For those not receiving thrombolytic therapy, BP may be lowered if it is markedly elevated (SBP >220 mm Hg or DBP >120 mm Hg). A reasonable goal would be to lower BP by approximately 15% during the first 24 hours after onset of stroke.
4. In hypotensive patients, the cause of hypotension should be sought. Hypovolemia and cardiac arrhythmias should be treated and in exceptional circumstances, vasopressors may be prescribed in an attempt to improve cerebral blood flow.

Hypertensive Emergency

- **The clinical situation should dictate which IV medication is used to treat hypertensive emergencies.**
- **Therapy should be provided in a hospital or emergency room setting with intra-arterial BP monitoring.**

Hypertensive Emergency

1. **Sodium nitroprusside was drug of first choice in the past.**
2. **IV nitroglycerin is ideal for the management of hypertensive emergency in the presence of myocardial ischemia.**

- **IV nitroglycerin is associated with tolerance when used over 24 to 48 hours and can cause severe headache.**

Hypertensive Emergency

3. **Fenoldopam is a D_1-receptor agonist. It can improve renal blood flow and may be especially useful for patients with renal insufficiency.**
4. **Nicardipine and clevidipine provide arterial vasodilation and can treat cardiac ischemia similar to nitroglycerin, and may provide more predictable reductions in BP. (use with caution)**

Hypertensive Emergency

Sodium nitroprusside:

- **Dose: 0.25-10 µg/kg/min IV infusion (requires special delivery system).**
- **Onset: immediate.**
- **Duration: 1-2 min.**
- **Adverse effects: Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication.**
- **Special indications: Most hypertensive emergencies.**
- **Caution with high intracranial pressure, azotemia, or in chronic kidney disease.**

Hypertensive Emergency

Nitroglycerin:

- **Dose: 5-100 µg/min IV infusion.**
- **Onset: 2-5 min.**
- **Duration: 5-10 min.**
- **Adverse effects: Headache, vomiting, methemoglobinemia, tolerance with prolonged use.**
- **Special indications: Coronary ischemia.**

Hypertensive Emergency

Clevidipine:

- **Dose: 1-2 mg/h (32 mg/h maximum).**
- **Onset: 2-4 min.**
- **Duration 5-15 min.**
- **Adverse effects: Headache, nausea, tachycardia, hypertriglyceridemia.**
- **Special indications: Most hypertensive emergencies except acute heart failure; caution with coronary ischemia.**
- **Contraindications: soy or egg allergy, defective lipid metabolism, and severe aortic stenosis.**

Hypertensive Emergency

Nicardipine:

- **Dose: 5-15 mg/h IV.**
- **Onset: 5-10 min.**
- **Duration: 15-30 min, may exceed 4 hours.**
- **Adverse effects: Tachycardia, headache, flushing, local phlebitis.**
- **Special indications: Most hypertensive emergencies except acute heart failure.**
- **Caution with coronary ischemia.**

Hypertensive Emergency

Enalaprilat:

- **Dose: 1.25-5 mg IV every 6 hours.**
- **Onset: 15-30 min.**
- **Duration: 6-12 hours.**
- **Adverse effects: Precipitous fall in pressure in high-renin states; variable response.**
- **Special indications: Acute left ventricular failure.**
- **Avoid in acute myocardial infarction, eclampsia.**

Hypertensive Emergency

Esmolol:

- **Dose: 250-500 µg/kg/min IV bolus, and then 50-100 µg/kg/min IV infusion; may repeat bolus after 5 minutes or increase infusion to 300 µg/min**
- **Onset: 1-2 min.**
- **Duration: 10-20 min.**
- **Adverse effects: Hypotension, nausea, asthma, first-degree heart block, heart failure.**
- **Special indications: Aortic dissection; perioperative.**
- **Avoid in patients already on β-blocker, bradycardic, or decompensated heart failure.**

Hypertensive Emergency

Fenoldopam:

- **Dose: 0.1-0.3 µg/kg/min IV infusion.**
- **Onset: <5 min.**
- **Duration: 30 min.**
- **Adverse effects: Tachycardia, headache, nausea, flushing.**
- **Special indications: Most hypertensive emergencies.**
- **Caution with glaucoma.**

Hypertensive Emergency

Hydralazine:

- **Dose: 12-20 mg IV; 10-50 mg intramuscular.**
- **Onset: 10-20; 20-30 min, respectively.**
- **Duration: 1-4; 4-6 hours, respectively.**
- **Adverse effects: Tachycardia, flushing, headache vomiting, aggravation of angina.**
- **Special indications: Eclampsia.**

Hypertensive Emergency

Labetalol:

- **Dose: 20-80 mg IV bolus every 10 minutes; 0.5-2 mg/min IV infusion.**
- **Onset: 5-10 min**
- **Duration: 3-6 hours.**
- **Adverse effects: Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension.**
- **Special indications: Most hypertensive emergencies except acute heart failure or heart block.**

Therapy of Venous Thromboembolism

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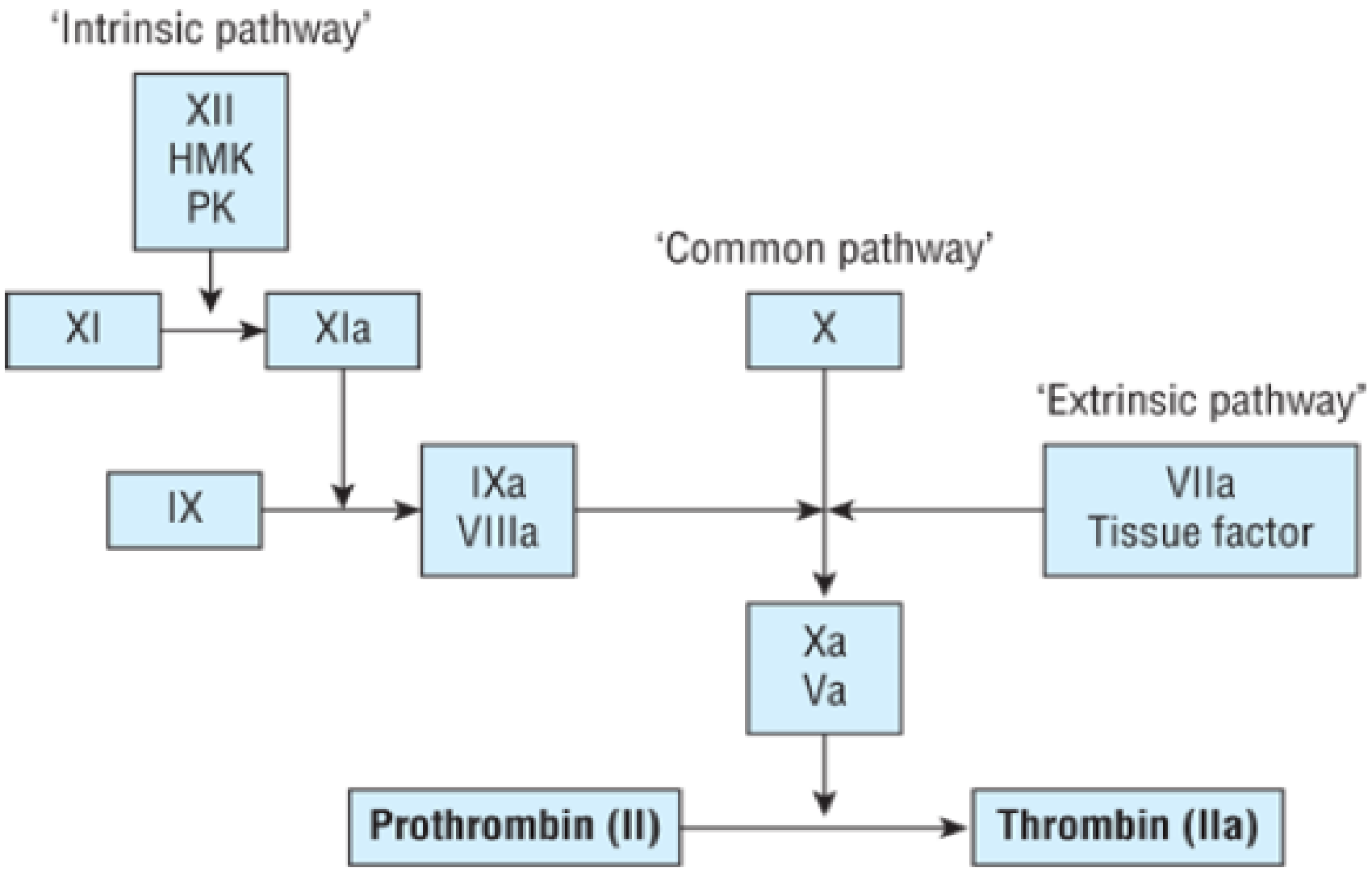
Therapy of Venous Thromboembolism

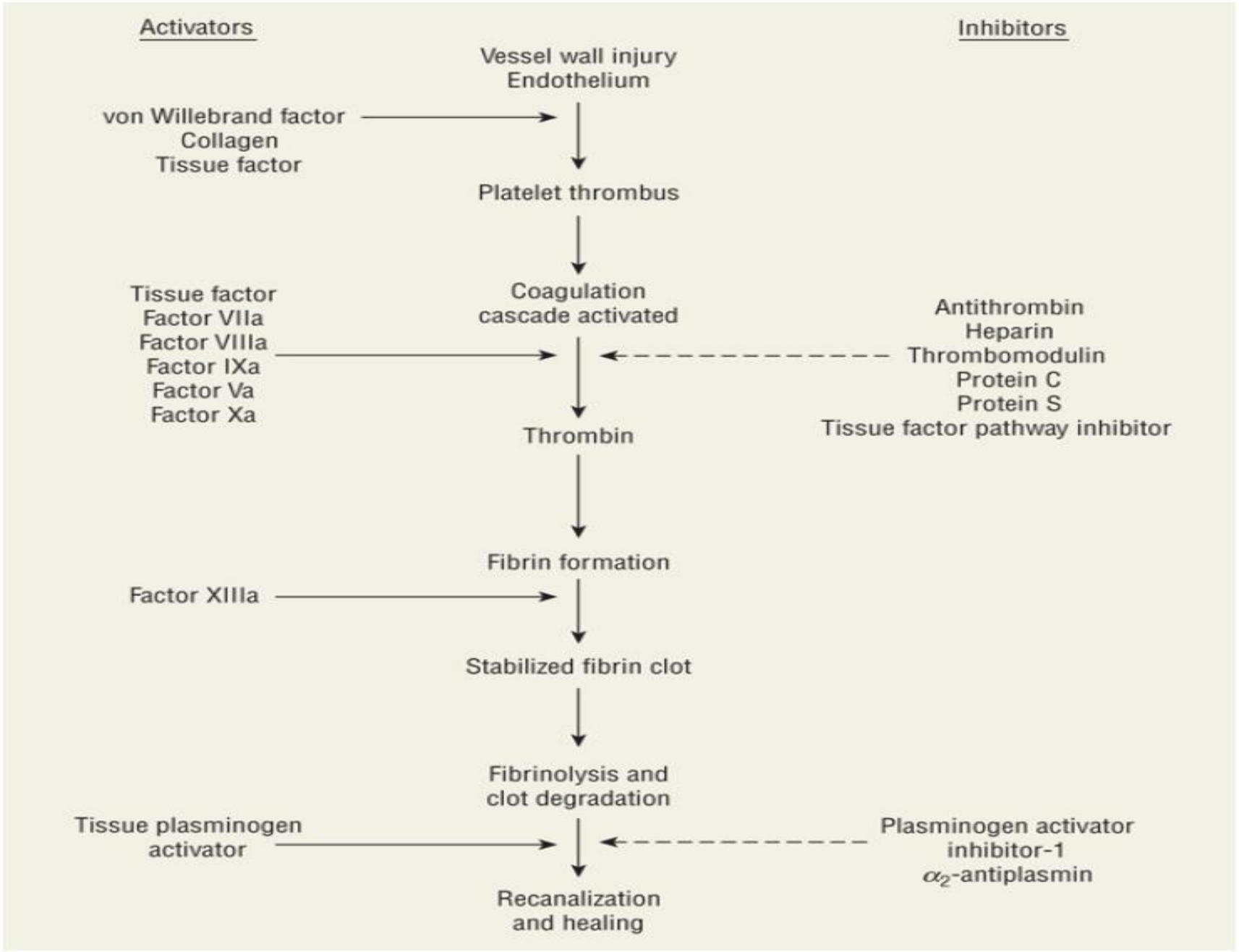
- **Venous thromboembolism (VTE) is a significant health problem and a potentially fatal disorder.**
- **VTE results from clot formation within the venous circulation and is manifested as deep vein thrombosis (DVT) and/or pulmonary embolism (PE).**

Classic depiction of the coagulation cascade.



HMK = high molecular weight kininogen; PK = prekallikrein

Overview of hemostasis.



Venous Thromboembolism Prophylaxis

Pharmacologic Prophylaxis:

- **Pharmacologic prevention significantly reduces the risk of VTE following:**

1. **hip and knee replacement**
2. **hip fracture repair**
3. **general surgery**
4. **myocardial infarction**
5. **ischemic stroke**
6. **Others.**

Venous Thromboembolism Prophylaxis

Medical Patients:

- **Hospitalized and acutely ill medical patients at high-VTE-risk and low-bleeding-risk should receive pharmacologic prophylaxis with low dose unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux during hospitalization or until fully ambulatory.**
- **Routine pharmacologic prophylaxis is NOT indicated in low-VTE-risk medical patients.**

Venous Thromboembolism Prophylaxis

Surgical Patients:

A. Preventing VTE following non-orthopedic surgery:

- **Patients at high-VTE-risk and low-bleeding-risk should receive low dose UFH or LMWH.**

B. Preventing VTE following high risk orthopedic surgery such as joint replacement surgery:

- **Aspirin, adjusted-dose warfarin, UFH, LMWH, fondaparinux, dabigatran, apixaban, or rivaroxaban for at least 10 days postsurgery.**

Therapy of Venous Thromboembolism

Treatment of Venous Thromboembolism:

- **Anticoagulation therapy is the mainstay of VTE (DVT & PE) treatment.**
- **Establish an accurate diagnosis to avoid bleeding.**
- **Then, anticoagulation therapy with a rapid-acting anticoagulant should be instituted as soon as possible.**

Therapy of Venous Thromboembolism

- **Traditionally, therapy is started with warfarin overlapped with LMWH or UFH for 5 days.**
- **Early initiation of warfarin (same day as parenteral therapy); or delayed initiation but with continuation of parenteral anticoagulation (UFH or LMWH) for a minimum of 5 days and until the international normalized ratio (INR) is ≥2 for at least 24 hours.**

Therapy of Venous Thromboembolism

- **The appropriate initial duration of therapy to effectively treat an acute first episode of VTE for all patients is 3 months.**
- **Circumstances surrounding the initial thromboembolic event, the presence of ongoing thromboembolic risk factors, bleeding risk, and patient preference determine extending anticoagulation therapy beyond 3 months.**

Clinically important bleeding risk factors

1. Age more than 75 years
2. Previous noncardioembolic stroke
3. History of gastrointestinal bleeding
4. Renal or hepatic impairment
5. Anemia
6. Thrombocytopenia
7. Concurrent antiplatelet use
8. Noncompliance
9. Poor anticoagulant control (for patients on warfarin)
10. Serious acute or chronic illness
11. The presence of structural lesions (tumor, recent surgery) that could bleed.

Therapy of Venous Thromboembolism

Unfractionated Heparin:

- **It may be administered by SC injection, or by continuous intravenous infusion.**
- **Response to UFH is highly variable, therefore, dose should be adjusted based on activated partial thromboplastin time (aPTT).**
- **Both weight-based, and fixed-UFH-dosing (5,000 unit bolus followed by 1,000 units/h continuous infusion) produce similar clinical outcomes.**

Therapy of Venous Thromboembolism

- **Intravenous UFH requires hospitalization with frequent aPTT monitoring and dose adjustment.**
- **Traditional intravenous UFH in the acute treatment of VTE may be replaced by LMWH or fondaparinux.**
- **As elimination of LMWH and fondaparinux is dependent on renal function, UFH will continue to have a role for acute VTE treatment in patients with CrCL < 30 mL/min.**

Therapy of Venous Thromboembolism

Low-Molecular-Weight Heparin:

- **Replaced UFH for initial VTE treatment due to improved pharmacokinetic and pharmacodynamic profiles and ease of use.**
- **LMWH given subcutaneously in fixed- or weight-based doses is at least as effective as UFH given intravenously for the treatment of VTE.**

Therapy of Venous Thromboembolism

- **LMWHs have reduced need for laboratory monitoring.**
- **Monitoring is indicated in obesity, pregnancy, & children by anti-Xa activity (goal anti–factor Xa levels 0.5 - 1.0 unit/mL), 4 - 6 hours following subcutaneous injection).**
- **Can be used on an outpatient basis for stable low-risk patients.**

Therapy of Venous Thromboembolism

- **In patients without cancer, acute treatment with LMWH is generally transitioned to long-term warfarin therapy after about 5 - 10 days.**
- **Rapidly reversible UFH is preferred if thrombolytic therapy or embolectomy is anticipated.**

Therapy of Venous Thromboembolism

Fondaparinux:

- **It is safe and effective alternative to LMWH for acute VTE treatment.**
- **It is dosed once daily via weight-based SC injection.**
- **Fondaparinux is contraindicated if CrCL < 30 mL/min.**

Therapy of Venous Thromboembolism

Warfarin:

- **Warfarin monotherapy is unacceptable for acute VTE treatment because the slow onset of action is associated with high incidence of recurrent thromboembolism.**
- **It is effective in the long-term VTE management provided it is started concurrently with rapid-acting parenteral anticoagulant.**

Therapy of Venous Thromboembolism

- **The initial dose of warfarin should be 5 to 10 mg for most patients and periodically adjusted to achieve and maintain an INR between 2 - 3.**

Therapy of Venous Thromboembolism

Direct Oral Anticoagulants:

- **Can be started as single-drug therapy with rivaroxaban or apixaban.**
- **Neither drug requires routine coagulation monitoring.**
- **Dabigatran and edoxaban can be used, but require prior parenteral anticoagulation.**
- **Patients with CrCL < 30 mL/min should NOT receive dabigatran, but can receive edoxaban at half the dose.**

Therapy of Venous Thromboembolism

Thrombolytic therapy:

- **Most VTE cases require only anticoagulation therapy.**
- **In rare cases the thrombus should be removed by pharmacologic or surgical means.**
- **Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin, which lyses the thrombus.**

Therapy of Venous Thromboembolism

- **Thrombolytic therapy improves early venous patency, but does not improve long-term outcomes.**
- **The same anticoagulation therapy duration and intensity is recommended as for patients with DVT not receiving thrombolysis.**
- **Patients with DVT involving the iliac and common femoral veins are at highest risk of post-thrombotic syndrome and may benefit from thrombus removal.**

Therapy of Venous Thromboembolism

- **In acute PE management successful clot dissolution with thrombolytic therapy reduces elevated pulmonary artery pressure and improves right ventricular dysfunction.**
- **The risk of death from PE should outweigh the risk of serious bleeding from thrombolytic therapy.**
- **Patients should be screened carefully for contraindications related to bleeding risk.**

Therapy of Venous Thromboembolism in Special Populations

Pregnancy

- **Anticoagulation therapy may be needed for the prevention and treatment of VTE during pregnancy.**
- **UFH and LMWH do NOT cross the placenta and are the preferred drugs.**
- **Warfarin crosses the placenta, and may produce fetal bleeding, central nervous system abnormalities, and embryopathy and should NOT be used.**
- **Pregnant women with a history of VTE should receive VTE prophylaxis for 6 to 12 weeks after delivery.**
- **Warfarin, UFH, and LMWH are safe during breast-feeding.**

Pediatric Patients

- **Venous thromboembolism in pediatric patients is increasing secondary to prematurity, cancer, trauma, surgery, congenital heart disease, and systemic lupus erythematosus.**
- **Pediatric patients rarely experience unprovoked VTE, but often develop DVT associated with indwelling central venous catheters.**

Pediatric Patients

- **Anticoagulation with UFH and warfarin is similar to that of adults.**
- **Obtaining blood for coagulation monitoring tests is problematic in some patients because of poor venous access.**
- **LMWH is preferred in pediatric patients due to low drug interaction potential and less frequent laboratory testing.**

Pediatric Patients

- **LMWHs should be monitored by anti-Xa activity (goal anti–factor Xa levels 0.5 - 1.0 unit/mL), 4 to 6 hours following subcutaneous injection).**
- **Warfarin can be started with UFH or LMWH therapy, which should be overlapped for 5 days and until the INR is therapeutic.**

Pediatric Patients

- **Warfarin should be continued for at least 3 months for provoked VTE and 6 months for unprovoked VTE.**
- **Routine use of thrombolysis and thrombectomy is NOT recommended in children.**

Patients with Cancer

- **Cancer-related VTE is associated with 3-fold higher rates of recurrent VTE, (2.5 – 6)-fold higher rates of bleeding, and more resistance to standard warfarin-based therapy compared to patients without cancer.**
- **Warfarin therapy in cancer patients is often complicated by drug interactions (chemotherapy and antibiotics) and the need to interrupt therapy for invasive procedures.**
- **Maintaining stable INR control is also more difficult in these patients because of nausea, anorexia, and vomiting.**

Patients with Cancer

- **Long-term LMWH monotherapy for cancer-related VTE decreases recurrent VTE rates without increasing bleeding risks compared with warfarin-based therapy.**
- **LMWH therapy should be used for at least the first 3 - 6 months of long-term treatment, at which time LMWH can be continued or warfarin therapy substituted.**
- **Anticoagulation therapy should continue for as long as the cancer is "active" and while the patient is receiving antitumor therapy.**

Patients with Cancer

- **Because of the diversity of cancer, the above recommendations may vary.**
- **See this site if you are interested.**

https://www.acc.org/latest-in-cardiology/articles/2020/05/05/08/31/treatment-of-malignancy-associated-venous-thromboembolism

Patients with Renal Insufficiency

- **UFH is preferred for acute VTE treatment in renal dysfunction.**
- **LMWH, fondaparinux, and direct-acting anticoagulants (DOACs) accumulate in renal dysfunction.**
- **LMWHs should be used with caution in patients with CrCL < 30 mL/min.**
- **DOACs require dose adjustment in renal impairment, and should be avoided in patients with CrCL < 30 mL/min (less than 25 mL/min for apixaban).**
- **Patients with chronic kidney disease are at increased risk of bleeding from other causes.**

Anticoagulant Drug Classes

Unfractionated Heparin

Pharmacology/Mechanism of Action:

- **Unfractionated heparin is a heterogeneous mixture of sulfated mucopolysaccharides of variable lengths.**
- **The anticoagulant effect of UFH is mediated through a specific pentasaccharide sequence that binds to antithrombin.**

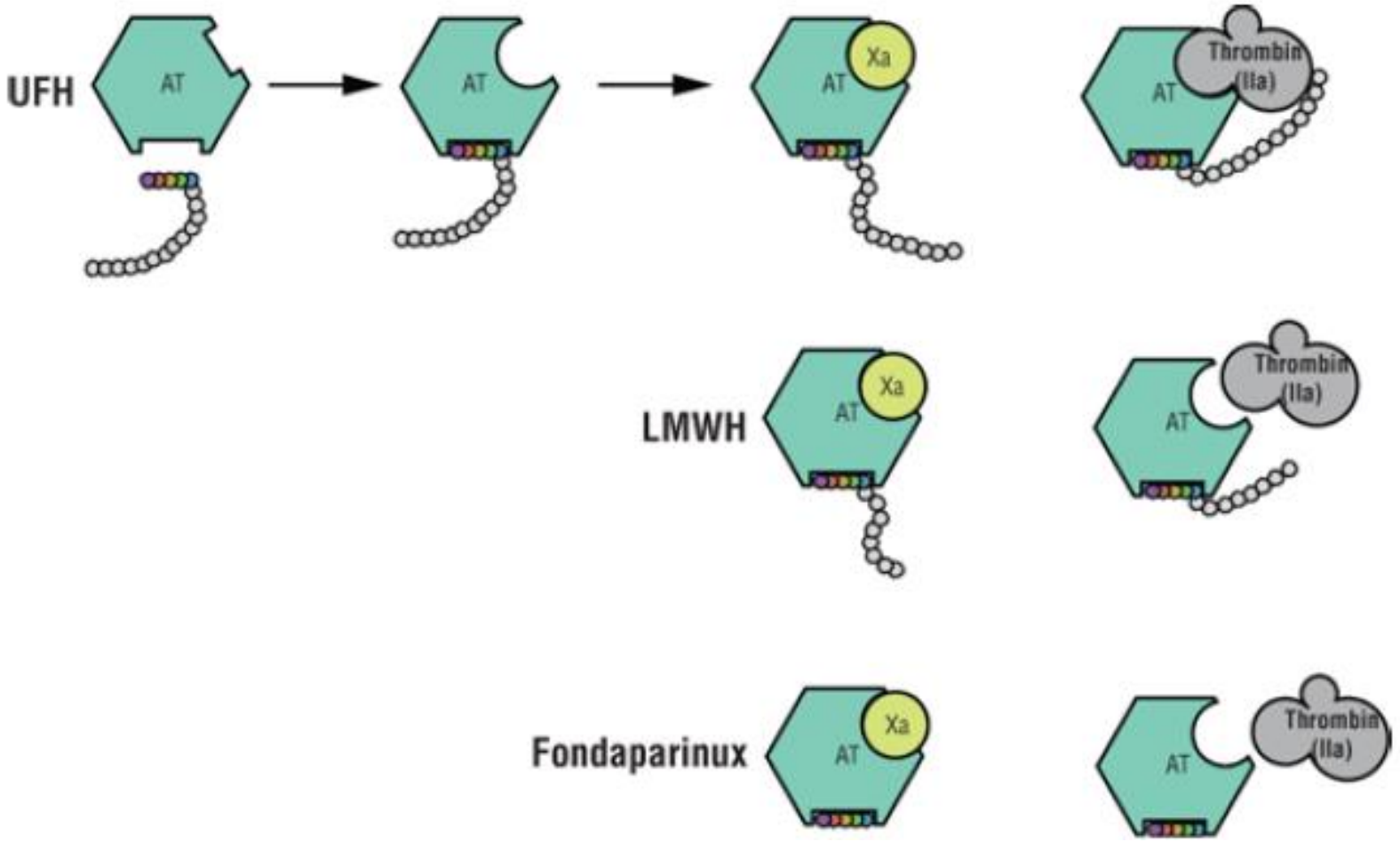
Unfractionated Heparin

- UFH accelerates the anticoagulant action of antithrombin 100 - 1,000 times.
- Antithrombin inhibits factor IIa, IXa, Xa, and XIIa activity.
- UFH prevents thrombus growth and propagation allowing endogenous thrombolytic systems to dissolve the clot.
- Thrombin (IIa) and Xa are most sensitive to UFH–antithrombin complex inhibition.

Unfractionated Heparin

- **To inactivate thrombin (IIa), the heparin molecule must form a ternary complex bridging between antithrombin and thrombin.**
- **The inactivation of factor Xa does NOT require UFH to form a bridge with antithrombin, but requires only UFH binding to antithrombin via the specific pentasaccharide sequence.**

Pharmacologic activity of unfractionated heparin, low-molecular-weight heparins (LMWHs), and fondaparinux



Unfractionated Heparin

- **It is preferred to administer UFH by continuous intravenous infusion.**
- **The onset of action of UFH after SC injection is 1 - 2 hours, peaking at 3 hours.**
- **Intramuscular administration should NOT be used because of the risk of bleeding & hematomas.**
- **UFH has a dose-dependent half-life of ~ 30 - 90 minutes, because its elimination follows zero-order kinetics.**

Unfractionated Heparin

Adverse Effects:

1. **bleeding:**

- **Protamine sulfate in a dose of 1 mg per 100 units of UFH (maximum of 50 mg) can be administered via slow intravenous infusion to reverse the anticoagulant effects of UFH. Protamine sulfate neutralizes UFH in 5 minutes, and action persists for 2 hours.**

Unfractionated Heparin

2. **Heparin-induced thrombocytopenia (HIT):**

- **Due to heparin-induced thrombocytopenia caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF4). These antibodies are prothrombotic and activate platelets.**
- **Leads to arterial thromboembolic events.**
- **Occur in 5 - 10 days after initiation of UFH.**
- **Alternative anticoagulation: direct thrombin inhibitors.**

Unfractionated Heparin

- **[Thrombosis seen with some *Covid*-19 vaccine is similar to HIT. It is mediated by antibodies to platelet factor 4-polyanion complexes. It represents vaccine-related variant of HIT. It is called "vaccine-induced immune thrombotic thrombocytopenia"].**

Unfractionated Heparin

3. **Significant bone loss and osteoporosis when used for more than 6 months (pregnancy).**

Drug–drug Interactions:

- **Concurrent use with other anticoagulant, thrombolytic, and antiplatelet agents increases bleeding risk.**

Low-Molecular-Weight Heparins (LMWHs)

(Enoxaparin, Dalteparin):

- **LMWH is produced by depolymerization of UFH.**
- **Have ~ one-third the mean UFH molecular weight.**

Advantages include:

a) **predictable anticoagulation dose response.**
b) **improved subcutaneous bioavailability.**
c) **dose-independent elimination (first-order).**
d) **longer half-life.**
e) **reduced need for routine laboratory monitoring.**

LMWHs

- **Low-molecular-weight heparin prevents thrombus growth and propagation by enhancing and accelerating the activity of antithrombin against factor Xa.**
- **Because of smaller chain lengths, LMWH has limited activity against thrombin (IIa).**

LMWHs

- **The bioavailability of LMWH is ~ 90% after SC injection.**
- **The peak anticoagulation at 3 - 5 hours.**
- **Mainly eliminated by renal excretion.**
- **The half-life of LMWHs is ~ 3 - 6 hours.**
- **Half-life may be prolonged in patients with renal impairment.**

LMWHs

Adverse Effects:

1. **Bleeding.**

- **IV protamine sulfate can be administered as antidote.**

2. **HIT is three times lower than that observed with UFH.**

- **LMWH should be avoided in patients with HIT, because of cross reactivity with antibodies.**

3. **Osteoporosis and osteopenia.**

LMWHs

Drug–drug Interactions:

- **Other anticoagulant, thrombolytics, antiplatelet agents, aspirin, NSAIDs, dipyridamole, or sulfinpyrazone enhance bleeding risk.**

Fondaparinux

- **Fondaparinux is a synthetic molecule consisting of the active pentasaccharide units that bind reversibly to antithrombin.**
- **It inhibits only factor Xa activity.**
- **It is effective in prevention of VTE.**

Fondaparinux

Pharmacokinetics:

- **It is rapidly and completely absorbed following SC administration, peak concentrations ~ 2 hours after a single dose and 3 hours with repeated once-daily dosing.**
- **It is eliminated unchanged in the urine, elimination half-life is ~19 hours.**
- **The anticoagulant effect of fondaparinux persists for 2 to 4 days following discontinuation of the drug in patients with normal renal function.**

Fondaparinux

Adverse Effects:

1. Bleeding.
2. Rare cause of HIT.

- No antidote to reverse its antithrombotic activity.

Drug–drug Interactions:

- Other drugs with anticoagulant, fibrinolytic, or antiplatelet activity increase the risk of bleeding.

Lepirudin

- **Hirudin** is derived from Leech.
- **Lepirudin** is from recombinant DNA technology.
- **Irreversible inhibitor, inactivates fibrin-bound thrombin.**
- **Used IV or SC.**
- **Monitored by aPTT.**
- **Eliminated by hepatic metabolism and renal excretion, accumulates in RF.**
- **Used for thrombosis related to HIT.**
- **No antidote is available.**

Bivalirudin

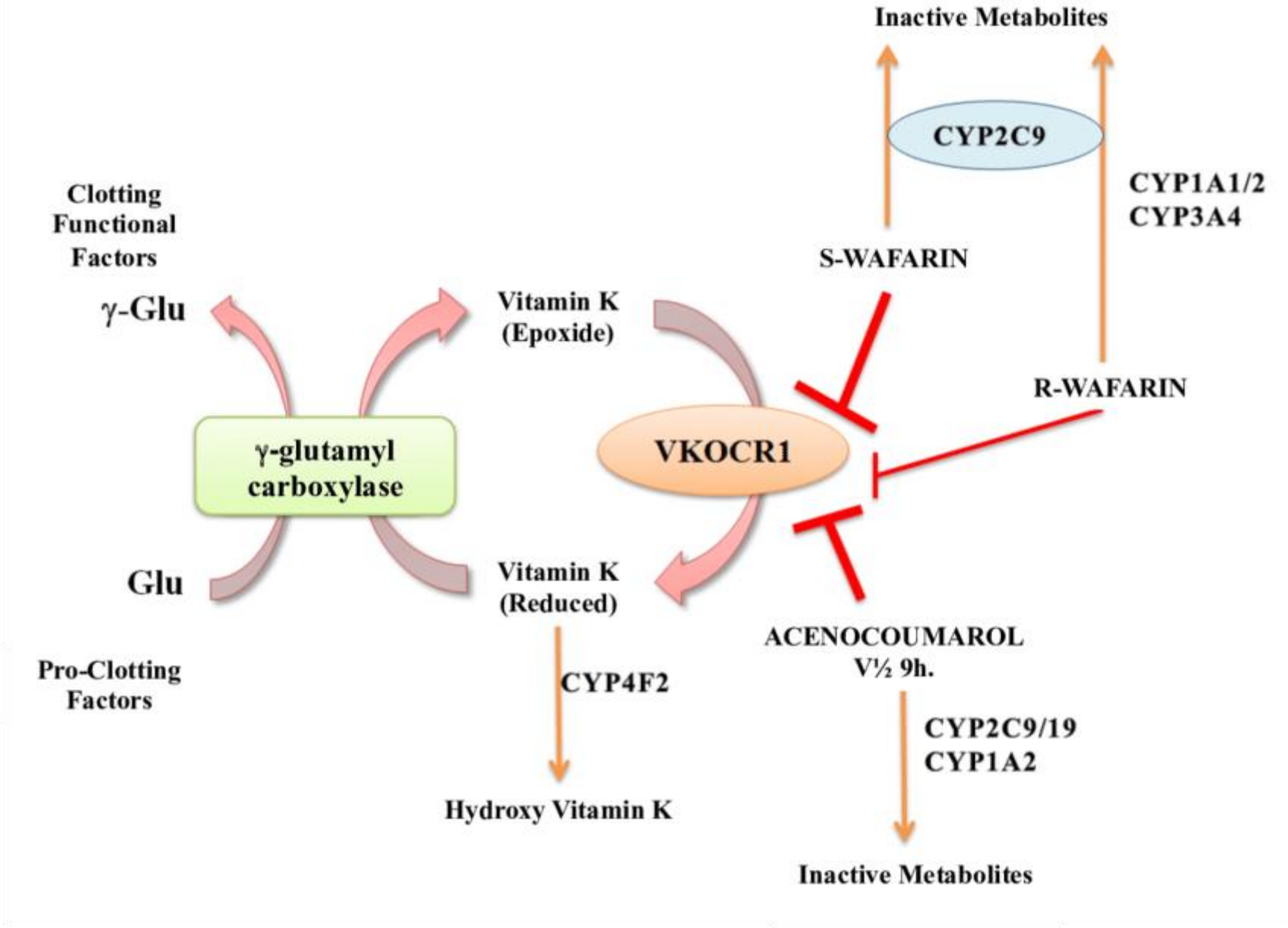
- **Bivalirudin is a direct thrombin inhibitor.**
- **It is a synthetic congener of the naturally occurring anticoagulant hirudin.**
- **Used IV.**
- **Elimination half-life is ~ 25 min.**
- **Cleared by hepatic and renal elimination and proteolytic cleavage.**
- **It inhibits both circulating and clot-bound thrombin, reversibly.**
- **Thus, it has less bleeding risk than other r-hirudins.**

Bivalirudin

- **It also inhibits thrombin-mediated platelet activation and aggregation.**
- **Used in PCI and for HIT.**
- **Monitored by "thrombin inhibitor assay" which is better than aPTT because it is NOT affected by antiphospholipid antibodies.**
- **It is contraindicated in severe renal impairment.**

Warfarin

- **Vitamin K in its reduced form is a required cofactor for vitamin K-dependent carboxylation of factors II, VII, IX, and X, as well as the endogenous anticoagulant proteins C and S; which is required for their biologic activity.**
- **Warfarin inhibits the reduction of vitamin K epoxide, reducing the formation of complete functioning clotting factors.**
- **It has NO effect on preformed clotting factors, thus, full antithrombotic effect is NOT achieved for at least 6 days after warfarin therapy initiation.**


Inactive Metabolites
CYP2C9
CYP1A1/2
CYP3A4
Clotting
Functional
Factors
γ-Glu
S-WAFARIN
Vitamin K
(Epoxide)
R-WAFARIN
γ-glutamyl
carboxylase
VKOCR1
Glu
Vitamin K
(Reduced)
ACENOCOUMAROL
V½ 9h.
Pro-Clotting
Factors
CYP4F2
CYP2C9/19
CYP1A2
Hydroxy Vitamin K
Inactive Metabolites

Warfarin

- **The time required for warfarin to achieve its pharmacologic effect is dependent on coagulation protein elimination half-lives (6 hours for factor VII and 72 hours for prothrombin).**
- **Because of its narrow therapeutic index, predisposition to drug and food interactions, and exacerbation of bleeding, warfarin requires continuous patient monitoring and education to achieve optimal outcomes.**

Half-Lives

Factor	Half-life (~ hours)
II	72
VII	6
IX	24
X	40
Protein C	8
Protein S	30

Warfarin

Adverse Effects:

1. **Bleeding (mild to life threatening).**

- **Vitamin K is the antidote, can be given parenterally or orally; the oral route is preferred in the absence of serious bleeding.**
- **In case of bleeding, warfarin should be temporarily stopped or the dose reduced.**

Warfarin

2. **“Purple toe syndrome” is thought to be the result of cholesterol microembolization into the arterial circulation of the toes.**
3. **Warfarin-induced skin necrosis (due to thrombosis) in the first week of therapy (starts as a painful maculopapular rash and ecchymosis or purpura that progresses to necrotic gangrene).**

- **Areas of the body rich in subcutaneous fat are most commonly affected (breasts, thighs, buttocks, and abdomen).**

Warfarin Drug–drug and Drug–food Interactions

Pharmacodynamic Interaction	Mechanism
ASA/NSAIDs	Antiplatelet, GI injury
Clopidogrel/TIclopidine	Antiplatelet
Tramadol	INR elevation (mech. Unknown)
Levothyroxine	Increased catabolism of clotting factors
Vitamin K containing food/Supplements	INR reduction (reverse warfarin mechanism of action)

INR Elevation	INR Reduction
Amiodarone	Rifampin
Fluoroquinolones	Barbiturates
Trimethoprim/sulfamethoxazole	Carbamazepine
Metronidazole	Phenytoin
Azole antifungals	St John's wort
Statins	Cigarette smoking
Isoniazid	Charcoal broiled food
NSAIDs	Cholestyramine (Bile acid binding resins)
Sertraline Gemfibrozil	Oral contraceptives (Estrogens)
Ethanol	Ginseng
Macrolides	Green tea
Cimetidine	Avocado
Omeprazole	Spinach & leafy green vegs.
Fluorouracil	Brocolli, Cabbage, Brussels sprouts, Red-leaf lettuce
Garlic	
Ginkgo	
Vitamin E	

Open this site or link to see tables for more comprehensive description of drug and food interactions with warfarin

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/486574

Pharmacogenomics

- **CYP2C9 is the hepatic microsomal enzyme responsible for metabolism of the more potent S-enantionmer of warfarin.**
- **Polymorphisms in CYP2C9 and the gene coding for VKOR (Vitamin K Epoxide Reductase) explain a substantial proportion of warfarin dose variability between patients.**
- **Poor metabolizer subtypes have been associated with increased risk of bleeding.**
- **Warfarin resistance can be due to mutations in the receptor gene.**
- **For individualized warfarin dosing consult (www.warfarindosing.org).**

Direct Oral Anticoagulants

(DOACs):

- **Rivaroxaban, apixaban, and edoxaban are potent and selective inhibitors of both free and clot-bound factor Xa.**
- **They do not require antithrombin to exert their anticoagulant effect.**
- **Dabigatran (prodrug) is a selective, reversible, direct factor IIa inhibitor.**

Direct Oral Anticoagulants

- These drugs are partially eliminated by the kidney to various extent, and should be used with caution in patients with renal dysfunction.
- Terminal half-lives ~10 hours for the Factor Xa inhibitors, and 16 hours for dabigatran.
- Rivaroxaban and apixaban are substrates of cytochrome CYP3A4, and P-glycoprotein.

Direct Oral Anticoagulants

Indications:

1. **The Xa inhibitors rivaroxaban and apixaban can prevent VTE following hip or knee replacement surgery.**
2. **Dabigatran, rivaroxaban and apixaban can be used for extended VTE treatment after the first 6 months of anticoagulant therapy.**

Direct Oral Anticoagulants

Adverse Effects:

1. **Gastrointestinal complaints.**
2. **Bleeding which ranges from minor – severe & fatal.**

- **Discontinuation of therapy and supportive management.**
- **Activated charcoal may provide some benefits if drug intake occurred within 2 hours of presentation, and dabigatran is hemodializable.**

Direct Oral Anticoagulants

- **Idarucizumab rapidly reverses the dabigatran anticoagulant effect following IV administration.**
- **It binds to dabigatran and its acylglucuronide with higher affinity than that of dabigatran to thrombin.**
- **It is used in life-threatening bleeding and when there is need for urgent surgical intervention.**

Direct Oral Anticoagulants

Drug–drug and Drug–food Interactions:

- **DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers.**
- **Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP3A4.**

Direct Oral Anticoagulants

Renal Function:

- **Periodic renal function assessment is important during long-term DOAC therapy, especially for patients with CrCL < 50 mL/min.**
- **DOACs should NOT be used in patients with CrCL < 25 mL/min (apixaban) or < 30 mL/min (rivaroxaban and dabigatran).**
- **Edoxaban dosing should be reduced in patients with CrCL 15 - 50 mL/min**

Therapy of Infections in Neutropenic Patients

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Introduction

An immunocompromised host is a patient with defects in host defenses that predispose to infection.

Risk factors include:

1. **Neutropenia.**
2. **Immune system defects (from disease or immunosuppressive drug therapy).**
3. **Compromise of natural host defenses.**
4. **Environmental contamination.**
5. **Changes in the normal flora of the host.**

Risk Factors for Infection

1. Neutropenia:

- **Neutropenia is defined as an abnormally reduced number of neutrophils circulating in peripheral blood.**
- **An absolute neutrophil count (ANC) of less than 1,000 cells/mm^3 indicates a reduction sufficient to predispose patients to infection.**
- **The development of infection depends on:**

a) **the severity of neutropenia.**

b) **the rate of neutrophil decline.**

c) **the duration of neutropenia.**

Risk Factors for Infection

- **All neutropenic patients are considered to be at risk for infection, but those with ANC less than 500 cells/mm^3 are at greater risk than those with ANCs of 500 - 1,000 cells/mm^3.**
- **Bacteria and fungi commonly cause infections in neutropenic patients.**

Risk Factors for Infection

2. Immune System Defects:

- **Defects in T-lymphocyte and macrophage function (cell-mediated immunity), B-cell function (humoral immunity), or both predispose patients to infection.**

Risk Factors for Infection

3. Destruction of Protective Barriers:

- **This is a major factor predisposing immunocompromised patients to infection.**

a) **Damage to skin and mucous membranes by surgery, venipuncture, IV and urinary catheters, radiation, and chemotherapy.**

b) **Chemotherapy-induced mucositis of the oropharynx and GIT establish a portal for subsequent infection by bacteria, HSV, and *Candida*.**

Risk Factors for Infection

c) **Medical and surgical procedures, such as transplant surgery, indwelling IV catheter placement, bone marrow aspiration, biopsies, and endoscopy, further damage the skin & mucous membranes and predispose patients to infection.**

- **Infections resulting from disruption of protective barriers usually are caused by skin flora such as *S. aureus*, *S. epidermidis*, and various streptococci.**

Risk Factors for Infection

4. Environmental contamination:

- **Contaminated equipment such as nebulizers and ventilators, and contaminated water supplies predispose for outbreaks of *P. aeruginosa* and *Legionella pneumophila* infections, respectively.**
- **Fruits and green leafy vegetables are sources of gram negative bacteria and fungal infections in immunocompromised hosts.**

Risk Factors for Infection

5. **Changes in the normal microbial flora of the host:**

- **Administration of broad-spectrum antimicrobial agents disrupts GIT flora and predisposes patients to infection with more virulent pathogens.**
- **Antineoplastic drugs (cyclophosphamide, doxorubicin, and fluorouracil, …) and acid-suppressive therapy (histamine H_2-receptor antagonists, proton-pump inhibitors, and antacids) also may disrupt GIT flora and predispose to infection.**

Risk Factors and Common Pathogens in Immunocompromised Patients

Risk Factor	Patient Condition	Common Pathogens
Neutropenia	Acute leukemia Chemotherapy	Bacteria: Staphylococcus aureus, Staphylococcus epidermidis, and other coagulase-negative staphylococci, streptococci, enterococci are most common, followed by Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Fungi: Candida, Aspergillus, Mucorales (Mucor) Viruses: Herpes simplex
Impaired cell-mediated immunity	Lymphoma Immunosuppressive therapy (steroids, cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine and anti-neoplastic agents	Bacteria: Listeria, Nocardia, Legionella, Mycobacteria Fungi: Cryptococcus neoformans, Candida, Aspergillus, Histoplasma capsulatum Viruses: Cytomegalovirus, varicella-zoster, herpes simplex Pneumocystis jiroveci **Yeast-like fungus**
Impaired humoral immunity	Multiple myeloma, Chronic lymphocytic leukemia (have progressive hypogammaglobulinemia) Splenectomy Immunosuppressive therapy (steroids, chemotherapy)	Bacteria: encapsulated organisms such as S. pneumoniae, H. influenzae, N. meningitidis Which might produce life-threatening infections

Loss of protective skin barriers	Venipuncture, bone marrow aspiration, urinary catheterization, vascular access devices, radiation, biopsies	Bacteria: S. aureus, S. epidermidis, Bacillus spp., Corynebacterium jeikeium Fungi: Candida
Loss of protective mucous membranes barriers	Respiratory support equipment, endoscopy, chemotherapy, radiation	Bacteria: S. aureus, S. epidermidis, streptococci, Enterobacteriaceae, P. aeruginosa, Bacteroides spp. Fungi: Candida Viruses: Herpes simplex
Surgery	Solid-organ transplantation	Bacteria: S. aureus, S. epidermidis, Enterobacteriaceae, P. aeruginosa, Bacteroides spp. Fungi: Candida Viruses: Herpes simplex
Alteration of normal microbial flora	Antimicrobial therapy Chemotherapy **Acid –lowering agents** Hospital environment	Bacteria: Enterobacteriaceae, P. aeruginosa, Legionella, S. aureus, S. epidermidis Fungi: Candida, Aspergillus
Blood products, donor organs	Bone marrow transplantation Solid-organ transplantation	Fungi: Candida Viruses: Cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C Protozoa: Toxoplasma gondii

Management of Febrile Episodes in Neutropenic Patients

Goals of therapy:

1. **Protect the patient from early death caused by undiagnosed infection.**
2. **Prevent breakthrough bacterial, fungal and viral infections during periods of neutropenia.**
3. **Effectively treat established infections.**
4. **Reduce morbidity.**

Management of Febrile Episodes in Neutropenic Patients

5. **Avoid unnecessary use of antimicrobials that contribute to increased resistance.**
6. **Minimize toxicities and cost of antimicrobial therapy while increasing patient quality of life.**

- **Empirical broad-spectrum antibiotic therapy is effective at reducing early mortality.**

Management of Febrile Episodes in Neutropenic Patients

Approach to Treatment:

- **Both treatment and prophylaxis of infectious complications, can be extremely challenging.**
- **Although published guidelines are available, the most optimal clinical management of these patients remains unclear in many aspects.**
- **Fever in the neutropenic patient should be considered to be due to infection until proven otherwise.**

Management of Febrile Episodes in Neutropenic Patients

1. High-dose broad-spectrum bactericidal, parenteral, empirical antibiotic therapy should be initiated at the onset of fever or at the first signs or symptoms of infection.

a) Withholding antibiotic therapy until an organism is isolated results in unacceptably high mortality rates.

Management of Febrile Episodes in Neutropenic Patients

b) Undiagnosed infection in immunocompromised patients can rapidly disseminate and results in death.

c) Empirical antibiotic therapy is 70-90% effective at reducing early morbidity and mortality.

2. Antimicrobial therapy must be appropriate and should be initiated promptly in afebrile patients with clinical signs and symptoms of infection.

Management of Febrile Episodes in Neutropenic Patients

3. When designing optimal empirical antibiotic regimens, physicians must consider infection patterns and antimicrobial susceptibility trends in their respective institutions.
4. Patient factors such as, risk of infection, drug allergies, concomitant nephrotoxins, and previous antimicrobial exposure (including prophylaxis) must be considered.

Management of Febrile Episodes in Neutropenic Patients

5. **Risk stratification drives both type and setting of antimicrobial therapy:**

I. **Low-risk patients:**

a) **have an anticipated duration of neutropenia ≤ 7 days.**

b) **are clinically stable.**

c) **have no or few co-morbidities.**

d) **have no bacterial focus or systemic signs of infection other than fever.**

Management of Febrile Episodes in Neutropenic Patients

II. High-risk patients:

a) are those with an anticipated duration of neutropenia of > 7 days

b) have profound neutropenia

c) are clinically unstable

d) have comorbid medical problems (focal or systemic signs of infection, GI symptoms, nausea, vomiting, diarrhea, hypoxemia, and chronic lung disease), or have a high-risk cancer (acute leukemia) and/or have undergone high intensity chemotherapy.

Management of Febrile Episodes in Neutropenic Patients

- **High-risk patients should be hospitalized for parenteral antibiotics, whereas low-risk patients may be candidates for oral or outpatient antibiotics.**
- **Because of their frequency and relative pathogenicity, *P. aeruginosa* and other gram-negative bacilli and *staphylococci* are the primary targets of empirical antimicrobial therapy.**

Management of Febrile Episodes in Neutropenic Patients

- **The optimal antibiotic regimen remains controversial.**
- **All empirical regimens must be: carefully monitored and appropriately revised on the basis of documented infections, susceptibilities of bacterial isolates, development of more defined clinical signs and symptoms of infection, or a combination of these factors.**

Management of Febrile Episodes in Neutropenic Patients

Recognized antibiotic regimens:

1. **Monotherapy with an antipseudomonal β-lactam (cefepime or ceftazidime), a carbapenem (imipenem–cilastatin or meropenem), or piperacillin–tazobactam. Disadvantages: limited gram positive activity, and high rate of superinfection).**
2. **Two-drug combination therapy with an antipseudomonal β-lactam + either an aminoglycoside or an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin).**
3. **Monotherapy or two-drug combination therapy as above, + the addition of vancomycin.**

Management of Febrile Episodes in Neutropenic Patients

- **There is no significant difference, overall, between monotherapy and combination therapy (β-lactam/aminoglycoside) in rates of survival, response, and bacterial/fungal superinfections.**
- **A higher rate of adverse effects was observed in aminoglycoside-containing combination regimens.**
- **Cefepime and antipseudomonal carbapenems have good activity against viridans streptococci and pneumococci but not all gram positive bacteria.**

Management of Febrile Episodes in Neutropenic Patients

Disadvantages:

Regimen 1:

limited gram positive activity, and high rate of superinfection).

Regimen 2:

1. Antipseudomonal β-lactam +aminoglycoside: limited gram positive activity, potential for nephrotoxicity and need of TDM.
2. Antipseudomonal β-lactam + fluoroquinolone: limited gram positive activity and development of resistance.

Regimen 3:

Selection of vancomycin resistant enterococci, risk of nephrotoxicity and need for TDM.

Management of Febrile Episodes in Neutropenic Patients

Oral antibiotic regimen for low risk patients:

Ciprofloxacin or levofloxacin + amoxicillin-clavulanate or clindamycin.

Disadvantages:

1) **Least studied.**
2) **Requires compliant patients with 24-hour access to medical care in case it is needed.**
3) **Requires supporting home environment.**

Antimicrobial Therapy After Initiation of Empirical Therapy

- After 2 to 4 days of empirical antimicrobial therapy, the clinical status and culture results should be reevaluated to determine whether therapeutic modifications are necessary.
- During periods of neutropenia, patients should continue to receive broad-spectrum therapy because of risk of secondary infections or breakthrough bacteremia when antimicrobial coverage is too narrow.

Antimicrobial Therapy After Initiation of Empirical Therapy

- **Duration of treatment should be appropriate for the particular organism and site, and should continue for at least the duration of neutropenia (until ANC ≥ 500 cells/mm^3) or longer if clinically necessary.**
- **In patients who become afebrile after 2 to 4 days of therapy with NO infection identified, continue antibiotic therapy until neutropenia has resolved (ANC ≥ 500 cells/mm^3).**

Antimicrobial Therapy After Initiation of Empirical Therapy

- **You may switch therapy to an oral regimen (ciprofloxacin plus amoxicillin–clavulanate) after 2 days of IV therapy, in low-risk patients who become afebrile and who have NO evidence of infection.**
- **In high-risk patients, parenteral antibiotic regimens should be continued until resolution of neutropenia.**

Antimicrobial Therapy After Initiation of Empirical Therapy

Fever after 2 or more days of antibiotic therapy can be due to:

1) nonbacterial infection
2) resistant bacterial infection or infection slow to respond to therapy
3) emergence of a secondary infection
4) inadequate drug concentrations
5) drug fever
6) infection at a non-vascular site (catheter infection or abscess)
7) noninfectious causes such as:

a. tumors
b. administration of blood products

Antimicrobial Therapy After Initiation of Empirical Therapy

- Persistently febrile patients should be evaluated carefully, but modifications generally are NOT made to initial antimicrobial regimens within the first 2 to 4 days of therapy unless there is evidence of clinical deterioration.
- Antibiotic regimens may require modification in patients experiencing toxicities as well as in patients with evidence of progressive disease, clinical instability, or documentation of an organism NOT covered by the initial regimen.

Antimicrobial Therapy After Initiation of Empirical Therapy

- **Addition of vancomycin should be considered, if NOT already part of the regimen.**
- **If vancomycin was included in the initial empirical regimen and the patient is still febrile after 2 to 3 days of therapy without isolating a gram-positive pathogen, discontinuation of vancomycin should be considered to reduce the risk of toxicities or resistance.**

Initiation of Antifungal Therapy

- **Neutropenic patients who remain febrile despite > 4 - 7 days of broad-spectrum antibiotic therapy are candidates for antifungal therapy.**
- **A significant percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy, even when they have NO evidence of fungal disease before death.**

Initiation of Antifungal Therapy

- **Persistence of fever or development of a new fever during broad-spectrum antibiotic therapy may indicate the presence of a fungal infection, most commonly *Candida* or *Aspergillus* spp.**
- **Blood cultures for fungi are positive in < 50% of neutropenic patients with invasive fungal infections, and waiting for isolation of fungal organisms is associated with high morbidity and mortality.**

Initiation of Antifungal Therapy

- **Empirical antifungal therapy, thus, should be initiated after 4 to 7 days of broad-spectrum antibiotic therapy in persistently febrile patients if the duration of neutropenia is expected to be greater than 1 week.**
- **Antifungal therapy must be adequate to treat undiagnosed fungal infection and prevent fungal superinfection in high-risk patients.**

Initiation of Antifungal Therapy

- **Empirical coverage for both *Candida* spp. and *Aspergillus* should be considered because these organisms are responsible for more than 90% of fungal infections in neutropenic patients.**

Initiation of Antifungal Therapy

- *Aspergillus* is particularly common in patients with hematologic malignancies and amphotericin B is the preferred agent.
- Lipid-associated amphotericin B (LAMB) products are similar in efficacy to conventional amphotericin B while causing fewer toxicities, and can be used at higher doses (3 mg/kg).
- LAMB products have significantly higher cost.

Initiation of Antifungal Therapy

- **The azole compounds are associated with emergence of resistant *Candida* strains.**
- **Fluconazole has good activity against *C. albicans* but lacks activity against *Aspergillus*.**
- **Voriconazole is a preferred agent for invasive aspergillosis (especially pulmonary) due to improved survival and less toxicity when compared to amphotericin B.**

Initiation of Antifungal Therapy

- **Posaconazole has extended activity against some *Mucorales,* in addition to *Candida* and *Aspergillus*, but is only approved for prophylaxis of *Aspergillus* and *Candidal* infections in neutropenic patients.**
- **TDM is recommended for some azole antifungals given the potential for interpatient variability, therapeutic failure associated with subtherapeutic concentrations, and toxicities associated with supratherapeutic concentrations.**

Initiation of Antifungal Therapy

- **The echinocandin antifungals (caspofungin, micafungin, and anidulafungin) have broad spectrum of antifungal activity and favorable adverse effect profiles.**
- **Caspofungin is as effective as, and better tolerated than, liposomal amphotericin B for empirical treatment of neutropenic patients with persistent fever. Therefore, it is considered an appropriate alternative to LAMB and voriconazole.**

Monitoring of Antifungal Agents

Drug	Adverse Reaction	Monitoring Parameters	Comments
Amphotericin B (lipid-associated)	Nephrotoxicity, hepatotoxicity, electrolyte disturbances, infusion reactions	Serum creatinine, electrolytes, LFTs, blood pressure, heart rate	Liposomal preparations associated with less renal toxicity, similar efficacy to standard preparation. Electrolyte disturbances occur before creatinine alterations. Pretreatment and slow infusion may decrease incidence of infusion reaction

Posaconazole	**Hepatotoxicity, rash; interactions with CYP3A4**	**LFTs, skin, posaconazole serum concentrations**	**Poor absorption with suspension, goals of >1 µg/mL for treatment and >0.7 µg /mL for prophylaxis. Parenteral formulation not recommended for patients with CrCL <50 mL/min. Multiple interactions with drugs metabolized by CYP 3A4, including immunosuppressants; close monitoring needed.**
Voriconazole	**Mental status changes, headache, hallucinations, visual disturbances, hepatotoxicity, QTc prolongation; interactions with CYPs 2C9, 2C19, and 3A4**	**Mental status, visual function, LFTs, ECG, voriconazole serum concentrations**	**Mental status/visual changes associated with elevated troughs > 5.5 µg /m; goal trough 1-5.5 µg/mL for treatment and prophylaxis, target trough of > 2 µg/ml in disease with poor prognosis. Parenteral formulation not recommended for patients with CrCL<50 mL/min. Multiple interactions**

Initiation of Antiviral Therapy

- **Febrile neutropenic patients with vesicular or ulcerative skin or mucosal lesions should be evaluated carefully for infection due to herpes simplex virus (HSV) or varicella-zoster virus (VZV).**
- **Mucosal lesions from viral infections provide a portal of entry for bacteria and fungi during periods of immunosuppression.**
- **If viral infection is presumed or documented, neutropenic patients should receive aggressive antiviral therapy to aid healing of primary lesions and prevent disseminated disease.**

Initiation of Antiviral Therapy

- **Acyclovir and the newer antivirals valacyclovir and famciclovir may be used.**
- **Routine use of antiviral agents in the management of patients without mucosal lesions or other evidence of viral infection is NOT recommended.**

Initiation of Antiviral Therapy

Adverse reactions of acyclovir:

Nausea, diarrhea, headache
IV administration may be associated with reversible crystalline nephropathy or interstitial nephritis; or neurologic toxicity (tremors, delirium, seizures).
These are uncommon with adequate hydration and avoidance of rapid infusion rates.
Drug Interactions:
Probenecid and cimetidine decrease acyclovir clearnce and increase exposure.
Acyclovir + zidovudine → somnolence and lethargy.

Duration of Antimicrobial Therapy

- **The optimal duration of antimicrobial therapy remains controversial.**
- **Decisions regarding discontinuation of empirical antimicrobial therapy are more difficult than those of initiation of therapy.**
- **The patient's ANC is the most important factor for the total duration of antibiotic therapy:**

Duration of Antimicrobial Therapy

- **If ANC is ≥ 500 cells/mm^3 for two consecutive days, if the patient is afebrile and clinically stable for 48 hours or more, and if NO pathogen has been isolated, then antibiotics may be discontinued.**
- **Some clinicians advocate that patients with ANC < 500 cells/mm^3 be maintained on antibiotic therapy until resolution of neutropenia, even if they are afebrile.**

Duration of Antimicrobial Therapy

- **Prolonged antibiotic use has been associated with superinfections resulting from resistant bacteria and fungi and increased risk of antibiotic-related toxicities.**
- **If low-risk patients are stable clinically with negative cultures but the ANC still is < 500 cells/mm^3) antibiotics may be discontinued after a total of 5 - 7 afebrile days.**

Duration of Antimicrobial Therapy

- **Patients with severe neutropenia (ANC > 100 but < 500 cells/mm^3), mucosal lesions, or unstable vital signs or other risk factors should continue to receive antibiotics until ANC becomes ≥ 500 cells/mm^3, and the patient is stable clinically.**

Duration of Antimicrobial Therapy

- **Patients with documented infections should receive antimicrobial therapy until the infecting organism is eradicated and signs and symptoms of infection have resolved (at least 10-14 days of therapy).**
- **Any way, therapy must be individualized based on individual patient parameters and response to therapy.**

Colony-Stimulating Factors (CSFs)

Granulocyte-macrophage colony-stimulating Factor (Sargramostim)

Granulocyte colony-stimulating factor (filgrastim)

- **May be used as adjunct therapy to antimicrobial treatment of febrile neutropenic patients.**

1. **They reduce total duration and severity of chemotherapy-related neutropenia.**
2. **They reduce duration of antibiotic use.**
3. **They reduce hospitalizations, and decrease hospital length of stay.**
4. **Overall mortality or infection-related mortality is NOT decreased.**

Colony-Stimulating Factors (CSFs)

- **CSFs should NOT be routinely used in patients with uncomplicated fever and neutropenia.**
- **Patients with prolonged neutropenia and documented severe infections who are NOT responding to appropriate antimicrobial therapy may benefit from treatment with CSFs.**
- **CSFs should be considered in patients who are at high risk for infection-associated complications, or who have factors that are predictive of poor clinical outcomes:**

Colony-Stimulating Factors (CSFs)

1) Profound neutropenia (ANC <100 cells/mm^3)
2) Expected prolonged period of neutropenia (>10 days)
3) Patient age >65 years
4) Uncontrolled primary disease
5) Sepsis syndrome, or severe infection manifest by hypotension and multiorgan dysfunction
6) Pneumonia
7) Invasive fungal infection
8) Other clinically documented infection
9) Hospitalized at the time of the development of fever
10) Severe complications during previous episode of febrile neutropenia.

Colony-Stimulating Factors (CSFs)

Granulocyte CSF (or GM-CSF) Common Adverse Effects:

1. Bone pain: because of proliferation of WBCs in bone marrow. Relieved with analgesics.
2. Leukocytosis.
3. Bruises, bleeding gum and nose bleeding: Due to drop in platelet count.
4. Headache
5. Fatigue: can be prolonged up to one year.
6. Back pain.
7. Hepatic problems: reversible with discontinuation of the drug
8. Diarrhea or constipation.

Colony-Stimulating Factors (CSFs)

9. Malaise.
10. Fever
11. Splenomegally
12. Splenic rupture is a rare but serious.
13. Inflammation around the injection site.
14. Abdominal pain
15. Edema in hands and feet, peripheral edema and pleural or pericardial effusions due to a capillary leak syndrome.
16. Insomnia.
17. Arthralgias & myalgias.

Clinical pharmacology

(Rheumatoid arthritis & Osteoarthritis)

5th year lecture

4 December 2017

Rheumatoid arthritis

Definition

- Chronic multisystem disease of unknown aetiology
- Characterized by synovitis
- Involves peripheral joints
- Not spine (Except C1)
- Symmetrical
- Leads to cartilage damage and bone erosions and subsequent joint damage

Pathogenesis

- hyperplasia and hypertrophy of the synovial lining cells
- vascular changes:
  - microvascular injury
  - Thrombosis
  - Neovascularization
- Oedema
- infiltration with mononuclear cells

Cells

- mononuclear cell collections are predominantly T lymphocyte.
- CD4+ T cells > CD8+ T cells
- autoantibodis (RF & CCP) are produced within the synovial tissue lead to the formation of immune complexes
- synovial fibroblasts produce enzymes such as collagenase and cathepsins that degrade components of the articular matrix
- Osteoclasts are also prominent at sites of bone erosion.

Cytokines

- secreted by activated lymphocytes, macrophages, and fibroblasts.

Treatment of RA

The goals of therapy are

- (1) relief of pain
- (2) reduction of inflammation
- (3) protection of articular structures
- (4) maintenance of function
- (5) control of systemic involvement

- None of the therapeutic interventions is curative
- The various therapies employed are directed at nonspecific suppression of the inflammatory or immunologic process

TREATMENT STRATEGIES

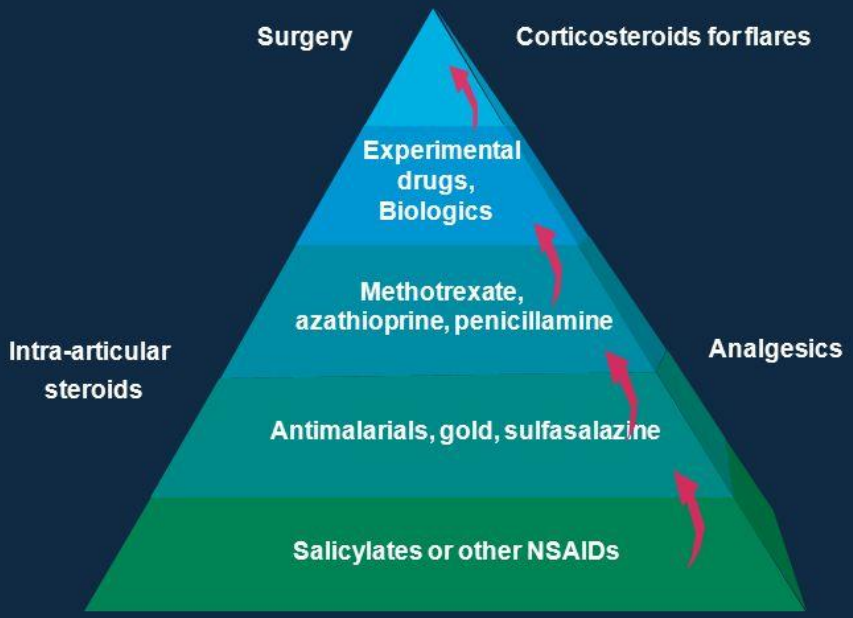
- **There are three general strategies for DMARD treatment of RA:**
- 1. sequential monotherapy
- 2. step-up combination therapy
- 3. initial combination (induction) therapy

- 1st approach has been abandoned in light of extensive data showing the superiority of step-up and induction approaches.

- Evidence suggests that “aggressive” treatment to rapidly achieve a low level of disease activity, which often necessitates a combination of agents, has superior efficacy to conservative approaches that involve sequential, low-dose monotherapy

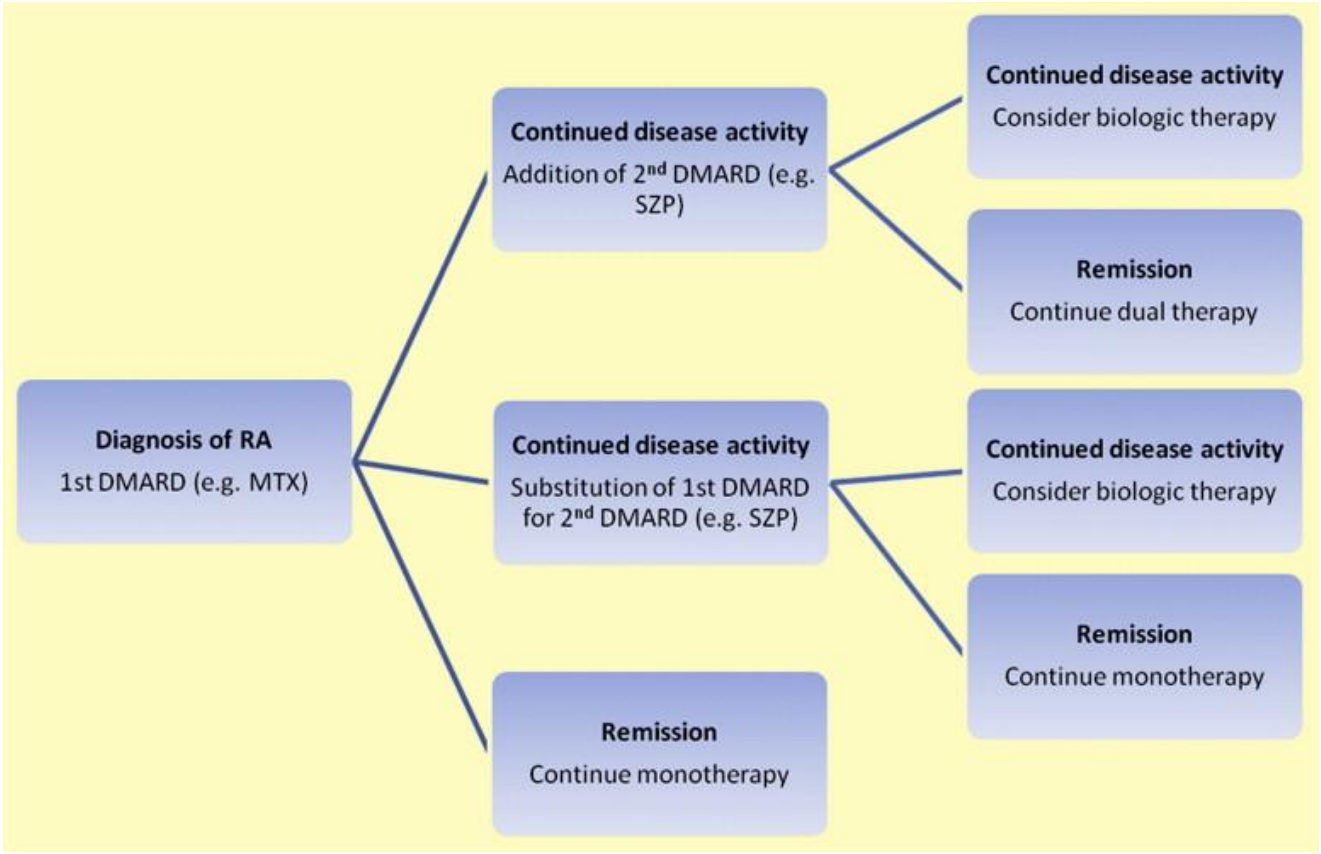
- Given the expense of combination therapy, especially with the biologic DMARDs the step-up combination approach remains the most common in clinical practice

The Traditional Treatment Pyramid for RA: Sequential Drug Therapy

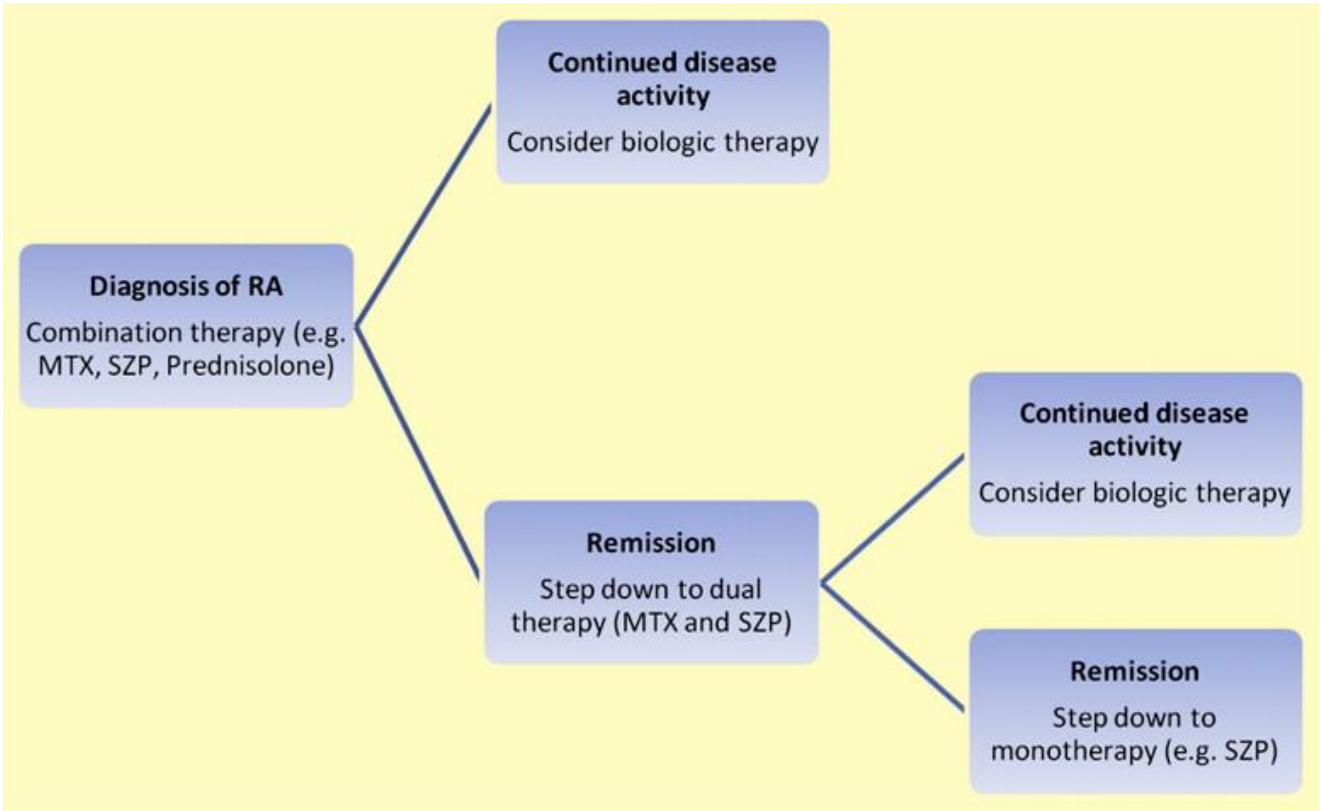


Adapted from *Primer on Rheumatic Diseases*. 10th ed. The Arthritis Foundation; 1993.

Step-up combination therapy



Initial combination (induction) therapy



- **Advantage of induction therapy**
  - more rapid control of synovitis and thus accumulation of joint damage

- **Disadvantages of induction approach:**
  - potential overtreatment
  - exposure to unnecessary toxicities in patients in whom disease may have been controlled by a single DMARD
  - difficulty in attribution of an adverse event to a specific drug.

Conventional DMARDs

TABLE 94.1 DISEASE-MODIFYING ANTIRHEUMATIC DRUGS	
DMARD	**Mechanism of action**
Conventional DMARDs	
Methotrexate	Inhibition of purine biosynthesis/cytokine expression. Induction of monocyte apoptosis
Sulfasalazine	Inhibition of cytokine expression/neutrophil migration
Leflunomide	Inhibition of pyrimidine biosynthesis/cytokine expression/neutrophil migration
Hydroxychloroquine	Unknown
Azathioprine	Active metabolite, 6-mercaptopurine, interferes with adenine and guanidine biosynthesis
Cyclosporine	Inhibition of T-cell response via calcineurin inhibition
Cyclophosphamide	Lymphocyte cytotoxicity

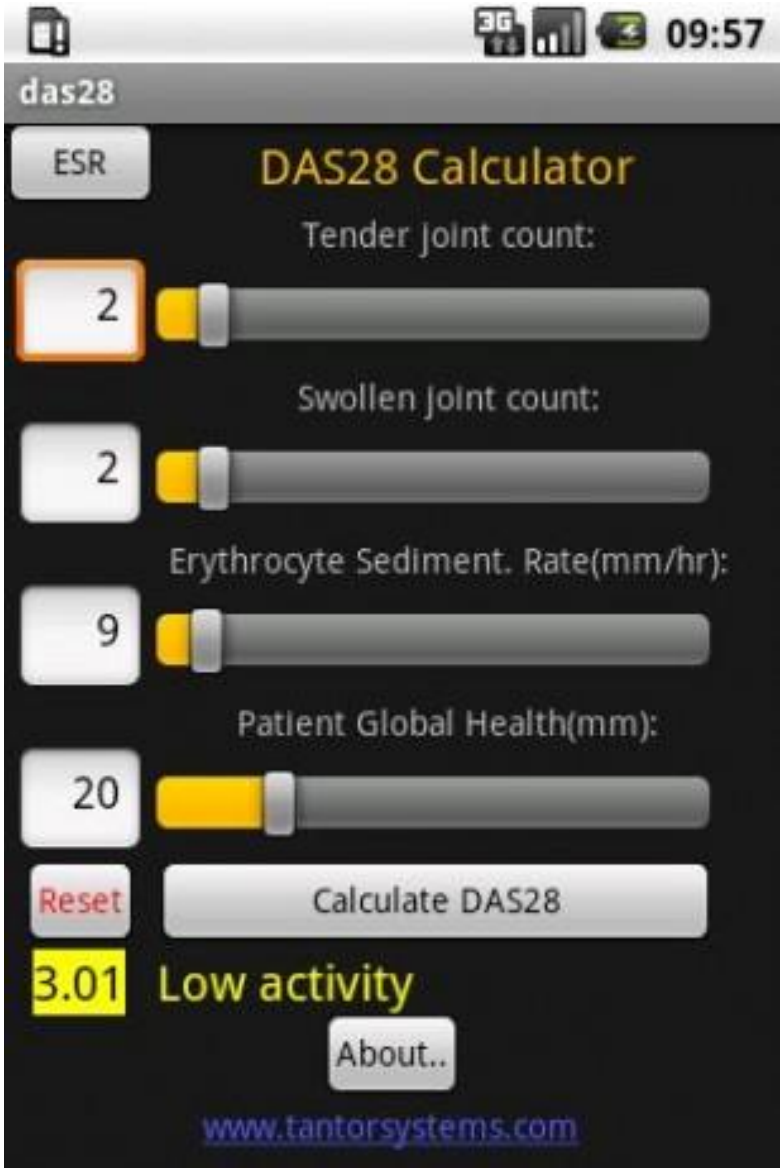
Biologic DMARDs

Biologic DMARDs	
Etanercept	Soluble 75kDa TNF receptor: inhibits biologic effects of TNF-α
Infliximab	Chimeric anti-TNF-α antibody: inhibits biologic effects of TNF-α. Cell lysis of TNF-α expressing cells
Adalimumab	Human anti-TNF-α antibody: inhibits biologic effects of TNF-α
Anakinra	Recombinant IL-1 receptor agonist: inhibits biologic effects of IL-1
Rituximab	Anti-CD20 monoclonal antibody: depletes B cells
Abatacept (CTLA4Ig)	Inhibits T-cell co-stimulation

Disease monitoring

- **When assessing how active the disease is the doctor will take four factors into account:**

1. Number of tender joints
2. Number of swollen joints
3. PGA: How active you think your disease is on a scale of one to ten
4. ESR or CRP


09:57
das28
ESR
DAS28 Calculator
Tender Joint count:
2
Swollen Joint count:
2
Erythrocyte Sediment. Rate(mm/hr):
9
Patient Global Health(mm):
20
Reset
Calculate DAS28
3.01
Low activity
About..
www.tantorsystems.com

DAS-28 interpretation

< 2.6 → remission

2.6 - 3.2 → low disease activity

3.2 - 5.1 → moderate disease activity

> 5.1 → high disease activity.

Initial DMARD

- Methotrexate is the first-line DMARD of choice
- Aggressive dose escalation of methotrexate
- Start 10 mg/wk & ↑ by 5 mg every 4 wk
- Because of the slow onset of action of MTX, an interval of 4 to 6 weeks is required to determine whether a patient has responded to a dose increase
- an interval of 3 months is recommended to evaluate the initial response to methotrexate

- patients who have had an inadequate response to 20 to 25/week of oral methotrexate → change to SC or IM methotrexate may be more efficacious

Alternative initial therapy

- Leflunomide
- Sulfasalazine
- Hydroxychloroquine

- Leflunomide & sulfasalazine have equivalent efficacy to MTX
- Sulfasalazine given to patients with contra-indications to MTX

- Hydroxychloroquine:
  - low toxicity profile
  - low cost
  - safe in pregnancy

- less potent than other DMARDs, especially in its ability to slow radiographic progression.

Screening prior to starting DMARDs

- All need LFT, KFT, CBC
- MTX: CXR
- Biologics: CXR, hepatitis B &C, PPD
- HCQ: ophthalmology

Treatment monitoring

- NSAIDs: regular KFT
- Steroids: annual DEXA
- DMARDs: CBC, KFT, LFT
  - After 2 weeks
  - 1 month
  - 3 monthly

The drugs

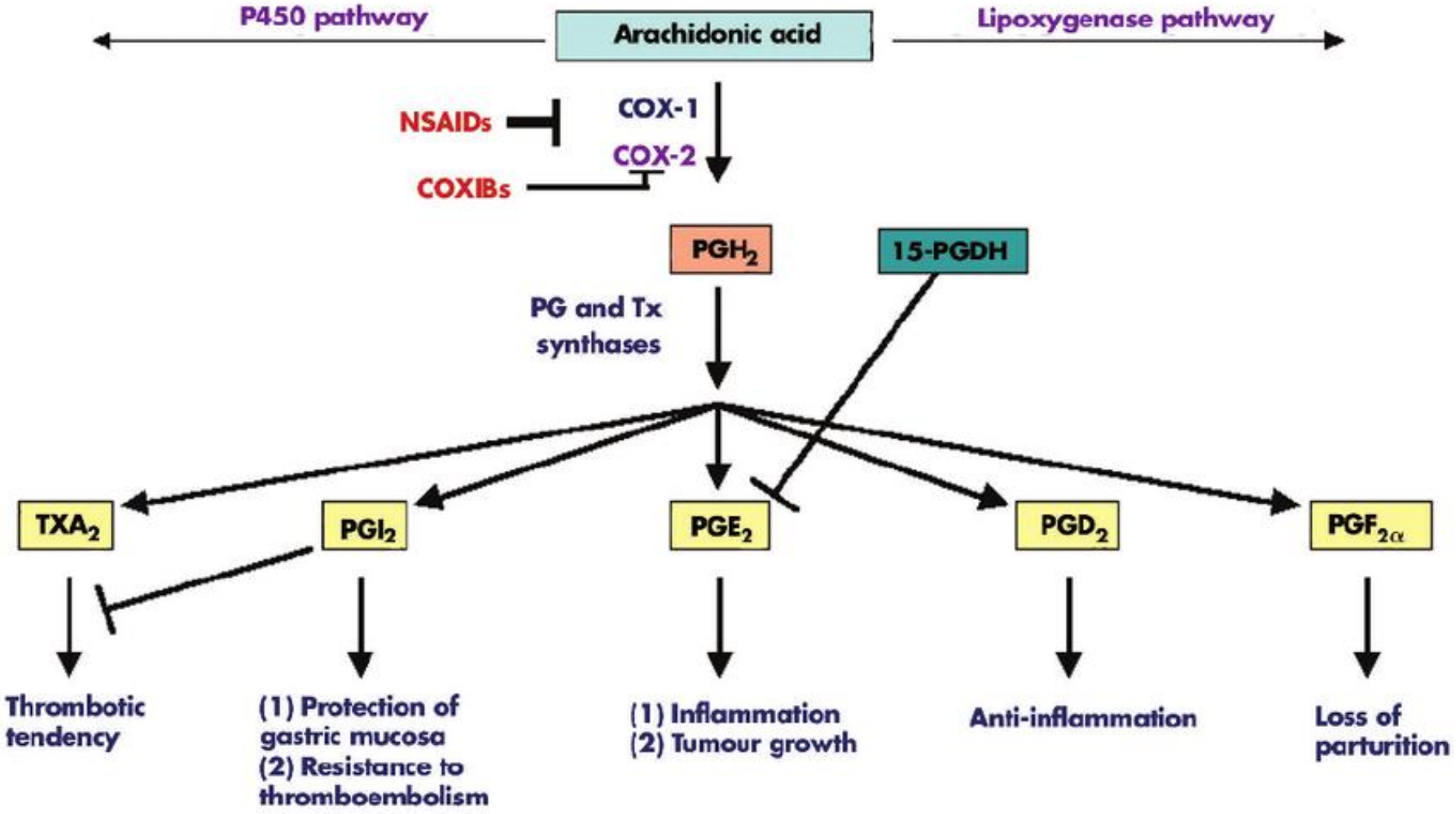
NSAIDs

- Chemically heterogeneous group of compounds that provide symptomatic relief of pain and inflammation
  - Analgesic
  - anti-inflammatory
  - antipyretic
- not disease modifying, so their use as monotherapy for a prolonged period of time should be avoided.

MECHANISM OF ACTION

- Inhibition of the cyclo-oxygenase (COX)
- prostanoids reproduce the main signs and symptoms of the inflammatory response
  - PGE2 and PGI2 cause erythema, an increase in local blood flow,
  - PGE2 can produce fever.

- PG-synthase is found in two isoforms
  - COX-1, which is expressed constitutively in all cells but is inducible under appropriate conditions
  - COX-2, which is inducible in response to inflammatory, mitogenic or hemodynamic stimuli

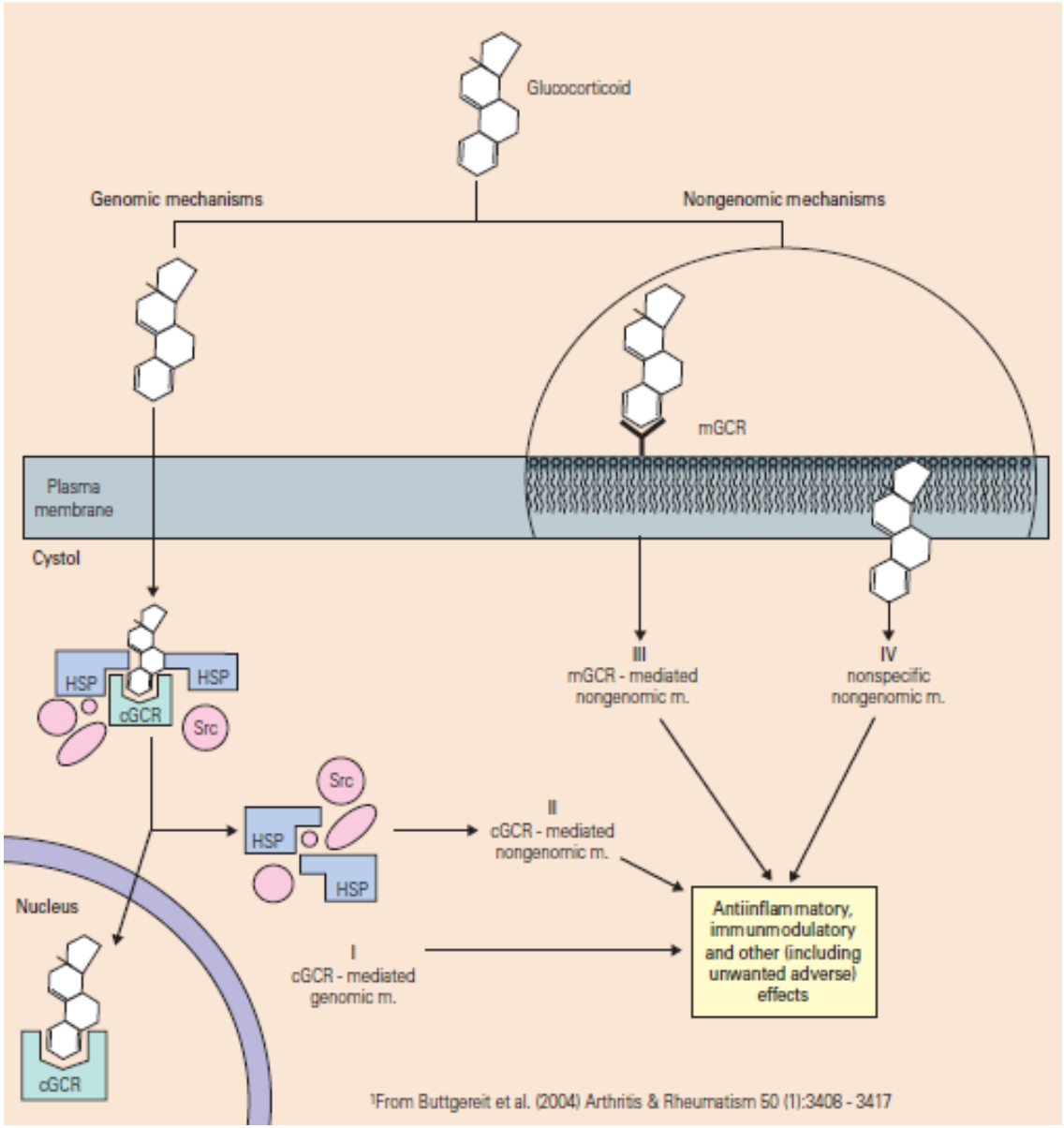

P450 pathway
Arachidonic acid
Lipoxygenase pathway
NSAIDs
COX-1
COX-2
COXIBs
PGH2
15-PGDH
PG and Tx synthases
TXA2
PGI2
PGE2
PGD2
PGF2α
Thrombotic tendency
(1) Protection of gastric mucosa
(2) Resistance to thromboembolism
(1) Inflammation
(2) Tumour growth
Anti-inflammation
Loss of parturition

Side effects of NSAIDs

- GI: erosions, ulcers, GI haemorrhage
- Renal: salt & water retenstion, ARF
- Hypersensitivity
- Ductus arteriosus
- Liver: raised LFTs
- Skin: EM, TEN, urticaria

Corticosteroids

MECHANISMS OF THE CELLULAR ACTIONS OF GLUCOCORTICOIDS



[1]From Buttgereit et al. (2004) Arthritis & Rheumatism 50 (1):3408 - 3417

Corticosteroids

- The glucocorticoid/glucocorticoid receptor complex inhibits transcription factors NF-κB and AP-1.
- result in the decreased synthesis of proinflammatory cytokines such as IL-1, IL-2, IL-2 receptor, IFN-α, IL-6, and TNF-α.

Efficacy of steroids in rheumatoid arthritis

- Short- to moderate-term glucocorticoid studies reveal improved disease activity and functional status
- low dose glucocorticoids prevent radiographic joint destruction in RA.

Route of administration

- Oral
- IM
- IV
- Intra-articular

Adverse effects

- long-term, relatively low-dose glucocorticoid use is a significant cause of numerous potentially serious adverse

Adverse effects

- Bone and muscle
- Cardiovascular
- Gastrointestinal
- Infections
- Metabolic and endocrine
- Dermatologic
- Neuropsychiatric
- Ophthalmologic

Muscle and bone

- Osteoporosis leading to fracture.
  - cumulative dose
- Osteonecrosis of bone
- Myopathy
  - peak dose of glucocorticoid rather than cumulative dose

Cardiovascular

- Hypertension
- Hyperlipidaemia
- atherosclerotic vascular disease.

Dermatologic

- skin thinning
- Ecchymoses
- cushingoid appearance
- Acne
- Hirsutism
- impaired wound healing

GI

- Gastritis
- Ulcers
- GI bleeding.
- Pancreatitis

Endocrine & metabolic

- Hyperglycemia
- adrenal suppression

Neuropsychiatric

- Insomnia
- depression
- Memory impairment

Ophthalmologic

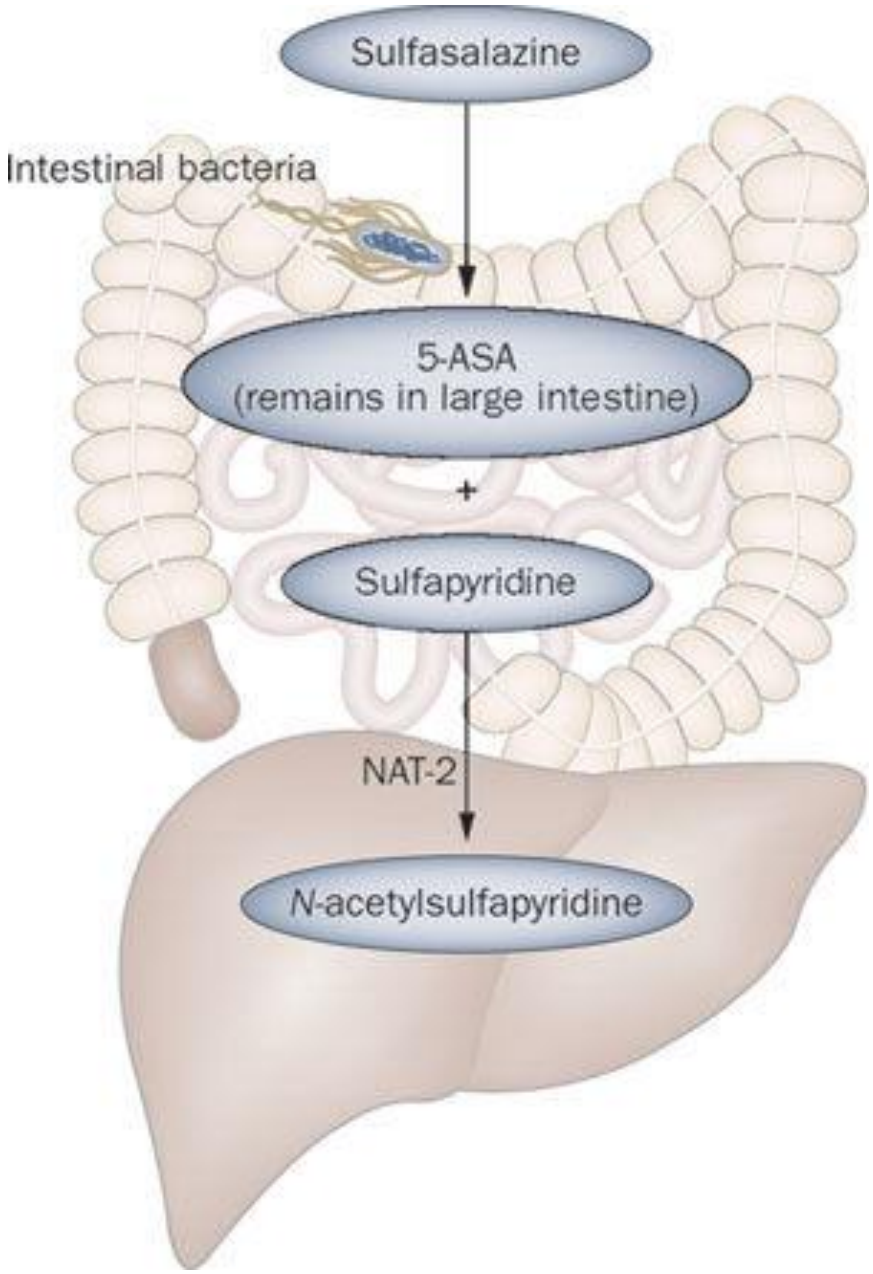
- Cataracts
- Glaucoma

Hydroxychloroquine

- limited efficacy when used alone
- more effective when used in combination with MTX or sulfasalazine
- Retinopathy
  - can lead to blindness
  - extremely rare
  - Depends on cumulative dose (max 5 mg/kg)

Sulfasalazine (SSP)

- Sulfapyridine + 5-ASA
- After ingestion it is split in the large intestine by bacterial enzymes into sulfapyridine (SP), which is then absorbed, and 5-ASA, which is excreted
- decreases the progression of radiologic damage


Sulfasalazine
Intestinal bacteria
5-ASA
(remains in large intestine)
+
Sulfapyridine
NAT-2
N-acetylsulfapyridine

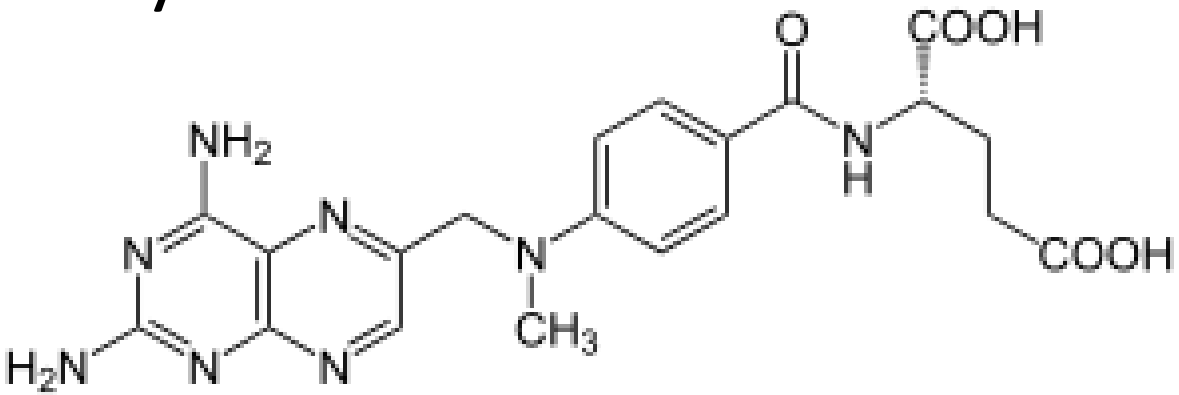
Adverse effects of SSP

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Leucopenia
- Rashes
- Hepatotoxicity

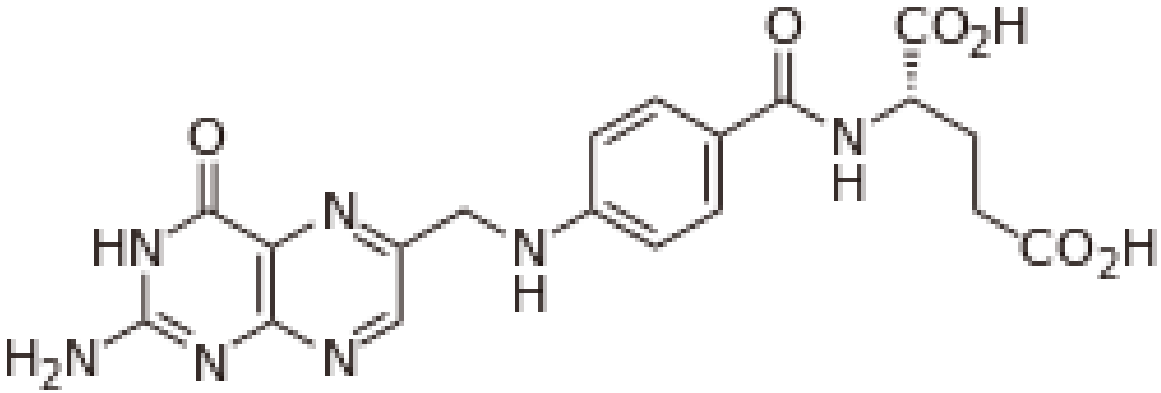
Methotrexate (MTX)

- first-line agent in the treatment of RA
- structurally similar to folic acid

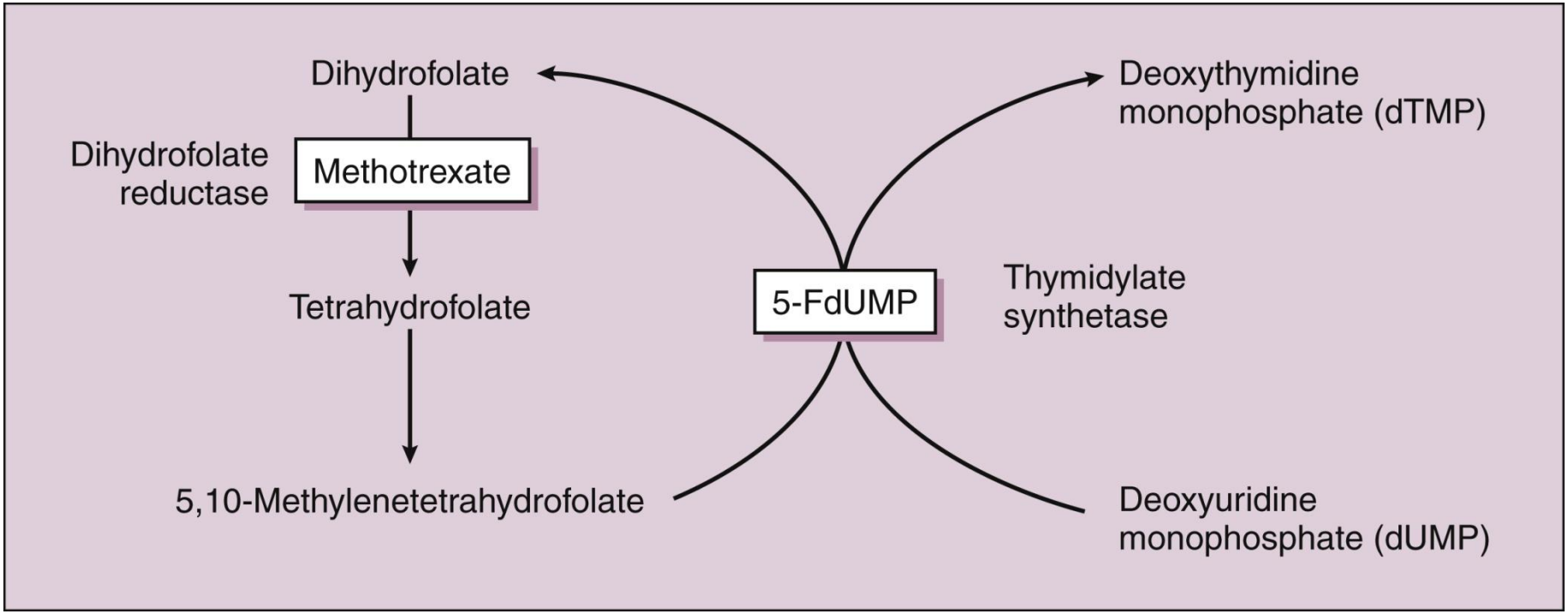
MTX



Folic acid



- Inhibits dihydrofolate reductase (DHFR) thereby deprives the cell of tetrahydrofolate
- slows radiographic progression of RA.



- monitoring of methotrexate therapy is required
- Serious liver disease and idiosyncratic pulmonary hypersensitivity are rare potential adverse effects.
- Methotrexate is a known teratogen and effective contraception should be considered in women with the potential for pregnancy.
- Men also

Adverse effects of MTX

- most common:
  - anorexia
  - Nausea
  - Vomiting
  - diarrhea
- Hematologic abnormalities:
  - leukopenia (most common)
  - Anemia
  - thrombocytopenia.

- hepatic toxicity
- lung toxicity:
  - acute interstitial pneumonitis
  - Pulmonary fibrosis

- To prevent adverse effects of MTX, folic acid or folinic acid (leucovorin) is given concomitantly.

MTX

- Small rheumatoid nodules may increase in size at start of MTX therapy
- Hepatic fibrosis & cirrhosis is rare with MTX & occurs in < 0.1% of patients
- Pulmonary toxicity may present as an unexplained cough or may present with fever, hypoxia, eosinophilia & interstitial infiltrates
- Avoid concomittant use of other antifolate drugs such as trimethoprim

Contraindications to MTX

- active liver disease (including chronic hepatitis B and C infection)
- alcohol abuse
- pregnancy
- breastfeeding.

Leflunomide

- Leflunomide inhibits pyrimidine synthesis, resulting in blockade of T-cell proliferation
- as effective as methotrexate and sulfasalazine
- provides additional benefit in patients partially responsive to methotrexate.
- The most common side effects are gastrointestinal symptoms and hepatotoxicity.
- Combination of leflunomide with methotrexate results in a significant increase in liver enzyme abnormalities.
- Leflunomide is teratogenic and is therefore contraindicated in women who may become pregnant.

Leflunomide

- Has a long half life & should be stopped at least 4 months before attempting pregnancy

- If elimination of leflunomide is desired (toxicity or pregnancy) cholstyramine 8 g TDS should be given for 11 days

Azathioprine

- pro-drug (active metabolite 6-mercaptopurine)
- Purine analogue. inhibits purine synthesis ➔↓T&B cell proliferation
- azathioprine use in RA is generally reserved for those patients who are intolerant of other agents

Biologic DMARDs

Anti-TNF

- BIOLOGIC EFFECTS OF TNF-**α**
  - Adhesion molecule expression (E selectin, ICAM-1)
  - Synthesis of other proinflammatory cytokines (IL-1, IL-6, GM-CSF)
  - Synthesis of chemokines (e.g., RANTES, IL-8, MIP-1)
  - Activation of numerous cell types (T cells, B cells, macrophages)
  - Inhibition of regulatory T cells
  - Matrix metalloproteinase induction
  - Upregulation of RANK ligand expression
  - Induction of apoptosis
  - Antiviral and antitumor effects

Anti-TNF

- TNF-α primarily mediates inflammation by promoting cellular activation and trafficking of leukocytes to inflammatory sites.

Anti-TNF

- Infliximab
- adalimumab
- Golimumab
- certolizumab
- etanercept

BOX 61.3 RELATIVE CONTRAINDICATIONS TO THE USE OF TUMOR NECROSIS FACTOR INHIBITORS

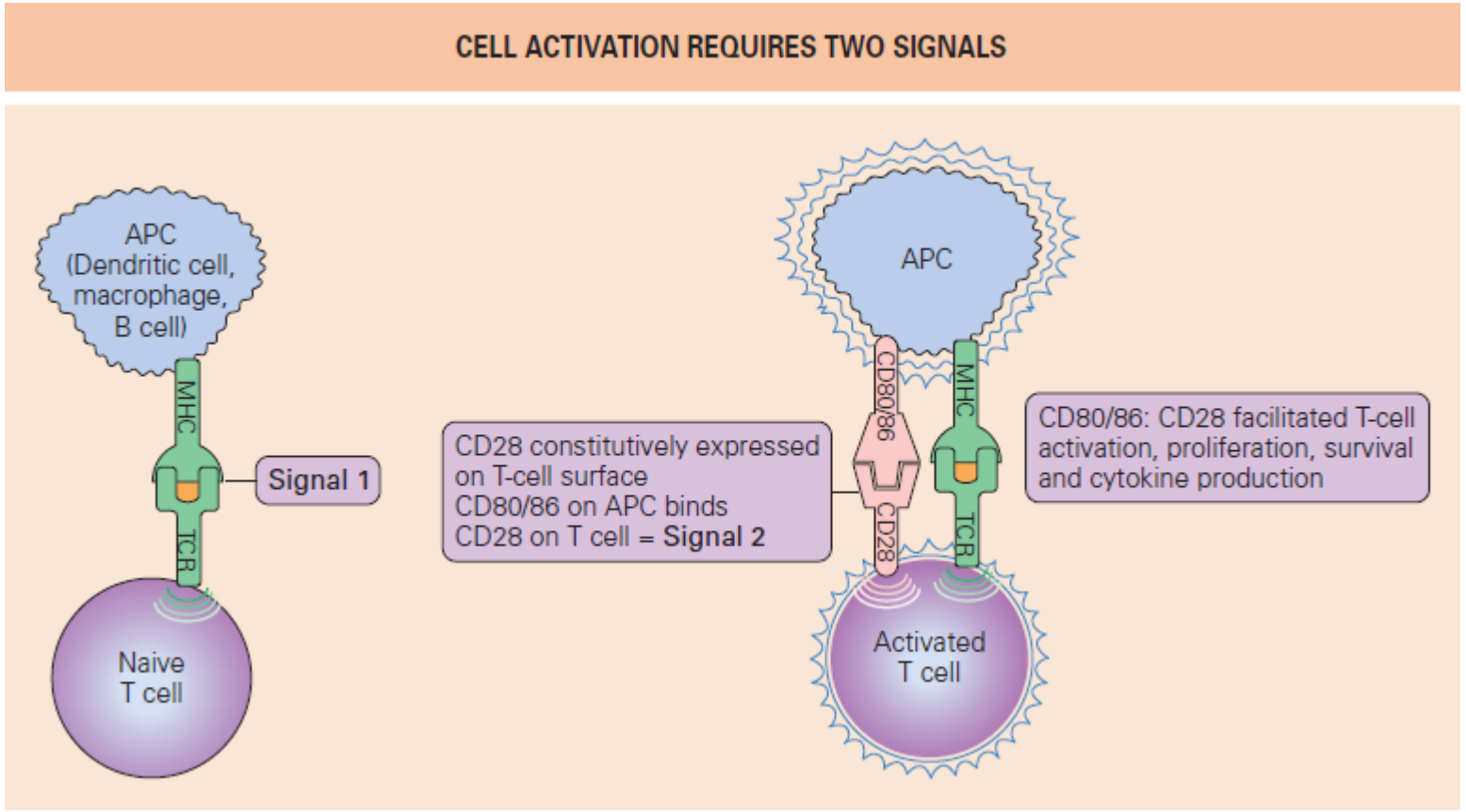
- Systemic lupus erythematosus, lupus overlap syndrome
- Multiple sclerosis, optic neuritis, demyelinating disorders
- Current, active, serious infections
- Recurrent or chronic infections
- Untreated latent or active mycobacterial infection
- Hepatitis B infection
- Congestive heart failure
- Pregnancy

T-cell co-stimulation

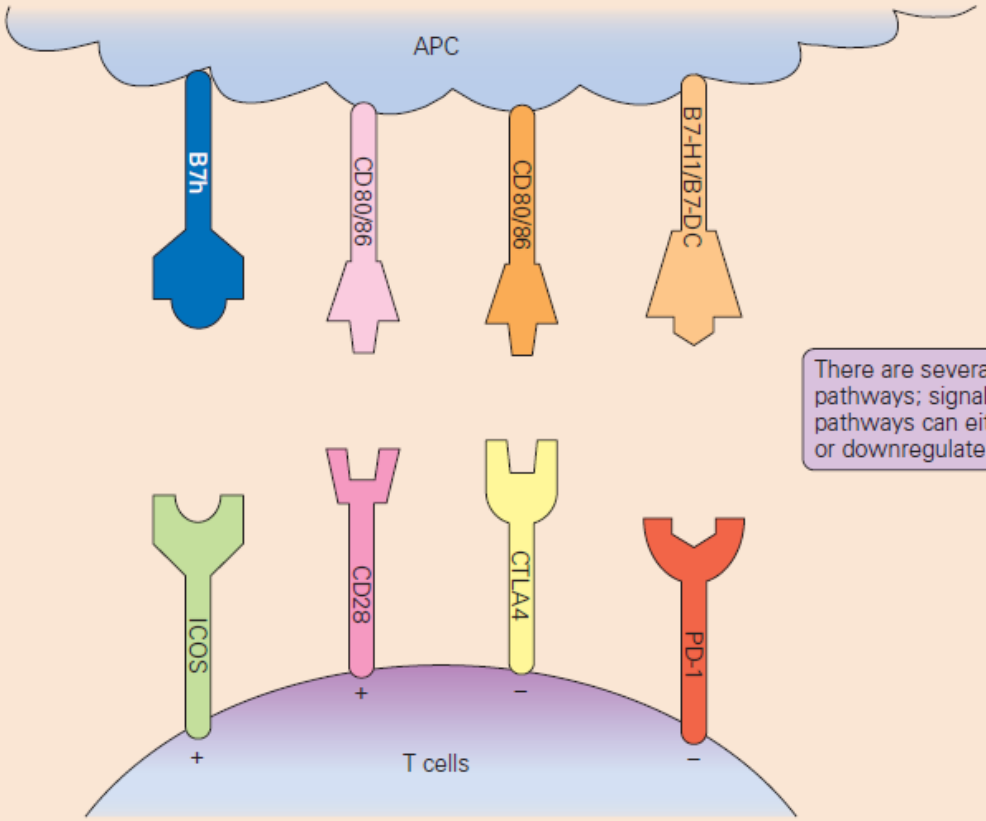
T-cell activation requires two signals:

First signal: engagement of the TCR with the MHC antigen complex

Second signal: transmitted by CD28 that interacts with either CD80 and CD86 ligands on APCs, leading to T-cell activation and proliferation

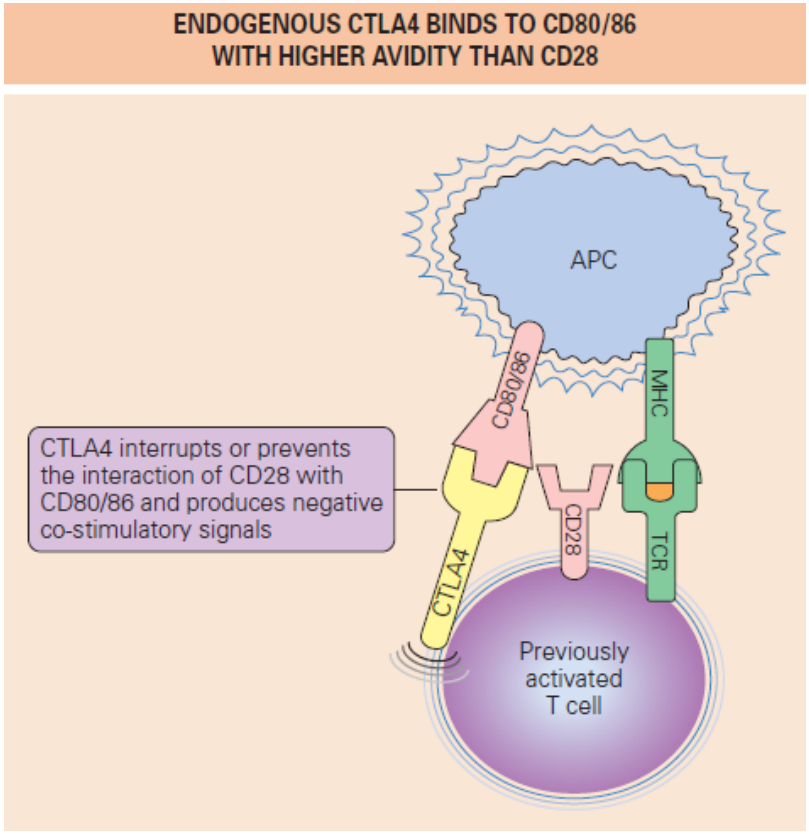


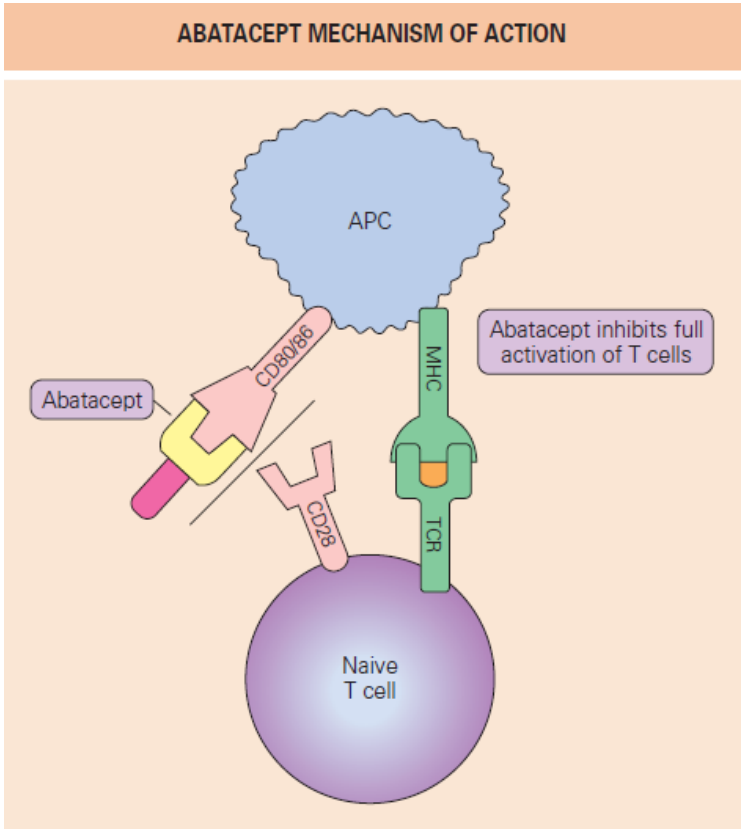
CO-STIMULATION IS REQUIRED FOR FULL T-CELL ACTIVATION



CTLA4 binds to CD80/86 with higher avidity than CD28

Abatacept binds to CD80/86 and inhibits T-cell co-stimulation



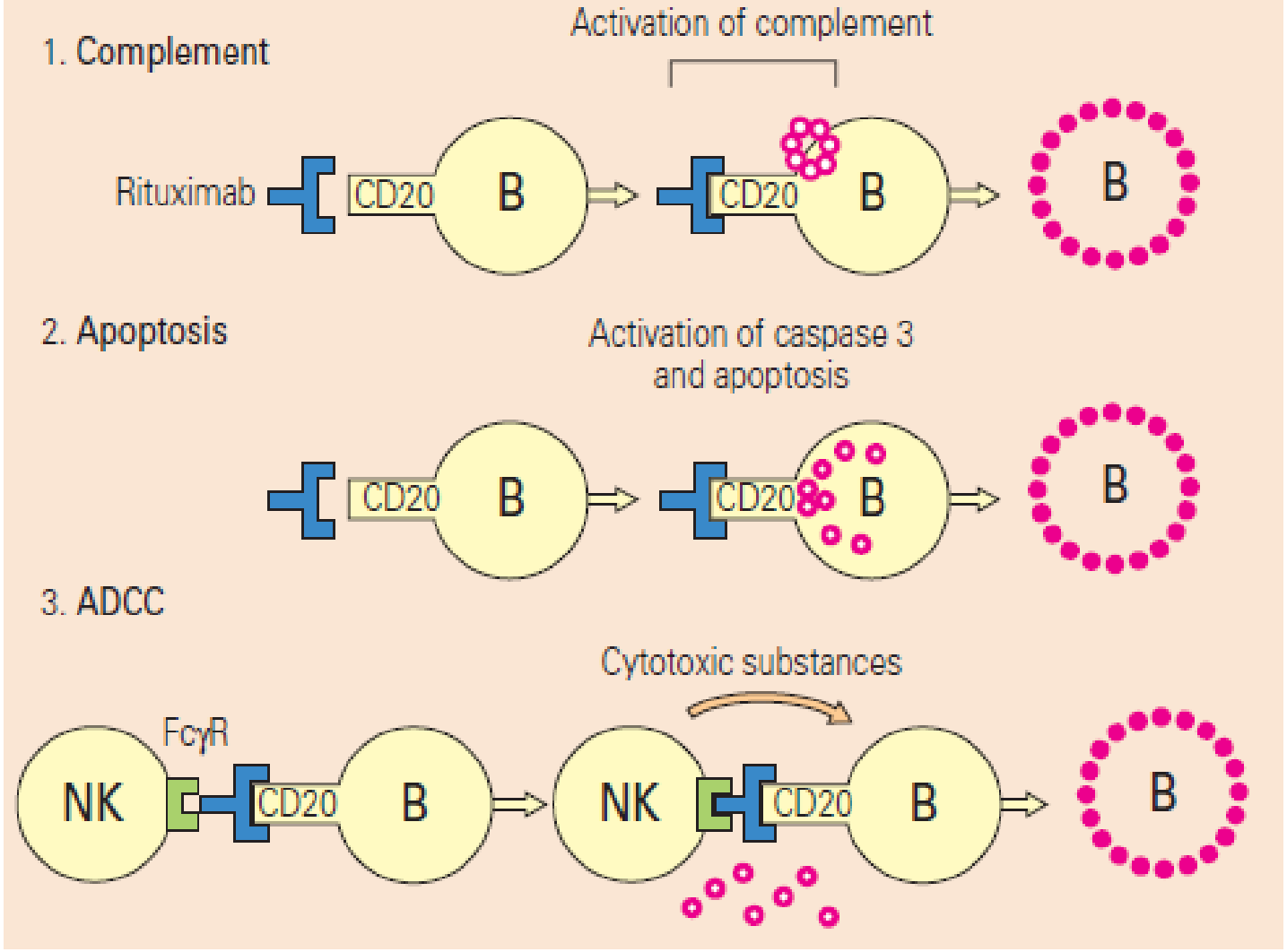


Anti-B Cell (Rituximab)

- CD20 is expressed on mature naïve B cells that have exited the bone marrow to enter blood
- it is not expressed on stem cells or on plasma cells
- Rituximab is a high-affinity chimeric monoclonal antibody specific to CD20

- Rituximab causes B-cell depletion by:
  1. antibody-dependent, cell-mediated cytotoxicity
  2. complement-dependent cytotoxicity
  3. apoptosis

MECHANISMS OF B-CELL KILLING BY RITUXIMAB

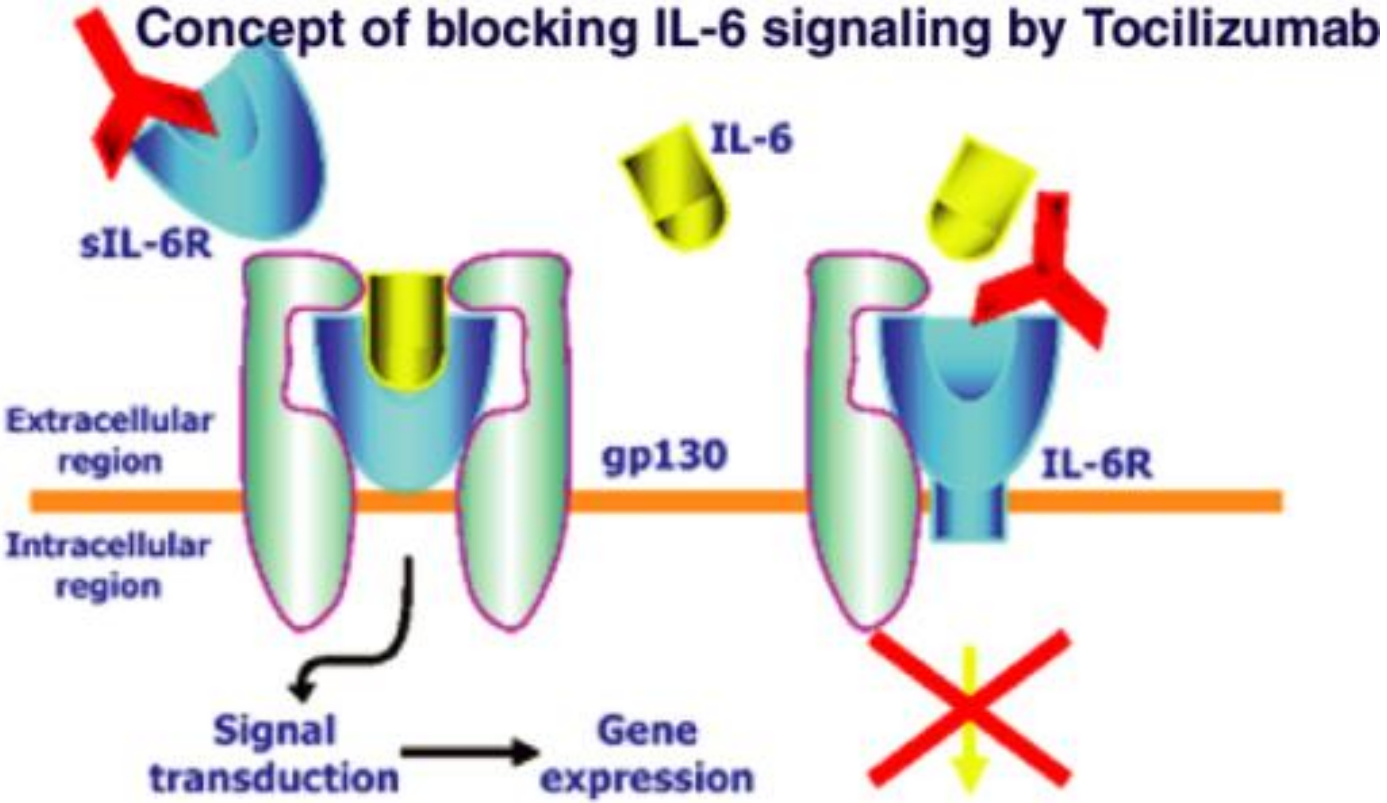


- Rituximab is given intravenously

IL-6

- Actions interleukin-6 (IL-6) include:
  - stimulation of B cell proliferation
  - immunoglobulin production
  - initiation of the acute-phase response.

- Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R).


Concept of blocking IL-6 signaling by Tocilizumab
IL-6
sIL-6R
Extracellular region
gp130
IL-6R
Intracellular region
Signal transduction
Gene expression

Osteoarthritis

- Osteoarthritis (OA) is the most common form of arthritis
- pain is the most common symptom.
- aims of treatment:
  - to reduce pain
  - improve function and quality of life.
- management requires a combination of non-pharmacologic and pharmacologic modalities

Non-pharmacologic therapies

- Patient education
- Self-management
- Aerobic exercise
- Strengthening exercise
- Water-based exercise
- Weight loss
- Insoles
- Braces
- Cane/stick
- Local heat/ice
- Acupuncture
- Transcutaneous electrical nerve stimulation
- Yoga
- Ultrasound

Pharmacologic therapies

- paracetamol
- Non-steroidal anti-inflammatory drugs
- COX-2 selective inhibitors
- Topical NSAIDs
- Topical capsaicin
- Opioid analgesics
- Glucosamine sulfate
- Chondroitin sulfate
- Intra-articular corticosteroids
- Intra-articular hyaluronic acid preparations

Surgical intervention

- Joint lavage
- Arthroscopic debridement
- Osteotomy
- Joint replacement
- Joint fusion

Thank you

Therapy of Migraine

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Migraine Headache

Pathophysiology:

- Mechanisms of migraine are not completely understood.
- Vasodilation of intracranial extracerebral blood vessels results in the activation of the perivascular trigeminal nerves that release vasoactive neuropeptides (calcitonin gene-related peptide (CGRP), neurokinin A, and substance P) from perivascular axons.
- The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation.

Migraine Headache

- **Orthodromic conduction along trigeminovascular fibers transmits pain impulses to the trigeminal nucleus caudalis, where information is relayed further to higher cortical pain centers.**
- **Continued afferent input can result in sensitization of these central sensory neurons, producing a hyperalgesic state that responds to previously innocuous stimuli and maintains the headache.**
- **Activation of central pain transmission and other brainstem nuclei results in associated symptoms (nausea, vomiting, photophobia, and phonophobia).**

Migraine Headache

- Aura occurs in a subgroup of migraine patients.
- The neurologic changes of the aura parallel those that occur during cortical spreading depression (sustained depolarization spreading in the brain tissues).
- The hyperresponsiveness of the migrainous brain may be the result of an inherited abnormality in calcium and/or sodium channels and sodium/potassium pumps that regulate cortical excitability through the release of serotonin (5-hydroxytryptamine [5-HT]) and other neurotransmitters.

Migraine Headache

- **Increased levels of excitatory amino acids (glutamate) and changes in extracellular potassium can affect the migraine threshold and initiate and propagate the phenomenon of cortical spreading depression.**
- **5-HT receptors are implicated in the pathophysiology of migraine headache.**
- **Specific antimigraine drugs (ergot alkaloids and triptans) are agonists at vascular and neuronal 5-HT_1 receptor subtypes, → vasoconstriction of meningeal blood vessels and inhibition of vasoactive neuropeptide release and pain signal transmission.**

Migraine Headache Therapy

Goals of acute migraine treatment:

1. Treat migraine attacks rapidly and consistently.
2. Reduce recurrence rate significantly.
3. Restore the patient's ability to function normally.
4. Cause minimal or no therapy related adverse effects.

Migraine Headache Therapy

Goals of long-term migraine treatment:

1. **Reduce migraine frequency, severity, and disability.**
2. **Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies.**
3. **Improve quality of life.**
4. **Prevent headache.**
5. **Avoid escalation of headache medication use.**
6. **Educate and enable patients to manage their disease.**
7. **Reduce headache-related distress and psychological symptoms.**

Migraine Headache Therapy

General Approach To Treatment:

- Drug therapy is the mainstay of treatment for most patients.
- Pharmacotherapeutic management of migraine can be acute (abortive) or preventive .
- Coexisting illnesses can limit and/or dectate treatment choices.
- Abortive or acute therapies can be migraine-specific (ergots and triptans) or nonspecific (analgesics, antiemetics, nonsteroidal antiinflammatory drugs [NSAIDs], and corticosteroids).
- These drugs are most effective when administered at the onset of migraine.

Migraine Headache Therapy

- **Initial treatment is based on headache-related disability and symptom severity.**
- **It is advised to use nonspecific agents for mild to moderate headache NOT causing disability while reserving migraine-specific medications for more severe attacks.**
- **The absorption and efficacy of orally administered drugs can be compromised by gastric stasis or nausea and vomiting that accompany migraine.**
- **Therefore, pretreatment with antiemetic agents or the use of non-oral treatment (suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe.**

Migraine Headache Therapy

Analgesics:

- **Acetaminophen (with or without caffeine or aspirin).**

Nonsteroidal antiinflammatory drugs:

- **Aspirin, Ibuprofen, Naproxen. Diclofenac.**

Ergot alkaloids:

- **Ergotamine/caffeine, Dihydroergotamine**

Serotonin agonists (triptans):

- **Sumatriptan, Zolmitriptan, Rizatriptan, Almotriptan, Frovatriptan, Eletriptan.**

Miscellaneous:

- **Metoclopramide, Prochlorperazine.**

Migraine Headache Therapy

- The frequent or excessive use of acute migraine medications can result in medication-overuse headache (or rebound headache).
- In this case the headache returns as the medication is eliminated, leading to use of more drug for relief.
- The patient experiences a daily or near-daily headache with superimposed episodic migraine attacks.
- This syndrome occurs more often with simple and combination analgesics, opiates, and triptans.

Migraine Headache Therapy

- **Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics.**
- **Detoxification can be accomplished on an outpatient basis.**
- **Hospitalization may be necessary for the control of refractory rebound headache and other withdrawal symptoms (nausea, vomiting, asthenia, restlessness, and agitation).**

Migraine Headache Therapy

- **Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months following medication withdrawal.**
- **It is recommend to limit the use of acute migraine therapies to < 10 days per month to avoid the development of medication overuse headache.**
- **Preventive migraine therapies are administered on a daily basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies.**

Migraine Headache Prevention

β-Adrenergic antagonists:

- **Propranolol, Atenolol, Metoprolol XL, Nadolol.**

Anticonvulsants:

- **Topiramate, Valproic acid.**

Antidepressants:

- **Amitriptyline, Venlafaxine**.

Nonsteroidal antiinflammatory drugs:

- **Ibuprofen, Ketoprofen, Napro**xen

Serotonin agonists (triptans):

- **Frovatriptan, Naratriptan, Zolmitriptan.**

Miscellaneous:

- Histamine, Magnesium, Riboflavin.

Migraine Headache Prevention

- **Preventive therapy should be considered in the following cases:**

1) **recurring migraines that produce significant disability despite acute therapy.**
2) **frequent attacks occurring more than twice per week with the risk of developing medication-overuse headache.**
3) **symptomatic therapies that are ineffective or contraindicated, or produce serious side effects.**

Migraine Headache Prevention

4) uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (hemiplegic migraine, basilar migraine, and migraine with prolonged aura).
5) Preventive therapy also may be administered intermittently when headaches recur in a predictable pattern (exercise-induced migraine or menstrual migraine).

Migraine Headache Prevention

- **Only propranolol, timolol, divalproex sodium, and topiramate have established efficacy, although other agents may be effective.**
- **The selection of an agent typically is based on its adverse effect profile and the patient's coexisting comorbid conditions.**
- **2 - 3 months are needed to achieve clinical benefit, but some reduction in attack frequency can be evident by the first month of therapy.**
- **Maximal benefits are typically observed by 6 months of treatment.**

Migraine Headache Prevention

- Drug therapy should be initiated with low doses and gradually increased until a therapeutic effect is achieved or side effects become intolerable.
- Drug doses for migraine prophylaxis are often lower than those necessary for other indications.
- Overuse of acute headache medications will interfere with the effects of preventive treatment.
- Prophylactic treatment usually is continued for at least 6 - 12 months after the frequency and severity of headaches have diminished, then gradual tapering or discontinuation may be reasonable.

Migraine Headache Therapy

Nonpharmacologic Therapy:

- Rest or sleep in a dark, quiet environment.
- Regular sleep, exercise, and eating habits, smoking cessation, and limited caffeine intake.
- Identification of migraine triggers to avoid.
- Behavioral interventions such as relaxation therapy, biofeedback, and cognitive therapy, are preventive treatment options.

Migraine Headache Therapy

Commonly Reported Triggers of Migraine:

A. Food triggers:

- Alcohol
- Caffeine/caffeine withdrawal
- Chocolate
- Fermented and pickled foods
- Monosodium glutamate (in Chinese food, seasoned salt, and instant foods)
- Nitrate-containing foods (processed meats)
- Saccharin/aspartame (diet foods or diet sodas)
- Tyramine-containing foods

Migraine Headache Therapy

B. Environmental triggers:

- Glare or flickering lights
- High altitude
- Loud noises
- Strong smells and fumes
- Tobacco smoke
- Weather changes

C. Hormones:

- Changes in estrogen levels (menarche, menstruation, pregnancy, menopause, and oral contraceptive use) can trigger, intensify, or alleviate migraine. A drop precipitates attacks.

Migraine Headache Therapy

D. Behavioral/Physiologic triggers:

- Excess or insufficient sleep
- Fatigue
- Menstruation, menopause
- Sexual activity
- Skipped meals
- Strenuous physical activity (prolonged overexertion)
- Stress or post-stress

Pharmacologic Management of Acute Migraine

Analgesics and NSAIDs:

- **Simple analgesics and NSAIDs are effective and are first-line choice for treatment of mild-to-moderate migraine attacks.**
- **Of the NSAIDs, aspirin, diclofenac, ibuprofen, ketorolac, naproxen sodium, tolfenamic acid, and the combination of acetaminophen plus aspirin / caffeine have demonstrated the most consistent evidence of efficacy.**
- **Acetaminophen alone is not generally recommended.**
- **They may have comparable efficacy to triptans in acute migraine.**

Pharmacologic Management of Acute Migraine

- **NSAIDs appear to prevent inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis.**
- **Metoclopramide can speed the absorption of analgesics and alleviate migraine-related nausea and vomiting.**
- **Suppository analgesic preparations are an option when nausea and vomiting are severe.**
- **Acute NSAID therapy is associated with gastrointestinal (dyspepsia, nausea, vomiting, and diarrhea) and CNS (somnolence, dizziness) adverse effects.**
- **NSAIDs should be avoided in patients with previous ulcer disease, renal disease, or hypersensitivity to aspirin.**

Pharmacologic Management of Acute Migraine

Opiate Analgesics:

- **Evidence for use is generally negative.**
- **Opiates can cause central sensitization, increasing the risk of medication-overuse headache and interfering with the efficacy of other treatments even with intermittent use.**

Pharmacologic Management of Acute Migraine

Antiemetics:

- **Adjunctive antiemetic therapy is useful for combating the nausea and vomiting of migraine headaches and that of medications used to treat attacks (ergotamine tartrate).**
- **A single dose of an antiemetic, such as metoclopramide, chlorpromazine, or prochlorperazine, administered 15 - 30 minutes before ingestion of oral abortive migraine medications is often sufficient.**
- **Suppository preparations are available when nausea and vomiting are particularly prominent.**

Pharmacologic Management of Acute Migraine

- Metoclopramide is also useful to reverse gastroparesis and improve absorption from the GI tract during severe attacks.
- In addition to antiemetic effects, dopamine antagonist drugs also have been used successfully as monotherapy for the treatment of intractable headache.
- The dopamine antagonists offer an alternative to the narcotic analgesics for the treatment of refractory migraine.
- Adverse effects include: drowsiness and dizziness, extrapyramidal adverse effects, and droperidol has a risk for QT prolongation.

Pharmacologic Management of Acute Migraine

Miscellaneous Nonspecific Medications:

1. Corticosteroids can be considered as rescue therapy for status migrainous (a severe, continuous migraine that can last up to 1 week). IV or intramuscular dexamethasone at a dose of 10 - 25 mg has also been used as an adjunct to abortive therapy.
2. IV valproate 500 - 1,000 mg and magnesium sulfate 1,000 mg are nonsedating options for use in acute migraine treatment.

Pharmacologic Management of Acute Migraine

Ergot Alkaloids and Derivatives:

- Ergotamine tartrate and dihydroergotamine can be used in moderate-to-severe migraine attacks.
- They are nonselective 5-HT_1 receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system.
- Ergotamine tartrate is available for oral, sublingual, and rectal administration.
- Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia.

Pharmacologic Management of Acute Migraine

- Dihydroergotamine is available for intranasal and parenteral administration by the intramuscular, subcutaneous, and IV routes.
- Mixing with 1-2% lidocaine can reduce burning at the injection site.
- Nausea and vomiting (resulting from stimulation of the chemoreceptor trigger zone) are among the most common adverse effects of the ergotamine derivatives.
- Therefore, their use requires pretreatment with antiemetic agents.

Pharmacologic Management of Acute Migraine

- Other common adverse effects include abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness.
- Severe peripheral ischemia (ergotism) is rare and include: cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, and claudication.
- Gangrenous extremities, myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported (less with dihydroergotamine).

Pharmacologic Management of Acute Migraine

- **Ergotamine derivatives are contraindicated in patients with renal or hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; and sepsis; and in women who are pregnant or nursing.**
- **Triptans and ergot derivatives should NOT be used within 24 hours of each other.**
- **Dihydroergotamine does not appear to cause rebound headache, but dosage restrictions for ergotamine tartrate should be observed strictly to prevent this complication.**

Pharmacologic Management of Acute Migraine

Serotonin Receptor Agonists (Triptans):

- Introduction of the 5-HT receptor agonists, or triptans, represented a significant advance in migraine pharmacotherapy.
- The first member of this class, sumatriptan, and the second-generation agents zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan are selective agonists at the 5-HT_{1B} and 5-HT_{1D} receptors.
- The triptans are appropriate first-line therapy for patients with mild to severe migraine and are used for rescue therapy when nonspecific medications are ineffective.

Pharmacologic Management of Acute Migraine

Relief of migraine headache is the result of three key actions:

1) **normalization of dilated intracranial arteries through enhanced vasoconstriction.**
2) **inhibition of vasoactive peptide release from perivascular trigeminal neurons.**
3) **inhibition of transmission through second-order neurons ascending to the thalamus.**

Pharmacologic Management of Acute Migraine

- Sumatriptan is available for subcutaneous, oral, and intranasal administration.
- Subcutaneous sumatriptan has a more rapid onset of action than the oral formulation.
- It is available as an autoinjector device for self-administration.
- Intranasal sumatriptan also has a faster onset of effect than the oral formulation.
- In general, triptans can be divided into those with a faster onset and higher efficacy and those with a slower onset and lower efficacy.

Pharmacologic Management of Acute Migraine

- **Compared with other triptans, frovatriptan and naratriptan have the longest half-lives, the slowest onset of action, and less headache recurrence.**
- **Faster-acting triptans are more efficacious when a rapid onset is necessary.**
- **Individual responses cannot be predicted, and if one triptan fails, a patient can be switched successfully to another triptan.**

Pharmacologic Management of Acute Migraine

Adverse effects:

- **Paresthesias, fatigue, dizziness, and somnolence.**
- **Flushing and warm sensations probably due to vasomotor autonomic dysfunction or part of migraine.**
- **Local adverse effects are subcutaneous injection site reactions and taste perversion, nasal discomfort after intranasal use.**
- **“Triptan sensations,” including tightness, pressure, heaviness, or pain in the chest, neck, or throat.**

Pharmacologic Management of Acute Migraine

- All triptans are partial agonists of human 5-HT coronary artery receptors in vitro, resulting in a small but significant vasoconstrictor response → myocardial infarction.
- The triptans are contraindicated in patients with a history of ischemic heart disease (angina pectoris, Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, cerebrovascular disease, and hepatic diseases (hepatotoxic).
- Postmenopausal women, men older than 40 years of age, and patients with uncontrolled risk factors should receive a cardiovascular assessment prior to triptan use and have initial doses administered under medical supervision.

Pharmacologic Management of Acute Migraine

- **Triptans are also contraindicated in patients with hemiplegic and basilar migraine and should NOT be used routinely in pregnancy.**
- **The triptans should NOT be given within 24 hours of the ergotamine derivatives.**
- **Administration of sumatriptan, rizatriptan, and zolmitriptan within 2 weeks of therapy with monoamine oxidase inhibitors (MAOIs) is NOT recommended. (MAOIs slow triptan metabolism)**

Pharmacologic Management of Acute Migraine

- **Eletriptan should NOT be administered with cytochrome P450 3A4 inhibitors such as macrolide antibiotics, antifungals, and some antiviral therapies.**
- **Concomitant therapy with the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine, and mirtazapine) can potentially cause "Serotonin syndrome".**
- **Frequent use of the triptans has been associated with the development of medication-overuse headache.**

Prophylactic Pharmacologic Therapy of Migraine

β-Adrenergic Antagonists:

- Are among the most widely used drugs for migraine prophylaxis.
- Metoprolol, propranolol, and timolol have established efficacy reducing the frequency of attacks by 50% in greater than 50% of patients.
- Their precise mechanism of antimigraine action is unknown.
- Adverse effects can include drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, impotence, bradycardia, heart failure, and hypotension.
- They should be used with caution in patients with congestive heart failure, peripheral vascular disease, atrioventricular conduction disturbances, asthma, depression, and diabetes.

Prophylactic Pharmacologic Therapy of Migraine

Antidepressants:

- **The beneficial effects of antidepressants in migraine are independent of their antidepressant activity and may be related to downregulation of central 5-HT_2 receptors, increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor actions.**
- **The tricyclic antidepressant (TCA) amitriptyline and SNRI venlafaxine are classified as probably effective for migraine prophylaxis.**

Prophylactic Pharmacologic Therapy of Migraine

Adverse effects:

- **Anticholinergic adverse effects (limit use of these agents in patients with benign prostatic hyperplasia and glaucoma).**
- **Sedation (give dose in the evening).**
- **Increased appetite and weight gain.**
- **Orthostatic hypotension and cardiac toxicity (slowed atrioventricular conduction).**
- **Nausea, vomiting, and drowsiness (venlafaxine).**
- **“Serotonin syndrome” (with SSRIs or SNRIs and a triptan).**

Prophylactic Pharmacologic Therapy of Migraine

Anticonvulsants:

- **The anticonvulsants valproate, divalproex, and topiramate all having established prophylactic efficacy.**
- **The beneficial effects of valproate may be due to:**

1) **enhancement of γ-aminobutyric acid (GABA)-mediated inhibition.**
2) **modulation of the excitatory neurotransmitter glutamate.**
3) **inhibition of sodium and calcium ion channel activity.**

- **They are particularly useful in patients with comorbid seizures, anxiety disorder, or bipolar illness.**

Prophylactic Pharmacologic Therapy of Migraine

Adverse effects:

- **Nausea and vomiting, alopecia, tremor, asthenia, somnolence, and weight gain.**
- **Hepatotoxicity.**
- **Valproate is contraindicated in pregnant women (owing to potential teratogenicity) and patients with a history of pancreatitis or chronic liver disease.**

Prophylactic Pharmacologic Therapy of Migraine

- **Topiramate is the most extensively studied medication for migraine prophylaxis.**
- **The benefits of topiramate are observed as early as 2 weeks after initiation of therapy, with significant reductions in migraine frequency within the first month.**
- **~ 50% of patients treated have 50% or greater reduction in mean headache frequency.**

Prophylactic Pharmacologic Therapy of Migraine

Adverse effects:

- Paresthesia, fatigue, anorexia, diarrhea, weight loss, hypesthesia, difficulty with memory, language problems, taste perversion, and nausea.
- Topiramate should be used with caution or avoided in patients with a history of kidney stones or cognitive impairment.
- Other anticonvulsants (carbamazepine, lamotrigine, gabapentin) may be effective.

Prophylactic Pharmacologic Therapy of Migraine

Nonsteroidal antiinflammatory drugs:

- **Nonsteroidal antiinflammatory drugs are modestly effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit the daily or prolonged use of these agents.**
- **NSAIDs have been used intermittently to prevent menstrual migraine.**
- **For migraine prevention, the evidence for efficacy is strongest for naproxen and weakest for aspirin.**

Prophylactic Pharmacologic Therapy of Migraine

Triptans:

- Triptans are also useful for the prevention of menstrual migraine.
- Frovatriptan has established efficacy, while naratriptan and zolmitriptan are probably effective.
- The triptan is usually started 1 or 2 days before the expected onset of headache and continued during the period of vulnerability.

Therapy of Certain Disorders During Pregnancy

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Department of Pharmacology, Faculty of Medicine

Pharmacokinetic Changes During Pregnancy

- Normal physiologic changes that occur during pregnancy may alter medication effects, resulting in the need to monitor or adjust dose or type of therapy.
- Physiologic changes begin in the first trimester and peak during the second.
- Maternal plasma volume, cardiac output and GFR increase by 30-50%, lowering the concentration of drugs excreted by the kidney.

Pharmacokinetic Changes During Pregnancy

- **Therefore, pregnant women may have different drug pharmacokinetics than non-pregnant women.**
- **As fat increases during pregnancy, the volume of distribution of fat-soluble drugs increases.**
- **Plasma albumin concentration decreases due to dilution, which increases the volume of distribution of highly protein-bound drugs.**
- **Unbound drug is also rapidly eliminated by the liver or the kidney.**

Pharmacokinetic Changes During Pregnancy

- **Hepatic perfusion increases, which may increase hepatic extraction of drugs.**
- **Nausea and vomiting as well as delayed gastric emptying may alter drug absorption.**
- **Pregnancy-induced increases in gastric pH may affect absorption of weak acids and basis.**
- **High levels of estrogen and progesterone may affect hepatic enzyme activity.**

Pregnancy-Influenced Issues

- **Pregnancy causes or exacerbates conditions that pregnant women experience: constipation, gastro-esophageal reflux, hemorrhoids, nausea and vomiting.**
- **Gestational diabetes, gestational hypertension, and venous thrombo-embolism have the potential to cause adverse pregnancy consequences.**

Pregnancy-Influenced Issues

1. **GIT:**

A. **Constipation is prevalent during pregnancy, and can exacerbate hemorrhoids.**

- **Management of constipation starts first with moderate physical exercise and increased dietary intake of fibers and fluids.**
- **If additional treatment is needed. Supplemental fiber and/or stool softener is appropriate.**

Pregnancy-Influenced Issues

- **Bulk-forming agents (psyllium, methylcellulose, and polycarbophil) are safe for long-term use because they are not absorbed.**
- **Osmotic laxative (polyethylene glycol, lactulose, and sorbitol) and stimulant laxatives (Senna and bisacodyl) can be used.**
- **Use of magnesium and sodium salts may cause electrolyte imbalance.**

Pregnancy-Influenced Issues

- **Castor oil should be avoided because it stimulates uterine contractions, causes diarrhea, dehydration, and GIT adverse effects.**
- **Mineral oil impairs fat-soluble vitamin absorption, and may cause severe bleeding in the newborn if used for long time.**
- **Hemorrhoides should be treated conservatively.**

Pregnancy-Influenced Issues

B. **Management of gastro-esophageal reflux disease includes:**

- **Life-style and dietary modification (small frequent meals, alcohol and tobacco avoidance, food avoidance at bedtime, elevation of the head of the bed).**
- **If symptoms are not relieved, antacids (aluminum, calcium or magnesium preparations) and sucralfate are acceptable.**

Pregnancy-Influenced Issues

- **Sodium bicarbonate (sodium overload) and magnesium trisilicate (no data available on safety) should be avoided.**
- **If the patient does not respond, histamine H_2-receptor blockers (ranitidine) can be used.**
- **Proton pump inhibitors (omeprazole) may not be associated with increased risk of major birth defects.**

Pregnancy-Influenced Issues

C. **Nausea and vomiting of pregnancy affect ~90% of pregnant women.**

- **It begins within 4-6 weeks of gestation, peeks between weeks 8-12 and resolves by 16-20 weeks.**
- ***Hyperemesis gravidarum* (severe vomiting causing weight loss, dehydration, electrolyte imbalance, and ketonuria) occurs in 0.5-2% of women.**

Pregnancy-Influenced Issues

- **Dietary modifications such as eating frequent small soft meals, and avoiding fatty and spicy meals may be helpful.**
- **Ginger (الزنجبيل) is effective and probably safe.**
- **Pyridoxine (vitamin B_6) and/or antihistamines (doxylamine) are effective and are first-line agents.**

Pregnancy-Influenced Issues

- **Metoclopramide and phenothiazines may cause sedation and extrapyramidal adverse effects including dystonia.**
- **Ondansetron (serotonin 5-HT_3 receptor antagonist) is controversial and may cause oral clefts.**
- **Corticosteroids may be effective. Reserved for use after the first trimester, because of risk of oral clefts.**

Pregnancy-Influenced Issues

2. Gestational diabetes (GDM):

- **GDM is diabetes diagnosed during the second and third trimester.**
- **It develops in 3-5% of pregnant women.**
- **Nutritional education with dietary modifications, exercise and blood glucose monitoring are considered first-line for all women with GDM.**

Pregnancy-Influenced Issues

- 85% of patients can achieve control with this first-line therapy.
- Human insulin is the drug of choice for GDM because it does not cross the placenta.
- ~~Glyburide and metformin are alternatives but long-term safety data are limited.~~
- Risks of GDM include: fetal loss, increased risk of congenital malformations, and macrosomia.

Pregnancy-Influenced Issues

3. Hypertensive disorders of pregnancy:

- **Complicate ~ 10% of pregnancies, and Include:**

1) **Gestational hypertension (without proteinuria developing after 20 weeks of gestation).**
2) **Preeclampsia/eclampsia.**
3) **Chronic hypertension (preexisting hypertension or developing before 20 weeks of gestation).**
4) **Chronic hypertension with superimposed preeclampsia.**

Pregnancy-Influenced Issues

- **Defined as hypertension > 140/90.**
- **Non-drug management: stress reduction, and exercise.**
- **Activity restriction (?): prolonged bed rest may increase the risk of venous thrombo-embolism.**
- **Use of supplemental calcium 1-2 g per day decreases the risk of hypertension and preeclampsia in patients with initial low calcium intake.**

Pregnancy-Influenced Issues

- **Calcium supplements are not effective in patients with adequate calcium intake.**
- **Initial drug choices include methyldopa, hydralazine, or labetelol.**
- **Oral nifedipine may be used (slow release, not fast-acting).**
- **Magnesium sulfate when preeclampsia is present.**

Pregnancy-Influenced Issues

Preeclampsia:

- **Develops after 20 weeks of gestation.**
- **Chronic and gestational hypertension may be complicated with preeclampsia.**
- **It is a multisystem syndrome: renal failure, maternal morbidity/mortality, preterm delivery, and intrauterine growth retardation.**

Pregnancy-Influenced Issues

- **Treatment: in addition to treatment of hypertension, low-dose aspirin 60-81 mg/day beginning late in the first trimester in women at risk of preeclampsia.**
- **The only cure is delivery of the placenta.**

Pregnancy-Influenced Issues

Eclampsia:

- **Seizures on top of preeclampsia.**
- **It is a medical emergency.**
- **May be prevented by low dose aspirin.**
- **Magnesium sulfate is effective in preventing eclampsia and treating its seizures.**
- **Usual dose 4-6 g IV over 15-20 min, followed by 2g/hr continuous IV infusion for 24 hours.**
- **Diazepam and phenytoin should be avoided.**

Pregnancy-Influenced Issues

4. **Venous Thrombo-embolism (VTE):**

- **Risk of VTE in pregnant women is 5-10 fold higher than that in non-pregnant women.**
- **Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for treatment of acute VTE in pregnancy.**
- **Treatment should be continued throughout pregnancy and for 6 weeks after delivery (minimum duration of therapy should not be < 3 months).**

Pregnancy-Influenced Issues

- **Fondaparinux (synthetic pentasaccharide) and injectable direct thrombin inhibitors (lepirudin, bivalirudin) should be avoided unless the patient has heparin-induced thrombocytopenia.**
- **The oral agents dabigatran (direct thrombin inhibitor), rivaroxaban (direct factor Xa inhibitor), apixapan (direct factor Xa inhibitor) are not recommended.**

Pregnancy-Influenced Issues

- **Warfarin should not be used because it may produce:**
- **Nasal hypoplasia.**
- **Stippled epiphysis (chondodysplasia punctata).**
- **Limb hypoplasia.**
- **Eye abnormalities.**

  (risk period 6-12 weeks of gestation)
- **CNS anomalies are associated with exposure during 2nd and 3rd trimesters.**

Pregnancy-Influenced Issues

- In women with high risk for VTE, antipartum LMWH prophylaxis, with 6 weeks postpartum prophylaxis with LMWH or warfarin is recommended.
- Women with prosthetic heart valves should receive LMWH twice daily (or UFH every 12 hours) during pregnancy.
- High risk women with prosthetic heart valves may also receive low-dose aspirin of 75-100 mg/day.

Pregnancy-Influenced Issues

- LMWH should be adjusted to achieve a peak anti-Xa level (0.7 - 1.2 U/mL) at 4 hour post-subcutaneous dose.
- This recommendation may be associated with subtherapeutic trough level.
- UFH treatment should target a mid-interval aPTT value at least twice the control value or an anti-Xa level of 0.35-0.7 U/mL.

Acute Care Issues in Pregnancy

1. **Urinary Tract Infections (UTIs):**

- ***Escherichia coli* is the primary cause of infection in 75-90 % of cases.**
- **Other gram-negative rods (*Proteus* and *Klebsiella*), as well as, group B *Streptococcus* (GBS) may cause UTI.**
- **The presence of GBS in urine indicates heavy colonization of the genitourinary tract, increasing the risk for GBS infection in the newborn.**

Acute Care Issues in Pregnancy

- UTIs are asymptomatic (asymptomatic bacteriuria) or symptomatic (cystitis and pyelonephritis).
- Treatment of asymptomatic bacteriuria and cystitis is necessary to prevent pyelonephritis. Duration of treatment 7-14 days.
- The most commonly used antibiotics to treat asymptomatic bacteriuria and cystitis are β-lactam antibiotics [amoxacillin and cephalosporins] and nitrofurantoin.

Acute Care Issues in Pregnancy

- **β-lactam antibiotics are not teratogenic, but *E. coli* resistance to ampicillin and amoxicillin limits their use as single agents.**
- **Nitrofurantoin is not active against *Proteus* species and should not be used after week 37 in patients with G6PD deficiency because of the risk of hemolytic anemia in the newborn.**
- **Sulfa-containing drugs (co-trimoxazole) can contribute to the development of newborn kernicterus, and should be avoided during the last week of gestation.**

Acute Care Issues in Pregnancy

- **Trimethoprim is a folate antagonist that is contraindicated during the first trimester because of association with cardiovascular malformations.**
- **Fluoroquinolones are containdicated because of association with impaired cartilage development.**
- **Tetracyclines are containdicated because of association with deciduous teeth discoloration, if given after 5 months of gestation.**

Acute Care Issues in Pregnancy

- **Pyelonephritis is more severe and is associated with premature delivery, low infant birth weight, hypertension, anemia, bacteremia, and transient renal failure.**
- **Hospitalization is the standard of care for pregnant women with pyelonephritis.**
- **Therapy include parenteral administration of 2nd and 3rd generation cephalosporins (cefuroxime and ceftriaxone), ampicillin + gentamicin, or ampicillin-sulbactam.**

Acute Care Issues in Pregnancy

- **Switching to oral therapy is likely if the woman is afebrile for 48 hours.**
- **The total duration of therapy for acute pyelonephritis is 10-14 days.**
- **Nitrofurantoin should be avoided because it does not achieve therapeutic levels outside urine.**

Acute Care Issues in Pregnancy

2. Sexually transmitted Infections (STIs):

Can be classified as:

a. **Infections that may be transmitted across the placenta and infect the fetus prenatally (syphilis).**
b. **Infections that can be transmitted during birth and cause neonatal infections (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Herpes simplex virus*).**

Acute Care Issues in Pregnancy

c. **Infections that pose a threat for preterm labor (bacterial vaginosis, BV).**

Treatment for some sexually transmitted diseases in pregnancy:

1. **Bacterial vaginosis:**

   Recommended: Metronidazole.

   Alternative: Clindamycin.

2. **Chlamydia:**

   Recommended: Azithromycin.

   Alternative: Erythromycin.

Acute Care Issues in Pregnancy

3. **Genital herpes:**

   Recommended: Acyclovir or valacyclovir.

4. **Gonorrhea:**

   Recommended: Ceftriaxone , treat chlamydial infection concurrently.

   Alternative: Azithromycin.

5. **Trichomoniasis:**

   Recommended: Metronidazole

   Tinidazole should be avoided during pregnancy.

Acute Care Issues in Pregnancy

3. **Headache:**

a. **Primary headaches : tension and migraine headaches.**

b. **Secondary headaches: those caused by eclampsia, stroke, postdural puncture, cerebral angiopathy, and cerebral venous thrombosis.**

- **Migraine headaches are associated with estrogen fluctuations in women of child-bearing age.**

Acute Care Issues in Pregnancy

- 60-70% of pregnant women with a history of migraine headaches experience improvement during pregnancy.
- 20% experience complete cessation of attacks.
- Improvement is more likely in

a) women who have migraine without aura.

b) women who have a history of menstrual migraine.

Acute Care Issues in Pregnancy

- Tension headaches are not well studied.
- Most women report no change in frequency or intensity.
- Relaxation, stress management, and biofeedback are all effective non-pharmacological treatments, with minimal risk.
- For tension headaches acetaminophen or ibuprofen can be used.

Acute Care Issues in Pregnancy

- While ibuprofen is considered safe (?), all NSAIDs are contraindicated in the third trimester because of the danger of premature closure of the ductus arteriosus.
- Aspirin should also be avoided in the third trimester because in addition, it can cause maternal and fetal bleeding as well as decreased uterine contractility (prolonged labor).

Acute Care Issues in Pregnancy

- For migraine headaches analgesics (acetaminophen and ibuprofen) are indicated.
- Opioids may contribute to migraine-associated nausea, and long-term use near term can cause neonatal withdrawal.
- For non-responsive migraine, sumatriptan can be used (other triptans lack information about use in pregnancy).
- Ergotamine is contraindicated because of effects on uterine tone.

Acute Care Issues in Pregnancy

- **Promethazine, prochlorperazine, metoclopramide may be used for patients with migraine-associated nausea.**
- **Propranolol (given at the lowest effective dose) and amitriptyline (10-25mg PO daily) can be used for prophylaxis in patients who experience severe migraine.**

Chronic Illnesses in Pregnancy

1. **Allergic Rhinitis:**

- **Treatment strategies for allergic rhinitis in pregnancy are similar to non-pregnant women: avoidance of allergen, immunotherapy, and pharmacotherapy.**
- **Drugs that can be used: intranasal corticosteroids, intranasal cromolyn, and first-generation antihistamines (chlorpheniramine, diphenhydramine, and hydroxyzine.**
- **Topical oxymetazoline (α-agonist) may be preferable to oral decongestants.**

Chronic Illnesses in Pregnancy

2. Bronchial Asthma:

- **Health consequences of untreated or poorly treated asthma include: preterm labor, preeclampsia, intrauterine growth retardation, premature birth, low birth weight, and stillbirth.**
- **Risks of medications use to the fetus are less than risks of untreated asthma.**

Chronic Illnesses in Pregnancy

Treatment:

1. **Step 1: short-acting β_2-agonists (SABA), albuterol + inhalational corticosteroids, budesonide.**
2. **Step 2: long-acting β_2-agonists (LABA), albuterol.**

Chronic Illnesses in Pregnancy

3. Diabetes Mellitus:

- **Poorly controlled diabetes can cause fetal malformations, fetal loss, and maternal morbidity.**
- **Women with diabetes should use effective contraception until optimal glycemic control is achieved before attempting pregnancy.**
- **Human insulin is safe during pregnancy.**
- ~~**Alternatives for type 2 DM include glyburide and metformin.**~~

Chronic Illnesses in Pregnancy

3. **Epilepsy:**

- **Seizure frequency does not change for most pregnant women with epilepsy.**
- **Seizures may become more frequent because of changes in:**

a) **maternal hormones.**

b) **sleep deprivation.**

c) **medication adherence problems because of fear of teratogenic risk.**

Chronic Illnesses in Pregnancy

d) changes of free serum concentration of antiseizure drugs resulting from:

i. increased maternal volume of distribution.

ii. decreased protein binding from hypoalbuminemia.

iii. increased hepatic drug metabolism.

iv. increased renal drug clearance.

v. Increased body fat.

Chronic Illnesses in Pregnancy

- **The risks of uncontrolled seizures to the fetus are greater than those associated with antiseizure drugs. (especially for tonic-clonic seizures).**
- **Major malformations are 2-3 times more likely to occur in children born to women taking antiseizure drugs than to those who do not.**

Chronic Illnesses in Pregnancy

ASDs status:

a. **Probably safest ASDs: Carbamazepine, lamotrigine, levetiracetam, phenytoin (??).**
b. **Lower risk than valproic acid (VPA): Gabapentin, oxcarbazepine, zonisamide.**
c. **Significant risk: VPA, topiramate, phenobarbital.**

Chronic Illnesses in Pregnancy

- **Use of valproic acids should be avoided during pregnancy.**
- **Major malformations with valproic acid are dose-related and range from 6-9%.**
- **Include neural tube defects (spina bifida), facial clefts and cognitive teratogenicity.**
- **Antiseizure drug monotherapy is recommended with dose optimized before conception.**

Chronic Illnesses in Pregnancy

- **All women taking antiepileptic drugs should receive folic acid supplementation (4-5 mg daily) starting before pregnancy and continuing at least through the first trimester, and preferably throughout pregnancy.**
- **Important !!**

Risk of Antiseizure Drugs During Pregnancy

https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/tog.12413

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784252/pdf/10.1177_1756285615623934.pdf

When to avoid or postpone pregnancy?

1. Uncontrolled epilepsy
2. Drug-resistant epilepsy
3. Polytherapy
4. High dose ASDs
5. Non-compliance
6. Poor general health

Antiseizure Drug (ASD)	Risk of Congenital Malformation
No ASD	2-%
Carbamazepine	**2-5%**
Lamotrigine	**2-5%**
Levetiracetam	1-2%
Oxcarbazepine	1-3%
Phenobarbital	2%, **5.5%**
Phenytoin	1-2% , **2.9-3.7%**
Sodium valproate	**6-10%**
Topiramate	**4-7%**
Gabapentin	0.7-3%
Clonazepam	3.1%
Monotherapy	**3-5%**
Polytherapy	**6-8%**
Polytherapy with valproate	**Up to 10%**

Chronic Illnesses in Pregnancy

4. Hypertension:

- A physiologic decrease in blood pressure occurs during the first part of pregnancy reaching lowest point between 16-18 weeks of gestation.
- By the third trimester, blood pressure returns to pre-pregnancy levels.

Chronic Illnesses in Pregnancy

Chronic hypertension of pregnancy:

Defined as :

1) **hypertension occurring before 20 weeks of gestation**
2) **the use of antihypertensive medications before pregnancy**
3) **or the persistence of hypertension beyond 12 weeks postpartum.**

Classified as:

a. **Mild/non-severe: 140-159/90-109 mmHg**
b. **Severe: ≥160/≥110 mmHg**

Chronic Illnesses in Pregnancy

- **Chronic hypertension can cause fetal growth restriction, maternal complications and hospital admissions.**
- **When treating chronic hypertension in pregnant women you should be careful NOT to compromise utero-placental blood flow. (should Lower BP over a period of hours).**
- **If there is no end organ damage, antihypertensive drugs may not be used to treat non-severe hypertension. (<160/<105 mmHg).**

Chronic Illnesses in Pregnancy

- **When using antihypertensive medication sustain blood pressure at 120-160 / 80-105 mmHg.**

Drugs:

- **Initial choice include methyldopa, hydralazine, or labetelol.**
- **Oral slow-release nifedipine may be used, but not fast-acting nifedipine.**
- **Magnesium sulfate when preeclampsia is present.**

Chronic Illnesses in Pregnancy

- **ACEis, ARBs, renin inhibitors (aliskiren), and mineralocorticoid receptor antagonists should be avoided, because of teratogenicity and toxicity to fetus.**
- **Atenolol may be associated with fetal growth restrictions.**
- **Thiazides are second line. They reduce plasma volume.**

Therapy of Hypertension

Treatment of Chronic Hypertension in Pregnancy

Drug/Class	Comments
Methyldopa	Long-term follow-up data supports safety; considered a preferred agent
Labetalol	Increasingly used over methyldopa because of fewer side effects; considered a first-line agent
ACEi, ARB, direct renin inhibitor	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)
β-Blockers	Intrauterine growth retardation reported (mostly with atenolol)
Clonidine, thiazides, CCBs	Limited data

Chronic Illnesses in Pregnancy

5. **Mental health conditions:**

- **Most women with mental health conditions discontinue or refuse treatment because of concern about teratogenicity, or because of paranoid or delusional thinking.**
- **In general, monotherapy is preferred over polytherapy, even if higher doses are required.**

Chronic Illnesses in Pregnancy

A. **Depression:**

- **Maternal depression is associated with greater risk for premature birth, low birth weight, miscarriage, and fetal growth restriction, and long-term implications for normal infant development.**
- **Selective serotonin reuptake inhibitors (SSRIs) (paroxetine) are not considered major teratogens, and are relatively safe.**
- **Risks with Serotonin and norepinephrine reuptake inhibitors (SNRIs) are less defined.**

Chronic Illnesses in Pregnancy

- **Use of SSRIs, SNRIs, and tricyclic antidepressants (TCAs) in the later part of pregnancy is associated with:**

1. **Persistent pulmonary hypertension of the newborn.**
2. **"Prenatal Antidepressant Exposure Syndrome" (cardiac, respiratory, neurological, GI, and metabolic complications from drug toxicity or withdrawal of drug therapy).**

- **Women who stop taking antidepressants are more likely to relapse, which have negative implications on the well being of the fetus.**

Chronic Illnesses in Pregnancy

Mood Stabilizers:

- **Commonly used drugs for bipolar illness in non-pregnant patients are lithium, lamotrigine, carbamazepine, and valproic acid.**
- **Lithium use for bipolar disorders during pregnancy was associated with increased risk of cardiac malformations (especially Ebstein's anomaly, which involves the tricuspid valve).**

Chronic Illnesses in Pregnancy

- **Other neonatal adverse effects include floppy baby syndrome, nephrogenic diabetes insipidus, hypoglycemia, cardiac arrhythmias, thyroid dysfunction.**
- **During pregnancy: polyhydramnios, and premature delivery.**
- **Lithium level, thyroid and renal functions should be monitored during pregnancy.**

Chronic Illnesses in Pregnancy

During lactation:

- **Lithium may cause lethargy, hypotonia, hypothermia, cyanosis, and changes in ECG in breastfed infants.**
- **In breastfed infants: lithium level, thyroid functions and CBC should be monitored.**

Chronic Illnesses in Pregnancy

B. Schizophrenia:

- **Maternal schizophrenia is associated with increased risk of perinatal death, low birth weight, small-for-gestational-age infants, cardiovascular malformation, pre-term delivery, stillbirth, and infant death.**

Chronic Illnesses in Pregnancy

- **Both the typical and the atypical antipsychotics were not adequately evaluated for use during pregnancy.**
- **The typical antipsychotics (chlorpromazine, haloperidol, and perphenazine) were used during pregnancy with no reported congenital malformations.**

Chronic Illnesses in Pregnancy

- **Atypical antipsychotics (olanzapine, clozapine, quetiapine, and resperidone) use during pregnancy showed a higher rate of low-birth-weight, and cardiovascular defects.**
- **Atypical antipsychotics can cause weight gain, gestational diabetes, and metabolic syndrome with poor obstetric outcomes.**

Chronic Illnesses in Pregnancy

Benzodiazepines (for anxiety):

- The use of diazepam during pregnancy is associated with increased risk of oral clefts.
- Benzodiazepines used in the third trimester can cause infant sedation and withdrawal symptoms (restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea and vomiting).
- "Floppy-Baby Syndrome" has also been described (low-Apgar scores, hypothermia, poor muscle tone, feeding difficulties, and poor temperature adaptation).

Chronic Illnesses in Pregnancy

6. Thyroid disorders:

- **Untreated hypothyroidism increases the risk of preeclampsia, premature birth, miscarriage, growth restriction, and impaired neurological development in the fetus.**
- **Thyroid replacement should be instituted with 0.1 mg/day levothyroxine.**

Chronic Illnesses in Pregnancy

- **Women taking thyroid replacement before pregnancy usually have increased requirement during pregnancy.**
- **Follow TSH level during pregnancy every 4-6 weeks for dose titration.**
- **Hyperthyroidism during pregnancy is associated with fetal death, low birth weight, intrauterine growth restriction, and preeclampsia.**

Chronic Illnesses in Pregnancy

- **Therapy include thionamides (methimazole and propylthiouracil (PTU).**
- **Use PTU in first trimester (it is significantly ionized at physiologic pH), and switch to methimazole in second & third trimesters to balance the risk of PTU-induced hepatotoxicity, and methimazole embryopathy (Choanal and esophageal atresia).**

Chronic Illnesses in Pregnancy

- **The risks of uncontrolled hyperthyroidism outweigh the risks of thionamides.**
- **Iodine 131 (I^{131}) is contraindicated because of the risk of damage of fetal thyroid.**

Labor and Delivery

1. **Preterm labor:**

- **Preterm labor occurs between 20-37 weeks of gestation.**
- **It is a leading cause of infant morbidity and mortality.**

Tocolytic therapy:

- **The purposes of tocolytic therapy:**

1. **Postpone delivery to allow for maximal effect of antenatal corticosteroid therapy.**

Labor and Delivery

2. **Allow for transportation of the mother to a facility equipped to deal with high-risk deliveries.**
3. **Prolongation of pregnancy when there are underlying, self-limiting conditions that can cause labor (pyelonephritis, abdominal surgery).**

- **Tocolytics are <u>not</u> used beyond 34 weeks of gestation.**

Labor and Delivery

- **Tocolytic therapy should not be used in cases of previability, intrauterine fetal demise, a lethal fetal anomaly, intrauterine infection, fetal distress, severe preeclampsia, vaginal bleeding, or maternal hemodynamic instability.**
- **Tocolytic agents: β-agonists, magnesium, calcium channel blockers, and prostaglandin inhibitors (NSAIDs).**
- **All prolong pregnancy 2-7 days, but do not reduce overall rates of respiratory distress syndrome, neonatal death or preterm delivery.**

Labor and Delivery

β_2-agonists (terbutaline, ritodrine):

- **Have higher incidence of maternal adverse effects: hypokalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema.**
- **Oral dosing or prolonged parenteral (sc) use may be associated with maternal cardiotoxicity and death.**

Labor and Delivery

Intravenous magnesium sulfate:

- **Its use is not supported by evidence of effectiveness as tocolytic agent.**
- **However, it has a neuroprotective role – it decreases the occurrence of cerebral palsy.**
- **Maternal adverse effects: pulmonary edema.**
- **Toxic effects: hypotension, muscle paralysis, tetany, cardiac arrest, and respiratory depression.**
- **Dose adjustment is needed in renal dysfunction.**

Labor and Delivery

Nifedipine (slow release):

- **It is associated with fewer adverse effects than β-agonists and magnesium sulfate.**
- **One significant adverse reaction is hypotension with consequent effect on utero-placental blood flow.**
- **Associated with reduced neonatal morbidity.**

Labor and Delivery

NSAIDs (Indomethacin):

- **Associated with increased rate of closure of the ductus arteriosus when used after 32 weeks of gestation, for more than 48 hours.**

Progesterone:

- **Reduces cervical ripening, reduces uterine wall contractility, and modulate inflammation.**
- **It prevents spontaneous preterm birth**

Labor and Delivery

Antenatal Corticosteroids:

- **Used for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage and death of infants in premature delivery. (given to the mother)**
- **Betamethasone 12 mg/day IM for 2 doses.**
- **Dexamethasone 6 mg IM every 12 hours for 4 doses.**

  (between 24-34 weeks of gestation)

Labor and Delivery

Group B *Streptococcus* (GBS) infection:

- **Maternal infection with GBS is associated with invasive disease of the newborn.**
- **Associated with increased risk of pregnancy loss, premature delivery, and transmission of the bacteria to the infant during delivery.**
- **Neonatal infections include bacteremia, pneumonia, meningitis leading to fatality.**
- **Penicillin G 5 million units given IV, followed by 2.5 million units every 4 hours until delivery is the recommended treatment.**

Labor and Delivery

- **Ampicillin is an alternative at 2g IV followed by 1g every 4 hours until delivery.**
- **In women with penicillin allergy but not at risk of anaphylaxis, cefazolin 2g IV, followed by 1g every 8 hours.**
- **In women with high risk of anaphylaxis, clindamycin 900 mg IV every 8 hours, or erythromycin 500 mg IV every 6 hours.**
- **If resistant to clindamycin and erythromycin, vancomycin 1g IV every 12 hours until delivery.**

Labor and Delivery

Cervical Ripening and Labor Induction:

- **Cervical ripening is mediated by hormonal changes, including final mediation by prostaglandin E_2 and $F_{2\alpha}$ which increase collagenase activity in the cervix leading to thinning and dilation.**
- **Concerns with induction of labor are ineffective labor and hyperstimulation that may adversely affect the fetus.**

Labor and Delivery

- **Prostaglandin E_2 analogs (dinoprostone) are commonly used for cervical ripening administered intracervically. The patient should remain supine for 30 min.**
- **The insert is removed when labor begins or after 12 hours.**
- **The patient should be attached to the fetal heart monitor for the entire period of insertion and 15 min after its removal.**

Labor and Delivery

- Prostaglandin E_1 analogs (Misoprostol) can be used and is effective.
- More effective when inserted intravaginally.
- Adverse effects: hyperstimulation, and meconium-stained amniotic fluid.
- Misoprostol is containdicated in women with previous uterine scar because of its association with uterine rupture.
- Oxytocin is most commonly used for labor induction after cervical ripening.

Labor and Delivery

Labor Analgesia:

1. **The first phase of labor starts from onset of labor to complete cervical dilation. Women perceive visceral pain because of uterine contractions.**
2. **The second phase of labor is the period between complete cervical dilation and delivery. Women perceive visceral pain because of perineal stretching.**

Labor and Delivery

Pharmacologic approach to labor pain management:

1. **Parenteral opioids:**

- **Commonly used to alleviate labor pain.**
- **In comparison with epidural analgesia, they have lower rates of oxytocin augmentation, result in shorter stages of labor, and require fewer instrumental deliveries and cesarean section for fetal distress.**

Labor and Delivery

2. **Epidural analgesia:**

- **Better pain relief than other analgesic modalities.**
- **Constitutes administration of an opioid or an anesthetic (fentanyl and/or bupivacaine) into the epidural space.**

Labor and Delivery

- **Adverse effects: hypotension, pruritus, inability to void, prolongation of the first and second stages of labor, higher numbers of instrumental deliveries and cesarean section for fetal distress, nausea and vomiting, and maternal fever.**
- **Rarely, puncture of subarachnoid space leading to sever headache.**

Labor and Delivery

3. **Nitrous oxide (laughing gas):**

- **It is an inhaled anesthetic gas that may help reduce anxiety and make patients less aware of pain, but does not eliminate it.**
- **Many patients ask for another method of analgesia (epidural analgesia).**
- **Nitrous oxide was found to be safe for the newborns.**

Therapy of Meningitis

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Therapy of Meningitis

Goals of treatment:

1. **Eradication of infection.**
2. **Amelioration of signs and symptoms.**
3. **Prevention of the development of neurologic sequelae, such as seizures, deafness, coma, and death.**

Therapy of Meningitis

It is important to:

1) **Prevent the disease through timely introduction of vaccination and chemoprophylaxis.**
2) **Understand antibiotic selection and the issues surrounding antibiotic penetration into the central nervous system.**

- **Until a pathogen is identified, immediate empirical antibiotic coverage is needed.**

Therapy of Meningitis

- **The first dose of antibiotics should NOT be withheld, even when lumbar puncture is delayed or neuro-imaging is being performed; because changes in the CSF after antibiotic administration usually take up to 12 - 24 hours to occur.**

Therapy of Meningitis

- **Continued therapy should be based on the assessment of clinical improvement, culture, and susceptibility testing results.**
- **Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.**

Etiologies and Empirical Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy
<1 month	*Streptococcus agalactiae* Gram-negative enterics *(E. coli, Klebsiella spp, Enterobacter spp)* *Listeria Monocytogenes*	Ampicillin + cefotaxime or Ampicillin + aminoglycoside
1-23 months	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *Streptococcus agalactiae*	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae
2-50 years	*Neisseria meningitidis* *Streptococcus pneumoniae*	Vancomycin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae
>50 years	*Streptococcus pneumoniae* *Neisseria meningitidis* Gram-negative enterics *(E. coli, Klebsiella spp, Enterobacter spp)* *Listeria monocytogenes*	Vancomycin + ampicillin + 3rd generation cephalosporin (cefotaxime or ceftriaxone) Vancomycin to cover penicillin-resistant S. pneumoniae

Penetration of Antimicrobial Agents into the CSF

Therapeutic Levels in CSF With/Without Inflammation:

Acyclovir, Levofloxacin, Chloramphenicol, Linezolid, Ciprofloxacin, Metronidazole, Fluconazole, Moxifloxacin, Flucytosine, Pyrazinamide, Foscarnet, Rifampin, Fosfomycin, Sulfonamides, Ganciclovir, Trimethoprim, Isoniazid, Voriconazole

Therapeutic Levels in CSF With Inflammation of Meninges:

Ampicillin ± sulbactam, Imipenem, Aztreonam, Meropenem, Cefepime, Nafcillin, Cefotaxime, Ofloxacin, Ceftazidime, Penicillin G, Ceftriaxone, Piperacillin/tazobactam, Cefuroxime, Pyrimethamine, Colistin, Quinupristin/dalfopristin, Daptomycin, Ticarcillin ± clavulanic acid, Ethambutol, Vancomycin

Antimicrobial Agents by Organism

Gram-Positive Organisms:

Streptococcus pneumoniae: **duration 10-14 days.**

1. Penicillin susceptible:

- **Antibiotics of First Choice: Penicillin G or Ampicillin.**
- **Alternatives: Cefotaxime, Ceftriaxone, Cefepime or Meropenem.**

2. Penicillin resistant:

- **Antibiotics of First Choice: Vancomycin + Cefotaxime or Ceftriaxone.**
- **Alternatives: Moxifloxacin.**

Antimicrobial Agents by Organism

3. Ceftriaxone resistant:

- **Antibiotics of First Choice: Vancomycin + Cefotaxime or Ceftriaxone.**
- **Alternative: Moxifloxacin.**

Staphylococcus aureus: **duration 14-21 days.**

1. Methicillin susceptible:

- **Antibiotics of First Choice: Nafcillin or Oxacillin.**
- **Alternative: Vancomycin or Meropenem.**

Antimicrobial Agents by Organism

2. Methicillin resistant:

- **Antibiotics of First Choice: Vancomycin.**
- **Alternative: TMP-SMX or Linezolid.**

Group B *Streptococcus:* duration 14-21 days.

- **Antibiotics of First Choice: Penicillin G or Ampicillin ± Gentamicin.**
- **Alternative: Ceftriaxone or Cefotaxime.**

***Staph. epidermidis:* duration 14-21 days.**

- **Antibiotics of First Choice: Vancomycin.**
- **Alternative: Linezolid.**

Antimicrobial Agents by Organism

***Listeria monocytogenes*: duration ≥ 21 days**

- **Antibiotics of First Choice: Penicillin G or Ampicillin ± Gentamicin.**
- **Alternative: Trimethoprim-sulfamethoxazole, Meropenem.**

Antimicrobial Agents by Organism

Gram-Negative Organisms:

***Neisseria meningitidis*: duration 7-10 days.**

1. Penicillin susceptible:

- **Antibiotics of First Choice: Penicillin G or Ampicillin.**
- **Alternatives: Cefotaxime or Ceftriaxone.**

2. Penicillin resistant:

- **Antibiotics of First Choice: Cefotaxime or Ceftriaxone.**
- **Alternatives: Meropenem or Moxifloxacin.**

Antimicrobial Agents by Organism

***Haemophilus influenzae*: duration 7-10 days.**

1. β-lactamase negative:

- **Antibiotics of First Choice: Ampicillin.**
- **Alternatives: Cefotaxime, Ceftriaxone, Cefepime or Moxifloxacin.**

2. β-lactamase positive:

- **Antibiotics of First Choice: Cefotaxime or Ceftriaxone.**
- **Alternatives: Cefepime or Moxifloxacin.**

Antimicrobial Agents by Organism

Enterobacteriaceae (*Including *E. coli* and *Klebsiella* spp.*):
duration 21 days.

- **Antibiotics of First Choice: Cefotaxime or Ceftriaxone.**
- **Alternatives: Cefepime, Moxifloxacin, Meropenem or Aztreonam.**

Pseudomonas aeruginosa: **duration 21 days.**

- **Antibiotics of First Choice: Cefepime or Ceftazidime ± Tobramycin.**
- **Alternatives: Ciprofloxacin, Meropenem, Piperacillin + Tobramycin, Colistin sulfomethate, Aztreonam.**

Therapy of Meningitis

- **Supportive care (administration of fluids, electrolytes, antipyretics, and analgesics) is critically important.**
- **Venous thromboembolism prophylaxis and intracranial pressure (ICP) monitoring may be needed in some patients.**
- **Mannitol 25% or hypertonic 3% saline may be needed to maintain an ICP of less than 15 mm Hg.**
- **Appropriate antibiotic therapy (empirical or definitive) should be started as soon as possible.**

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- **Dexamethasone is a commonly used adjunctive therapy in the treatment of meningitis.**
- **Corticosteroids inhibit the production of TNF, PAF and IL-1, potent proinflammatory cytokines.**
- **They also reduce cerebral edema, high ICP, neuronal injury, and vasculitis.**
- **Some clinical studies have shown that treatment with corticosteroids reduces both mortality and neurological sequelae in adults with community-acquired bacterial meningitis.**

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- **Other studies have shown that corticosteroid use in bacterial meningitis was associated with lower rates of severe hearing loss, and neurological sequelae, but did not reduce overall mortality.**
- **Current recommendations are with the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with H. influenza meningitis.**

Dexamethasone as an Adjunctive Treatment for Bacterial Meningitis

- **The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 - 20 minutes prior to /or concomitant with, but not after, the first dose of antibiotics.**
- **With adjunctive dexamethasone use, signs and symptoms of GI bleeding and hyperglycemia, should be monitored carefully.**
- **However, routine use of dexamethasone in meningitis is still controversial.**

Bacterial Brain Abscess

Etiology:

1. **Those arising from spread of infection from oropharynx, middle ear, and paranasal sinuses are commonly caused by streptococci and oral anaerobes (Actinomyces spp., Bacteroides spp., Fusobacterium spp., Peptostreptococcus).**
2. **Staphylococci, aerobic and gram-negative bacilli are commonly involved in postoperative abscesses or those following head trauma.**

Bacterial Brain Abscess

3. ***P. aeruginosa*** **and** ***Nocardia*** **spp. can cause brain abscesses but are more commonly seen in immunocompromised patients.**

- **Brain abscesses are commonly polymicrobial, thus, empiric antimicrobial therapy should include antibiotics with activity against gram-positive, gram-negative, and anaerobic organisms:**

a) **Vancomycin + a third- or fourth-generation cephalosporin + metronidazole, depending on risk factors.**

Bacterial Brain Abscess

b) A carbapenem (meropenem) could replace the cephalosporin and metronidazole.

- De-escalation of therapy should be performed once a causative organism is identified.
- De-escalation means changing an empiric broad-spectrum antibiotic regimen to a narrower antibiotic regimen by changing the antimicrobial agent or changing from combination therapy to monotherapy.

Bacterial Brain Abscess

- **Duration of therapy should be determined for each individual patient and should include consideration of the causative pathogen, size of abscess, use of surgical treatment, and response to therapy.**
- **Duration is usually prolonged to 4-8 weeks.**
- **United Kingdom guidelines recommend 4-6 weeks if the abscess has been drained or excised and 6-8 weeks if the abscess is treated without drainage.**

Bacterial Brain Abscess

The following categories require a longer duration of therapy (6-8 weeks or longer):

1. **Patients with an organized capsule with evidence of tissue necrosis.**
2. **Patients with a multiloculated abscess.**
3. **Patients with lesions in vital locations such as the brain stem or the motor strip (particularly if not surgically drained).**
4. **Immunocompromised patients.**
5. **In case of needle aspiration rather than open surgical excision.**

Bacterial Brain Abscess

- **Anticonvulsant therapy is recommended for at least 1 year, because seizures are common complication of brain abscesses.**
- **The benefit of dexamethasone in the treatment of brain abscess is unclear and not routinely recommended, unless signs of cerebral edema are identified.**

Cryptococcus neoformans

- **Mainly affect persons with underlying impaired immunity.**
- **Acquired by inhalation of spores from the environment leading to CNS infection and less commonly pulmonary disease.**
- **Rapid sterilization of CNS through rapid fungicidal activity is the main approach of induction therapy (2 - 6 weeks), followed by consolidation therapy for 8 weeks.**

Cryptococcus neoformans

- **Amphotericin B was the drug of choice for the treatment of acute cryptococcal meningitis due to its rapid fungicidal activity, despite poor penetration into the CSF.**
- **Amphotericin B (1 mg/kg/day) combined with flucytosine (100 mg/kg/day) for 2 weeks was more effective than amphotericin alone for 4 weeks, or in combination with fluconazole (400 mg twice daily) for 2 weeks in HIV-positive patients.**
- **Voriconazole in combination with amphotericin B can be used.**

Cryptococcus neoformans

- **Flucytosine is poorly tolerated, causing bone marrow suppression and GI distress.**
- **Careful monitoring of hematologic parameters, therapeutic drug monitoring (TDM) and dose adjustment for patients with renal insufficiency are recommended to avoid flucytosine-associated toxicities.**
- **Lipid formulations of amphotericin B at higher doses (3-5 mg/kg/day) can be used for HIV-positive patients with or predisposed to renal dysfunction and are recommended for organ-transplant recipients.**

Mycobacterium tuberculosis

- **Initial regimen of four drugs for empirical treatment of *M. tuberculosis* is recommended.**
- **This regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid plus rifampin for the remaining duration of therapy.**
- **Duration of treatment 9 - 12 months or longer with multiple-drug therapy.**
- **With rifampin-resistant strains duration may be 18 - 24 months.**

Mycobacterium tuberculosis

- **The recommended therapy for HIV-positive individuals is the same as for immunocompetent patients.**
- **Duration of treatment ≥ 24 months.**
- **Rifabutin may replace other rifamycins (rifampin) to minimize drug interactions with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors.**

Chemoprophylaxis of Meningitis

- **The spread of some types of bacterial meningitis can be prevented by administering prophylactic antimicrobials to contacts of patients with bacterial meningitis.**
- **This prevents transmission of the bacteria to susceptible hosts, and eradicates the organism from the nasopharynx of those who are already colonized.**
- **Such therapy is recommended for close contacts of patients infected with:**

  H. influenzae* or *N. meningitidis.

Chemoprophylaxis of Meningitis

- **Close contacts are defined as house-hold or day-care members who sleep or eat in the same dwelling as the index patient.**
- **Therefore, health care workers do not require chemoprophylaxis unless close contact with the patient's secretions occurs, as in mouth-to-mouth resuscitation.**

Chemoprophylaxis of Meningitis

Chemoprophylaxis for *Neisseria meningitidis*

Children < 5years	Ciprofloxacin single dose 30mg/kg po (max 125mg)
Children 5-12 years	Ciprofloxacin 250mg po single dose
Pregnant women	Ceftriaxone 250mg IM stat
Female adults on the oral contraceptive pill	Ciprofloxacin 500mg po single dose
Adults and children >12 years	Ciprofloxacin 500mg po single dose

Rifampin can be used, but the duration of therapy is 2 days.

Chemoprophylaxis of Meningitis

Chemoprophylaxis for *Haemophilus influenzae*

Infants under 1 year of age	Rifampicin 10mg/kg once daily for 4 days
Adults and children	Rifampicin 20mg/kg once daily for 4 days up to max of 600mg/day
Pregnant women	Not indicated

Vaccination

- **With *Haemophilus influenzae* type b, pneumococcal meningitis or *Neisseria meningitidis* Groups C, A, Y and W135, vaccination of contacts and index may be indicated.**

Therapy of Pneumonia

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Pneumonias

- **Pneumonia is one of the most common causes of severe sepsis, and infectious cause of death in children and adults.**
- **It affects all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill.**
- **Mortality rate is high.**

Pneumonias Causative Agents

- **The most prominent pathogen causing community-acquired pneumonia (CAP) in otherwise healthy adults is *Streptococcus pneumoniae* and accounts for up to 35% (12%-68%) of all acute cases.**
- **Other common pathogens include:**

1. ***H. influenza* (2.5%-45%).**
2. **Atypical pathogens: *Mycoplasma pneumoniae*, *Legionella* sps, and *Chlamydia pneumoniae* (~20%).**
3. **A variety of viruses including influenza.**

Pneumonia Causative Agents

- The leading causative agents in hospital-acquired pneumonia (HAP) are Gram-negative aerobic bacilli, *S. aureus*, and multidrug-resistant (MDR) pathogens.
- In pneumonia that follows the aspiration of gastric or oropharyngeal contents, anaerobic bacteria are the most common etiologic agents.
- Ventilator-associated pneumonia (VAP) is also associated with MDR pathogens.

Pneumonia Causative Agents

- **Pneumonia in infants and children is caused by a wider range of microorganisms, and viruses predominate: especially RSV, parainfluenza, and adenovirus.**
- ***M. pneumoniae* is an important pathogen in older children.**

Pneumonia Causative Agents

- **Beyond the neonatal period, *S. pneumoniae* is the major bacterial pathogen in childhood pneumonia, followed by group A *Streptococcus* and *S. aureus*.**
- ***H. influenzae* type b, once a major childhood pathogen, has become an infrequent cause of pneumonia since the introduction of active vaccination against this organism in the late 1980s.**

Pneumonia Causative Agents

- **Pneumonia in non-ambulatory residents of nursing homes and other long-term care facilities is similar to hospital-acquired pneumonia and should be treated according to the HAP guidelines.**
- **Certain other patients may be better served by management in accordance with CAP guidelines.**

Therapy of Pneumonia

Treatment:

The goals of therapy are:

1. **Eradication of the offending organism through selection of the appropriate antibiotic**
2. **Achieving complete clinical cure, with minimal drug-induced toxicity.**

Therapy of Pneumonia

General Approach to Treatment:

Supportive care:

1) Humidified oxygen for hypoxemia.
2) Bronchodilators when bronchospasm is present.
3) Chest physiotherapy and postural drainage with evidence of retained secretions.
4) Adequate hydration (IV if necessary).
5) Optimal nutritional support.
6) Control of fever.

Therapy of Pneumonia

- **Appropriate sputum samples should be obtained to determine the microbiologic etiology.**
- **Selection of an appropriate antimicrobial must be made based on the patient's probable or documented microbiology.**

Pharmacologic Therapy:

- **Antibiotic concentrations in respiratory secretions in excess of the pathogen MIC are necessary for successful treatment of pulmonary infections.**

Therapy of Pneumonia

Selection of Antimicrobial Agents:

- **Treatment, initially involves the empirical use of a relatively broad-spectrum antibiotic that is effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained.**
- **Therapy should be narrowed to cover specific pathogens after the results of cultures are known.**

Management of CAP in Adults

- **This discussion is in accordance of the "Infectious Diseases Society of America / American Thoracic Society" Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2016).**

Antibiotic Treatment:

- **Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.**

Table 6. Most common etiologies of community-acquired pneumonia.

Patient type	Etiology
Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses[a]
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* species Aspiration Respiratory viruses[a]
Inpatient (ICU)	*S. pneumoniae* *Staphylococcus aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

NOTE. Based on collective data from recent studies [171]. ICU, intensive care unit.

[a] Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

Management of CAP in Adults

Outpatient treatment:

1. **Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:**

A. **A macrolide (azithromycin, clarithromycin, or erythromycin).**

B. **Doxycycline is an alternative.**

Management of CAP in Adults

2. Presence of comorbidities (chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months, etc):

A. A β-lactam plus a macrolide (High-dose amoxicillin [1g x3] or amoxicillin-clavulanate [2g x2] is preferred.

- **Alternatives include ceftriaxone, and cefuroxime.**

B. A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

Management of CAP in Adults

Inpatient, non-ICU treatment:

1. **A β-lactam plus a macrolide. (Preferred β-lactam agents include cefotaxime, ceftriaxone or ampicillin; ertapenem for selected patients).**

- **Use doxycycline as an alternative to the macrolide.**
- **A respiratory fluoroquinolone should be used for penicillin-allergic patients.**

2. **A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin.**

Management of CAP in Adults

Inpatient, ICU treatment:

1. **A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) + either azithromycin, or a fluoroquinolone.**
2. **For *Pseudomonas* infection, use an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) + either ciprofloxacin or levofloxacin.**

Management of CAP in Adults

3. **For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.**

Management of CAP in Adults

Pathogen-directed therapy:

- **Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at the specific pathogen.**

Time to first antibiotic dose:

- **For patients admitted through the emergency department (ED), the first antibiotic dose should be administered while still in the ED.**

Management of CAP in Adults

Switch from intravenous to oral therapy:

1. **Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract.**
2. **Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is NOT necessary.**

Management of CAP in Adults

Duration of antibiotic therapy:

1. **Patients with CAP should be treated for a minimum of 5 days, and should be afebrile for 2-3 days.**
2. **A longer duration of therapy may be needed if initial therapy was NOT active against the identified pathogen, or if it was complicated by extra-pulmonary infection such as meningitis or endocarditis.**

Management of CAP in Adults

Remember the importance of:

1. **The local pattern of causative pathogens.**
2. **The local pattern of antibiotic sensitivity and/or resistance.**

Management of HAP and VAP in Adults

Common causes of HAP:

1. ***P. aeruginosa***
2. ***Staphylococcus aureus,*** **including methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)**
3. ***Klebsiella pneumoniae***
4. ***Escherichia coli***
5. **Non-Enterobacteriaceae bacteria such as Serratia *marcescens, Stenotrophomonas maltophilia,* and *Acinetobacter* species are less common causes**

Management of HAP and VAP in Adults

Common causes of VAP:

1. ***P aeruginosa***
2. ***S Aureus,* including MSSA and MRSA**
3. ***Stenotrophomonas maltophilia***
4. ***Acinetobacter* species**
5. **Enterobacteriaceae are less commonly seen in VAP than in hospital-acquired pneumonia (HAP)**

Management of HAP and VAP in Adults

- **Each hospital should generate an antibiogram as a guide for the optimal choice of antibiotics.**
- **Patients with suspected HAP (non-VAP) may be treated according to the results of microbiologic studies performed on respiratory samples obtained noninvasively, rather than being treated empirically (??).**
- **VAP may be treated empirically according to the local distribution of pathogens associated with it and their antimicrobial susceptibilities.**

Empiric Treatment of Clinically Suspected VAP

- **Cover for *S. aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli in all empiric regimens.**
- **A regimen including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem is acceptable [This regimen covers MSSA (not MRSA)].**
- **Oxacillin, nafcillin, or cefazolin are preferred for treatment of proven MSSA, but are not necessary if one of the above agents is used.**

Empiric Treatment of Clinically Suspected VAP

- For MRSA, either vancomycin or linezolid is indicated.
- If resistance is suspected, 2 antipseudomonal antibiotics from different classes are indicated.
- If risk of resistance is low, one antibiotic active against *P. aeruginosa* is indicated.
- Avoid aminoglycosides and colistin if alternative agents with adequate gram-negative activity are available.

Empiric Treatment of Clinically Suspected VAP

- **If patient has structural lung disease increasing the risk of gram-negative infection (cystic fibrosis or bronchiectasis), 2 antipseudomonal agents are recommended.**

Empiric Treatment of Clinically Suspected VAP

Role of Inhaled Antibiotic Therapy:

- **For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), It is suggested to use both inhaled and systemic antibiotics, rather than systemic antibiotics alone.**
- **Adjunctive inhaled antibiotic therapy is a last resort for patients who are NOT responding to intravenous antibiotics alone, whether the infecting organism is or is NOT multidrug resistant (MDR).**

Empiric Treatment of Clinically Suspected HAP (Non-VAP)

- When there is high risk for MRSA infection, use an antibiotic with activity against MRSA (vancomycin or linezolid).
- For patients with NO risk factors for MRSA infection, use oxacillin, nafcillin, or cefazolin.
- When empiric treatment may include coverage for MSSA (and not MRSA) use a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem.

Empiric Treatment of Clinically Suspected HAP (Non-VAP)

- **Also use antibiotics with activity against *P. aeruginosa* and other gram-negative bacilli.**
- **In patients who have factors increasing the likelihood for *Pseudomonas* or other gram-negative infection, use antibiotics from 2 different classes with activity against *P. aeruginosa*.**

Empiric Treatment of Clinically Suspected HAP (Non-VAP)

- **All other patients with HAP who are being treated empirically may be prescribed a single antibiotic with activity against *P. aeruginosa*.**
- **Do not use an aminoglycoside as the sole antipseudomonal.**

Pathogen-Specific Therapy

- **Treatment for MRSA HAP/VAP: Vancomycin or linezolid.**
- **HAP/VAP Due to *P. aeruginosa*: Definitive (NOT empiric) therapy based upon the results of antimicrobial susceptibility testing.**
- **No aminoglycoside monotherapy.**

Pathogen-Specific Therapy

- **For patients with HAP/VAP due to *P. aeruginosa* who are NOT in septic shock, or NOT at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, use monotherapy with an antibiotic to which the isolate is susceptible.**
- **For patients with HAP/VAP due to *P. aeruginosa* who remain in septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known, use combination therapy with 2 antibiotics to which the isolate is susceptible.**

Pathogen-Specific Therapy

- **Treatment of patients with HAP/VAP due to extended-spectrum β-lactamase (ESBL) –producing gram-negative bacilli (Klebsiella species, *E. coli, Proteus mirabilis, Acinetobacter*, and *Pseudomonas aeruginosa*):**
- **The choice of an antibiotic for definitive (NOT empiric) therapy should be based upon the results of antimicrobial susceptibility testing and patient-specific factors (allergies and comorbidities that may confer an increased risk of adverse effects).**
- **Usually carbapenems are active but resistance develops.**

Pathogen-Specific Therapy

- **Treatment of patients with HAP/VAP due to *Acinetobacter* species: use either a carbapenem or ampicillin/sulbactam if the isolate is susceptible to these agents.**
- **In patients with HAP/VAP caused by *Acinetobacter* species sensitive only to polymyxins, use intravenous polymyxin (colistin or polymyxin B), with adjunctive inhaled colistin.**
- **Do not use tigecycline.**

Pathogen-Specific Therapy

- **Treatment of patients with HAP/VAP due to carbapenem-resistant pathogens: If the pathogen is sensitive only to polymyxins, use intravenous polymyxins (colistin or polymyxin B), with adjunctive inhaled colistin.**

Length of therapy

- **For patients with VAP or HAP, a 7-day course of antimicrobial therapy rather than a longer duration is recommended.**
- **A shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.**

Should Antibiotic Therapy be De-escalated or Fixed in Patients with HAP/VAP?

- **De-escalation therapy means changing an empiric broad-spectrum antibiotic regimen to a narrower antibiotic regimen by changing the antimicrobial agent or changing from combination therapy to monotherapy.**
- **Fixed antibiotic therapy refers to maintaining a broad-spectrum antibiotic regimen until therapy is completed.**
- **For patients with HAP/VAP, antibiotic therapy should be de-escalated rather than fixed.**

Neonatal Pneumonia

Onset:

1) **May be within hours of birth, and as part of a generalized sepsis syndrome.**
2) **After 7 days (most commonly in neonatal ICUs among infants who require prolonged endotracheal intubation because of lung disease).**

Neonatal Pneumonia

Organisms are acquired from the maternal genital tract or the nursery, and include:

a) **Gram-positive cocci (groups A and B streptococci, both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*)**
b) **Gram-negative bacilli (*E. coli, Klebsiella* sp, *Proteus* sp).**
c) ***Pseudomonas, Citrobacter, Bacillus,* and *Serratia* in infants who have received broad-spectrum antibiotics.**

Neonatal Pneumonia

Treatment:

- **Antimicrobial therapy in early-onset disease is similar to that for neonatal sepsis: Vancomycin and a broad-spectrum β-lactam drug such as meropenem, piperacillin/tazobactam, or cefepime are the initial treatment of choice.**
- **This regimen treats sepsis as well as pneumonia with typical hospital-acquired pathogens including *P. aeruginosa* and MRSA.**

Neonatal Pneumonia

- **Local patterns of infection and bacterial resistance should always be used to help guide empiric choices of antimicrobials.**
- **More specific antibiotics are substituted after sensitivity results are available.**

Neonatal Pneumonia

Chlamydial pneumonia:

- **Exposure to chlamydial organisms (*Chlamydia trachomatis*) occurs during delivery.**
- **May result in development of chlamydial pneumonia at 2 to 18 wk.**

Treatment:

- **Erythromycin or azithromycin lead to rapid resolution.**
- **Erythromycin may cause hypertrophic pyloric stenosis in neonates.**
- **The mother and father should also be treated for chlamydia.**

Community-Acquired Pneumonia in Children

- **The most likely etiology depends on the age of the child.**
- **Viral and *Streptococcus pneumoniae* infections are most common in preschool-aged children, whereas *Mycoplasma pneumoniae* is common in older children.**

Community-Acquired Pneumonia in Children

- **Preschool-aged children with uncomplicated bacterial pneumonia should be treated with amoxicillin.**
- **Macrolides are first-line agents in older children.**
- **Immunization with the 13-valent pneumococcal conjugate vaccine is important in reducing the severity of childhood pneumococcal infections.**

CAP Etiologies in Children

Age	*Common etiologies*	*Less common etiologies*
2 to 24 months	Respiratory syncytial virus Human metapneumovirus Parainfluenza viruses Influenza A and B Rhinovirus Adenovirus Enterovirus *Streptococcus pneumoniae* *Chlamydia trachomatis*	*Mycoplasma pneumoniae* *Haemophilus influenzae* (type B and nontypable) *Chlamydophila pneumoniae*

CAP Etiologies in Children

2 to 5 years	Respiratory syncytial virus Human metapneumovirus Parainfluenza viruses Influenza A and B Rhinovirus Adenovirus Enterovirus *S. pneumoniae* *M. pneumoniae* *H. influenzae* (B and nontypable) *C. pneumoniae*	*Staphylococcus aureus* (including methicillin-resistant *S. aureus*) Group A streptococcus

CAP Etiologies in Children

Older than 5 years	*M. pneumoniae* *C. pneumoniae* *S. pneumoniae* Rhinovirus Adenovirus Influenza A and B	*H. influenzae* (B and nontypable) *S. aureus* (including methicillin-resistant *S. aureus*) Group A streptococcus Respiratory syncytial virus Parainfluenza viruses Human metapneumovirus Enterovirus

Recommended Empiric Outpatient Treatment of Childhood CAP

60 days to 5 years of age:

- **Preferred regimens: Amoxicillin for 7-10 days.**
- **Alternative regimens for patients allergic to penicillin or beta-lactam antibiotics: Azithromycin (5 days), clarithromycin (7-10 days), or erythromycin (7-10 days).**

5 to 16 years of age: Azithromycin (5 days).

Recommended Empiric Inpatient Treatment of Childhood CAP

60 days to 5 years of age:

- **Cefuroxime for 10-14 days.**
- **In critically ill patients: Cefuroxime + erythromycin 10-14 days, or cefotaxime + cloxacillin for 10-14 days**

5 to 16 years of age: Cefuroxime + erythromycin 10-14 days, or azithromycin for 5 days.

Rational Antimicrobial Selection & Antimicrobial Prophylaxis

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Rational Antimicrobial Selection

- **The initial selection of antimicrobial therapy may be empirical, prior to documentation and identification of the offending organism.**
- **A delay in antimicrobial therapy for some infections may result in serious morbidity and mortality.**

Rational Antimicrobial Selection

Empirical antimicrobial therapy selection should be based on:

1. **The patient's history and physical examination.**
2. **Results of Gram stains or other rapidly performed tests on specimens from the infected site.**
3. **Knowledge of the most likely offending organism for the infection in question.**
4. **Institution's local susceptibility patterns.**

Rational Antimicrobial Selection

- **Identification of the pathogen and its antimicrobial susceptibility are the most important factors in determining the choice of antimicrobial therapy.**

Rational Antimicrobial Selection

Infected materials must be sampled with starting antimicrobial therapy for two reasons:

a) **A Gram stain might reveal bacteria, and an acid-fast stain might detect mycobacteria.**

b) **The premature use of antimicrobials can suppress the growth of pathogens which might result in false-negative cultures results.**

Rational Antimicrobial Selection

- **Blood cultures should be performed in the acutely ill and febrile patient.**
- **Infected materials (blood, sputum, urine, stool, abscesses, wound or sinus drainage, spinal fluid, and joint fluid, …), from the suspected infection site must be obtained and tested.**
- **When a pathogenic microorganism is identified, antimicrobial susceptibility testing should be performed.**

Rational Antimicrobial Selection

- **When the pathogen has been identified, specific definitive antimicrobial therapy should be promptly administered.**

Selection of presumptive therapy:

A variety of factors must be considered:

1) **The severity and acuity of the disease.**
2) **Local epidemiology and antibiogram.**
3) **Patient's history and host factors.**
4) **Factors related to the drug(s) to be used.**
5) **The necessity for using multiple agents.**

Rational Antimicrobial Selection

- **In addition, there are generally accepted drugs of first choice for the treatment of most pathogens.**
- **Drugs of choice are compiled from a variety of sources and are intended as guidelines rather than as specific rules for antimicrobial use.**

Antibiograms (antibiotic susceptibilities):

- **Local antimicrobial susceptibility data, NOT that from other institutions or national compilations.**
- **Susceptibility of bacteria can differ substantially among hospitals within a community.**

Rational Antimicrobial Selection

Patient History:

- **As part of the medical history, the place where the infection was acquired should be determined, home (community acquired), nursing home environment, or hospital (nosocomial).**
- **Nursing home patients can be exposed to potentially more resistant organisms because they are often surrounded by ill patients who are receiving antibiotics.**

Rational Antimicrobial Selection

Host Factors:

Allergy:

- **Allergy to an antimicrobial agent generally precludes its use.**
- **Cephalosporins should be avoided in patients allergic to penicillin for immediate or accelerated reactions (anaphylaxis, laryngospasm), but can be given under close supervision in patients with skin rash.**

Rational Antimicrobial Selection

Age:

- **Age is an important factor for identification of the likely etiologic agent and in the ability to eliminate the drug.**
- **In bacterial meningitis, the pathogens differ as the patient grows from the neonatal period through infancy and childhood into adulthood.**
- **For neonates, hepatic and liver functions are not well developed.**

Rational Antimicrobial Selection

- **Neonates (especially when premature) can develop kernicterus when given sulfonamides, because of displacement of bilirubin from serum albumin.**
- **The major change in the elderly is decreased renal function, leading to increased adverse effects of antimicrobials eliminated by the kidney (aminoglycosides).**

Rational Antimicrobial Selection

Pregnancy:

- **During pregnancy, the fetus is at risk for drug teratogenicity.**
- **The disposition of certain drugs by the mother may be altered.**
- **Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy, because of increases in intravascular volume, glomerular filtration rate, and hepatic metabolic activities.**

Rational Antimicrobial Selection

- **This results in a maternal serum antimicrobial concentrations 50% lower than in the nonpregnant state.**
- **Thus, increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy.**

Rational Antimicrobial Selection

Metabolic or Genetic Variation:

- **Inherited or acquired metabolic abnormalities will influence therapy of infectious diseases in a variety of ways.**
- **Patients with impaired blood flow may NOT absorb drugs given by intramuscular injection.**
- **Patients who are slow acetylators of isoniazid are at greater risk for peripheral neuropathy.**

Rational Antimicrobial Selection

- **Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to dapsone, sulfonamides, nitrofurantoin, nalidixic acid, and antimalarials.**
- **The antiretroviral drug abacavir is associated with severe hypersensitivity reaction (fever, rash, abdominal pain, and respiratory distress) in the presence of a human leukocyte antigen allele HLA-B*5701.**

Rational Antimicrobial Selection

Organ Dysfunction:

- **Patients with diminished renal or hepatic function or both will need dosage adjustment to prevent drug accumulation and toxicity.**
- **Antibiotics that should be adjusted in severe liver disease: clindamycin, erythromycin, metronidazole, rifampin.**
- **Significant accumulation can occur when both liver dysfunction and renal dysfunction are present for: sulfamethoxazole, cefotaxime, nafcillin, piperacillin.**

Rational Antimicrobial Selection

Concomitant Drugs:

- **May influence the drug selection, dose, and monitoring.**
- **Administration of isoniazid with phenytoin can result in phenytoin toxicity due to inhibition of phenytoin metabolism by isoniazid.**
- **Drugs that possess similar adverse effect profiles can produce enhanced adverse effects (e. g: two drugs that cause nephrotoxicity or neutropenia).**

Rational Antimicrobial Selection

Major Drug Interactions with Antimicrobials:

1. **Amino glycosides with:**

A. **Neuromuscular blocking agents: additive NMJ block.**

B. **Nephro- and Oto-toxins (Amphotericin, cisplatin, cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast media [N], vancomycin [N]) have additive toxicity.**

Rational Antimicrobial Selection

2. Amphotericin B with nephrotoxins (aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine): additive adverse effects.
3. Chloramphenicol decreases metabolism of phenytoin, tolbutamide, ethanol.
4. Foscarnet with pentamidine IV: increased risk of severe nephrotoxicity/hypocalcemia.
5. Isoniazid decreases metabolism of carbamazepine, phenytoin → nausea, vomiting, nystagmus, ataxia.

Rational Antimicrobial Selection

6. Macrolides/azalides with

A. Digoxin: increased digoxin bioavailability.

B. Theophylline: decreased metabolism of theophylline.

7. Metronidazole with ethanol (drugs containing ethanol): disulfiram-like reaction.

8. Penicillins and cephalosporins with probenecid, aspirin: blocked excretion of β-lactams.

Rational Antimicrobial Selection

9. Ciprofloxacin/norfloxacin with theophylline: decreased metabolism of theophylline.

10. Quinolones with:

A. Classes Ia and III antiarrhythmics: increased Q-T interval.

B. Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy products), citric acid, didanosine: decreased absorption of quinolones.

Rational Antimicrobial Selection

11. Rifampin increases metabolism of azoles, cyclosporine, methadone, propranolol, protease inhibitors, oral contraceptives, tacrolimus, warfarin.

12. Sulfonamides with sulfonylureas, phenytoin, warfarin: displacement from binding to albumin.

13. Tetracyclines with:

A. Antacids, iron, calcium, sucralfate: decreased absorption of tetracycline.

B. Digoxin: increased digoxin bioavailability (WHY?).

Rational Antimicrobial Selection

Drug Factors:

PK and PD Considerations:

- **Important parameters to be considered are the minimal inhibitory concentration (MIC) and the time the concentration is above MIC.**
- **Aminoglycosides exhibit concentration-dependent bactericidal effects, which allows a once-daily aminoglycosides administration.**
- **These drugs are given as a single large daily dose to maximize the peak/MIC ratio.**

Rational Antimicrobial Selection

- They also possess a postantibiotic effect (persistent suppression of organism growth after concentrations decrease below the MIC) that appears to contribute to the success of high-dose, once-daily administration.
- Fluoroquinolones also exhibit concentration-dependent killing activity, but optimal killing appears to be characterized by the AUC/MIC ratio.

Rational Antimicrobial Selection

- **β-Lactams display time-dependent bactericidal effects.**
- **Therefore, the important pharmacodynamic relationship for these antimicrobials is the duration that drug concentrations exceed the MIC.**
- **Frequent small doses, continuous infusion, or prolonged infusion of β-lactams appears to be correlated with positive outcomes.**

Rational Antimicrobial Selection

Tissue Penetration:

- **One important factors in treating an infection is the presence of the antimicrobial agent in an active form and at adequate concentration at the site of infection.**
- **Drugs that have low biliary fluid concentrations are NOT useful in the treatment of cholecystitis and cholangitis.**

Rational Antimicrobial Selection

- **Some drugs have poor penetration to deep infections, such as abscesses, where various factors such as acidic pH, WBC products, and various enzymes can inactivate even high concentrations of certain drugs.**
- **Drugs that do NOT reach significant concentrations in the CSF should NOT be used in treatment of bacterial meningitis.**

Rational Antimicrobial Selection

- **Body fluids where drug concentration data are clinically relevant include CSF, urine, synovial fluid, and peritoneal fluid.**
- **Parenteral therapy is indicated in: febrile neutropenia, meningitis, endocarditis, and osteomyelitis.**
- **Severe pneumonia often is treated initially with IV antibiotics then switched to oral therapy with clinical improvement.**

Rational Antimicrobial Selection

- **Patients treated in the ambulatory setting for upper respiratory tract infections (pharyngitis, bronchitis, sinusitis, and otitis media), lower respiratory tract infections, skin and soft-tissue infections, uncomplicated urinary tract infections, and selected sexually transmitted diseases can usually receive oral therapy.**

Rational Antimicrobial Selection

Drug Toxicity:

- **Toxic drugs should be avoided.**
- **Antibiotics associated with CNS toxicities, when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem.**
- **Reversible nephrotoxicity classically is associated with aminoglycosides and vancomycin.**
- **Irreversible ototoxicity can occur with aminoglycosides.**

Rational Antimicrobial Selection

- **Hematologic toxicities occur with prolonged use of nafcillin (neutropenia), piperacillin (platelet dysfunction), cefotetan (hypoprothrombinemia), chloramphenicol (bone marrow suppression, both idiosyncratic and dose-related toxicity), and trimethoprim (megaloblastic anemia).**

Rational Antimicrobial Selection

- **In the outpatient setting, patients must be counseled regarding photosensitivity with azithromycin, quinolones, tetracyclines, pyrazinamide, sulfamethoxazole, and trimethoprim.**
- **Many antibiotics have been implicated in causing diarrhea and colitis secondary to *Clostridium difficile* superinfection.**

Rational Antimicrobial Selection

Penicillins & Cephalosporins:

- **Hypersensitivity reactions and rash, drug fever, diarrhea, emesis, abdominal pain, hepatitis, interstitial nephritis, leukopenia, thrombocytopenia, Coomb's positive-hemolytic anemia, *C. difficile* colitis, electrolyte abnormalities, seizures.**

Rational Antimicrobial Selection

Carbapenems:

- **Hypersensitivity reactions and rash, headache, nausea, diarrhea, seizures, drug fever, eosinophilia, thrombocytopenia, hepatitis, *C. difficile* colitis.**

Monobactams:

- **Rash, diarrhea, nausea, hepatitis, thrombocytopenia, *C. difficile* colitis.**

Rational Antimicrobial Selection

Aminoglycosides:

- **Tubular necrosis and renal failure, vestibular and cochlear toxicity, neuromuscular blockade, vertigo, anemia, hypersensitivity.**

Glycopeptides:

- **Red man syndrome, phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever.**

Rational Antimicrobial Selection

Lipopeptides (daptomycin):

- **Hepatotoxicity, CPK elevation with or without myopathy, diarrhea, eosinophilic pneumonia, *C. difficile* colitis.**

Oxazolidinones (linezolid):

- **Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, blindness, lactic acidosis, diarrhea, nausea, serotonin syndrome, interstitial nephritis.**

Rational Antimicrobial Selection

Tetracyclines:

- **GI upset, nausea, vomiting, diarrhea, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, deposition on teeth, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis.**

Chloramphenicol:

- **Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity.**

Rational Antimicrobial Selection

Rifamycines:

- **Discoloration of urine, tears, contact lens, sweat, hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis, thrombocytopenia.**

Macrolides/azalide:

- **GI intolerance, diarrhea, prolonged QTc, cholestatic hepatitis, reversible ototoxicity, *torsade de pointes*, rash, hypothermia, exacerbation of myasthenia gravis.**

Rational Antimicrobial Selection

Clindamycin:

- **Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity.**

Fluoroquinolones:

- **GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis.**

Rational Antimicrobial Selection

Sulfonamides and trimethoprim:

- **GI intolerance, rash, hyperkalemia, bone marrow suppression (anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, pancreatitis, interstitial nephritis, neurologic toxicity.**

Rational Antimicrobial Selection

Metronidazole:

- **GI intolerance, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram-like reactions with alcohol, insomnia, stomatitis, aseptic meningitis, dysarthria.**

Polymyxins (polymyxin B & colistin):

- **Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blurred vision, slurred speech), neuromuscular blockade, bronchospasm (administered via inhalation).**

Rational Antimicrobial Selection

Failure of antimicrobial therapy:

- **Patients who fail to respond over 2 to 3 days require a thorough reevaluation.**

Causes:

a) **The disease is NOT infectious or is nonbacterial in origin.**

b) **There is an undetected pathogen in a polymicrobial infection.**

c) **Factors directly related to drug selection, the host, or the pathogen.**

d) **Laboratory error in identification, susceptibility testing, or both.**

Rational Antimicrobial Selection

Failures Caused by Drug Selection:

1) Inappropriate selection of drug, dosage, or route of administration.
2) Reduced absorption of a drug, resulting in subtherapeutic concentrations, because of:

a. GI disease (short-bowel syndrome).
b. Drug interaction (complexation of fluoroquinolones with multivalent cations).

3) Accelerated drug elimination (cystic fibrosis or during pregnancy), resulting in low concentrations.

Rational Antimicrobial Selection

4) Poor penetration into the site of infection (for sites such as the CNS, eye, and prostate gland).

5) Chemical inactivation of the drug at the site of infection.

Rational Antimicrobial Selection

Failures Caused by Host Factors:

- **Patients who are immunosuppressed (granulocytopenia from immunosuppressants, chemotherapy or AIDS) may respond poorly because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.**
- **The need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both. These infections will NOT be effectively treated without surgical procedures.**

Rational Antimicrobial Selection

Failures Related to Pathogens (Resistance):

- **Intrinsic resistance: when the antimicrobial agent never had activity against the bacterial species. (Gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of gram negative bacteria).**
- **Acquired resistance: is when the antimicrobial agent was originally active against the bacterial species but the genetic makeup of the bacteria has changed so the drug can NO longer be effective.**

Rational Antimicrobial Selection

Bacteria develop acquired resistance by any of the following mechanisms:

a. **Alteration in the target site.**
b. **Change in membrane permeability.**
c. **Expression of an efflux pump.**
d. **Drug inactivation through either β-lactamases or aminoglycoside-modifying enzymes is the predominant mechanism of resistance. The expression of β-lactamases can be induced or constitutive.**

Rational Antimicrobial Selection

The increased resistance results from:

1. **Continued overuse of antimicrobials in the community and in hospitals.**
2. **Long-term suppressive antimicrobials for the prevention of infections in immunosuppressed patients.**

Rational Antimicrobial Selection

- **Enterococci with multiple resistance patterns have been isolated.**
- **They may be resistant to:**

1. **β-lactams (β-lactamase production, altered penicillin-binding proteins [PBPs], or both)**
2. **Vancomycin (alterations in peptidoglycan synthesis).**
3. **Aminoglycosides (high levels of AGs-degrading enzymes.**

Rational Antimicrobial Selection

- **Pneumococci resistant to penicillins, certain cephalosporins, and macrolides are increasingly common.**
- **These organisms generally are susceptible to vancomycin, the new fluoroquinolones (moxifloxacin and trovafloxacin), and cefotaxime or ceftriaxone.**

Rational Antimicrobial Selection

- **Antimicrobial agents such as linezolid, daptomycin, telavancin (semi-synthetic derivative of vancomycin), and tigecycline (new tetracycline) have been used for resistant gram-positive bacteria.**

Rational Antimicrobial Selection

- **Treatment of infections caused by *Enterobacter*, *Citrobacter*, *Serratia*, or P. *aeruginosa* with a third-generation cephalosporin or aztreonam may produce an initial clinical response by eradicating the susceptible bacteria.**
- **Within a few days, the highly resistant subpopulations can overgrow at the infection site to produce a relapse.**
- **These bacteria usually retain susceptibility to fluoroquinolones, aminoglycosides, carbapenems, but are resistant to all other β-lactams.**

Rational Antimicrobial Selection

- **Host defenses are extremely important in this scenario.**
- **Debilitated patients with pulmonary infections, abscesses, or osteomyelitis are at high risk for drug failure.**
- **In these situations, a combination regimen to prevent the emergence of resistance or the use of carbapenem or a fluoroquinolone may be used for empiric therapy.**

Rationale For Combination Antimicrobial Therapy

- **Most infections should be treated with a single antimicrobial agent.**
- **Although indications for combination therapy do exist, antimicrobial combinations are often overused in clinical practice.**
- **The unnecessary use of antimicrobial combinations increases toxicity and costs and may occasionally result in reduced efficacy due to antagonism of one drug by another.**

Rationale For Combination Antimicrobial Therapy

- **Antimicrobial combinations should be selected for one or more of the following reasons:**

1. **To provide broad-spectrum empiric therapy in seriously ill patients.**
2. **To treat polymicrobial infections (intra-abdominal abscesses, which are due to a combination of anaerobic and aerobic gram-negative organisms, and enterococci).**

Rationale For Combination Antimicrobial Therapy

- **The antimicrobial combination chosen should cover the most common known or suspected pathogens but not cover all possible pathogens.**

3. **To decrease the emergence of resistant strains – tuberculosis.**
4. **To obtain enhanced inhibition or killing.**

Rationale For Combination Antimicrobial Therapy

5. **To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.**

- **The use of flucytosine in combination with amphotericin B for the treatment of cryptococcal meningitis in non–HIV-infected patients allows for a reduction in amphotericin B dosage with decreased amphotericin B-induced nephrotoxicity.**

Rationale For Combination Antimicrobial Therapy

Broadening the Spectrum of Coverage:

- **Increasing the coverage of antimicrobial therapy generally is necessary in the following cases:**

1. **In mixed infections where multiple organisms are likely to be present (in intra-abdominal and female pelvic infections), in which a variety of aerobic and anaerobic bacteria can produce disease.**
- **A combination of a drug active against aerobic Gram-negative bacilli (aminoglycoside) and a drug active against anaerobic bacteria (metronidazole or clindamycin) is selected.**

Rationale For Combination Antimicrobial Therapy

2. **For critically ill patients with health care-associated infections.**

- **These infections are frequently caused by multi-drug resistant pathogens.**
- **Combination therapy is used in this setting to ensure that at least one of the antimicrobials will be active against the pathogen(s).**

Rationale For Combination Antimicrobial Therapy

Synergism:

- **This is necessary for infections caused by enteric Gram-negative bacilli in immunosuppressed patients.**
- **Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria.**

Rationale For Combination Antimicrobial Therapy

- **Synergistic combinations may produce better results in infections caused by *Pseudomonas aeruginosa* and *Enterococcus* species.**
- **The most obvious example of the use of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of streptomycin or gentamicin to a penicillin.**

Rationale For Combination Antimicrobial Therapy

Preventing Resistance:

- **The use of antimicrobial combinations to prevent the emergence of resistance has been demonstrated in the treatment of tuberculosis.**
- **Combinations of drugs with different mechanisms should be used in this case.**

Disadvantages of Combination Therapy

1. **Increased cost.**
2. **Greater risk of drug toxicity (nephrotoxicity) with aminoglycosides, amphotericin, and vancomycin.**
3. **Superinfection with more resistant bacteria.**
4. **Antagonistic effects: when one drug induces β-lactamase production and the other is susceptible to β-lactamase.**

- **Cefoxitin and imipenem are capable of inducing β-lactamases and may result in more rapid inactivation of penicillins.**

Antimicrobial Prophylaxis

- **Antimicrobial agents are effective in preventing infections in many settings.**
- **Antimicrobial prophylaxis should be used in circumstances in which efficacy has been demonstrated and benefits outweigh the risks of prophylaxis. (Evidence-Based Medicine).**

Antimicrobial Prophylaxis

Surgical Prophylaxis:

- **Surgical wound infections are a major category of nosocomial infections.**
- **Risk factors for postoperative wound infections:**

a) **operations on the abdomen.**

b) **operations lasting more than 2 hours.**

c) **contaminated or dirty wound.**

d) **at least three medical diagnoses.**

Antimicrobial Prophylaxis

- **Surgical procedures that carry a significant risk of postoperative site infection and necessitate the use of antimicrobial prophylaxis include:**

a) **contaminated and clean-contaminated operations.**
b) **selected operations in which postoperative infection may be catastrophic such as open heart surgery.**
c) **clean procedures that involve placement of prosthetic materials.**
d) **any procedure in an immunocompromised host.**

National Research Council (NRC) Wound Classification Criteria

Clean: Elective, primarily closed procedure; respiratory, gastrointestinal, biliary, genitourinary, or oropharyngeal tract not entered; no acute inflammation and no break in technique; expected infection rate ≤ 2%.

Clean contaminated: Urgent or emergency case that is otherwise clean; elective, controlled opening of respiratory, gastrointestinal, biliary, or oropharyngeal tract; minimal spillage or minor break in technique; expected infection rate ≤ 10%.

Contaminated: Acute nonpurulent inflammation; major technique break or major spill from hollow organ; penetrating trauma less than 4 hours old; chronic open wounds to be grafted or covered; expected infection rate about 20%.

Dirty: Purulence or abscess; preoperative perforation of respiratory, gastrointestinal, biliary, or oropharyngeal tract; penetrating trauma more than 4 hours old; expected infection rate about 40%.

Antimicrobial Prophylaxis

- **General principles of antimicrobial surgical prophylaxis include the following:**

1. **The antibiotic should be active against common surgical wound pathogens; unnecessary broad coverage should be avoided.**
2. **The antibiotic should have proved efficacy in clinical trials.**
3. **The antibiotic must achieve concentrations greater than the MIC of the suspected pathogens, and these concentrations must be present at the time of incision.**

Antimicrobial Prophylaxis

4. **The shortest possible course — ideally a single dose — of the most effective and least toxic antibiotic should be used.**
5. **The newer broad-spectrum antibiotics should be reserved for therapy of resistant infections.**
6. **If all other factors are equal, the least expensive agent should be used.**

TABLE 51–7 Recommendations for surgical antimicrobial prophylaxis.

Type of Operation	Common Pathogens	Drug of Choice
Cardiac (with median sternotomy)	Staphylococci, enteric gram-negative rods	Cefazolin
Noncardiac, thoracic	Staphylococci, streptococci, enteric gram-negative rods	Cefazolin
Vascular (abdominal and lower extremity)	Staphylococci, enteric gram-negative rods	Cefazolin
Neurosurgical (craniotomy)	Staphylococci	Cefazolin
Orthopedic (with hardware insertion)	Staphylococci	Cefazolin
Head and neck (with entry into the oropharynx)	*Staphylococcus aureus,* oral flora	Cefazolin + metronidazole
Gastroduodenal	*S aureus,* oral flora, enteric gram-negative rods	Cefazolin
Biliary tract	*S aureus,* enterococci, enteric gram-negative rods	Cefazolin
Colorectal (elective surgery)	Enteric gram-negative rods, anaerobes	Oral erythromycin + neomycin[1]
Colorectal (emergency surgery or obstruction)	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, ertapenem, or cefazolin + metronidazole
Appendectomy, nonperforated	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, or cefazolin + metronidazole
Hysterectomy	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin, cefotetan, or cefoxitin
Cesarean section	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin

[1]In conjunction with mechanical bowel preparation.

Antimicrobial Prophylaxis

- **The selection of vancomycin over cefazolin may be necessary in hospitals with high rates of methicillin-resistant *S. aureus or S. epidermidis infections.***
- **The antibiotic should be present in adequate concentrations at the operative site before incision and throughout the procedure.**

Antimicrobial Prophylaxis

- **Parenteral agents should be administered during the interval beginning 60 minutes before incision up to the time of incision.**
- **In cesarean section, the antibiotic is administered after umbilical cord clamping.**
- **If short-acting agents such as cefoxitin are used, doses should be repeated if the procedure exceeds 3–4 hours in duration.**
- **Single-dose prophylaxis is effective for most procedures and results in decreased toxicity and decreased antimicrobial resistance.**

Antimicrobial Prophylaxis

Common errors in antibiotic prophylaxis include:

a) Selection of the wrong antibiotic.

b) Administering the first dose too early or too late.

c) Failure to repeat doses during prolonged procedures.

d) Excessive duration of prophylaxis.

e) Inappropriate use of broad-spectrum antibiotics.

Antimicrobial Prophylaxis

Nonsurgical Prophylaxis:

- **Nonsurgical prophylaxis includes:**

a) **The administration of antimicrobials to prevent colonization and asymptomatic infection.**

b) **The administration of drugs following colonization by or inoculation of pathogens but before the development of disease.**

- **Nonsurgical prophylaxis is indicated in:**

a) **Individuals who are at high risk for selected virulent pathogens**

b) **Immunocompromised hosts.**

TABLE 51–8 Recommendations for nonsurgical antimicrobial prophylaxis.

Infection to Be Prevented	Indication(s)	Drug of Choice	Efficacy
Anthrax	Suspected exposure	Ciprofloxacin or doxycycline	Proposed effective
Cholera	Close contacts of a case	Tetracycline	Proposed effective
Diphtheria	Unimmunized contacts	Penicillin or erythromycin	Proposed effective
Endocarditis	Dental, oral, or upper respiratory tract procedures[1] in at-risk patients[2]	Amoxicillin or clindamycin	Proposed effective
Genital herpes simplex	Recurrent infection (≥ 4 episodes per year)	Acyclovir	Excellent
Perinatal herpes simplex type 2 infection	Mothers with primary HSV or frequent recurrent genital HSV	Acyclovir	Proposed effective
Group B streptococcal (GBS) infection	Mothers with cervical or vaginal GBS colonization and their newborns with one or more of the following: (a) onset of labor or membrane rupture before 37 weeks' gestation, (b) prolonged rupture of membranes (> 12 hours), (c) maternal intrapartum fever, (d) history of GBS bacteriuria during pregnancy, (e) mothers who have given birth to infants who had early GBS disease or with a history of streptococcal bacteriuria during pregnancy	Ampicillin or penicillin	Excellent
Haemophilus influenzae type B infection	Close contacts of a case in incompletely immunized children (> 48 months old)	Rifampin	Excellent
HIV infection	Health care workers exposed to blood after needle-stick injury	Tenofovir/emtricitabine and raltegravir	Good
	Pregnant HIV-infected women who are at ≥ 14 weeks of gestation; newborns of HIV-infected women for the first 6 weeks of life, beginning 8–12 hours after birth	HAART[3]	Excellent
Influenza A and B	Unvaccinated geriatric patients, immunocompromised hosts, and health care workers during outbreaks	Oseltamivir	Good

Malaria	Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine	Excellent
	Travelers to areas endemic for chloroquine-resistant disease	Mefloquine, doxycycline, or atovaquone/proguanil	Excellent
Meningococcal infection	Close contacts of a case	Rifampin, ciprofloxacin, or ceftriaxone	Excellent
Mycobacterium avium complex	HIV-infected patients with CD4 count < 75/μL	Azithromycin, clarithromycin, or rifabutin	Excellent
Otitis media	Recurrent infection	Amoxicillin	Good
Pertussis	Close contacts of a case	Azithromycin	Excellent
Plague	Close contacts of a case	Tetracycline	Proposed effective
Pneumococcemia	Children with sickle cell disease or asplenia	Penicillin	Excellent
Pneumocystis jiroveci pneumonia (PCP)	High-risk patients (eg, AIDS, leukemia, transplant)	Trimethoprim-sulfamethoxazole, dapsone, or atovaquone	Excellent
Rheumatic fever	History of rheumatic fever or known rheumatic heart disease	Benzathine penicillin	Excellent
Toxoplasmosis	HIV-infected patients with IgG antibody to *Toxoplasma* and CD4 count < 100/μL	Trimethoprim-sulfamethoxazole	Good
Tuberculosis	Persons with positive tuberculin skin tests and one or more of the following: (a) HIV infection, (b) close contacts with newly diagnosed disease, (c) recent skin test conversion, (d) medical conditions that increase the risk of developing tuberculosis, (e) age < 35 y	Isoniazid or rifampin or isoniazid + rifapentine	Excellent
Urinary tract infections (UTI)	Recurrent infection	Trimethoprim-sulfamethoxazole	Excellent

[1]Prophylaxis is recommended for the following: dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, and invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy.

[2]Prophylaxis should be targeted to those with the following risk factors: prosthetic heart valves, previous bacterial endocarditis, congenital cardiac malformations, cardiac transplantation patients who develop cardiac valvulopathy.

[3]Highly active antiretroviral therapy. See http://aidsinfo.nih.gov/ for updated guidelines.

Tigecycline differs in spectrum:

1. ***Staphylococcus aureus*** **including coagulase-negative, methicillin-resistant and vancomycin-resistant strains.**
2. **Streptococci including penicillin- resistant strains.**
3. **Enterococci including vancomycin- resistant strains.**
4. **Gram positive rods.**
5. **Enterobacteriaceae**
6. **Acinetobacter sp**
7. **Gram positive and gram negative anaerobes.**
8. **Atypical agents, rickettsiae, chlamydia and Legionella and rapidly growing Mycobacteria.**

Adverse Effects:

1. **Hypersensitivity reactions including drug fever and skin rash, and anaphylaxis.**
2. **GIT: nausea, vomiting and diarrhea.**
3. **Superinfections: *Pseudomonas, Proteus, Staphylococcus aureus*, Coliforms, Clostridia and Candida.**
4. **Bone & teeth:**

a) **Fetal teeth: fluorescence, discoloration, and enamel dysplasia.**

b) **Fetal bone: deformity or growth inhibition.**

c) **Similar changes occur in children below 8 years of age.**

5. **Liver toxicity: hepatic necrosis and impairment of hepatic function.**
6. **Pancreatitis.**
7. **Kidney toxicity: renal tubular acidosis and other renal injury.**
8. **Local tissue toxicity: Thrombophlebitis after IV administration, Local pain after IM administration.**
9. **Photosenstivity.**
10. **Vestibular reactions: dizziness, vertigo, nausea, vomiting.**