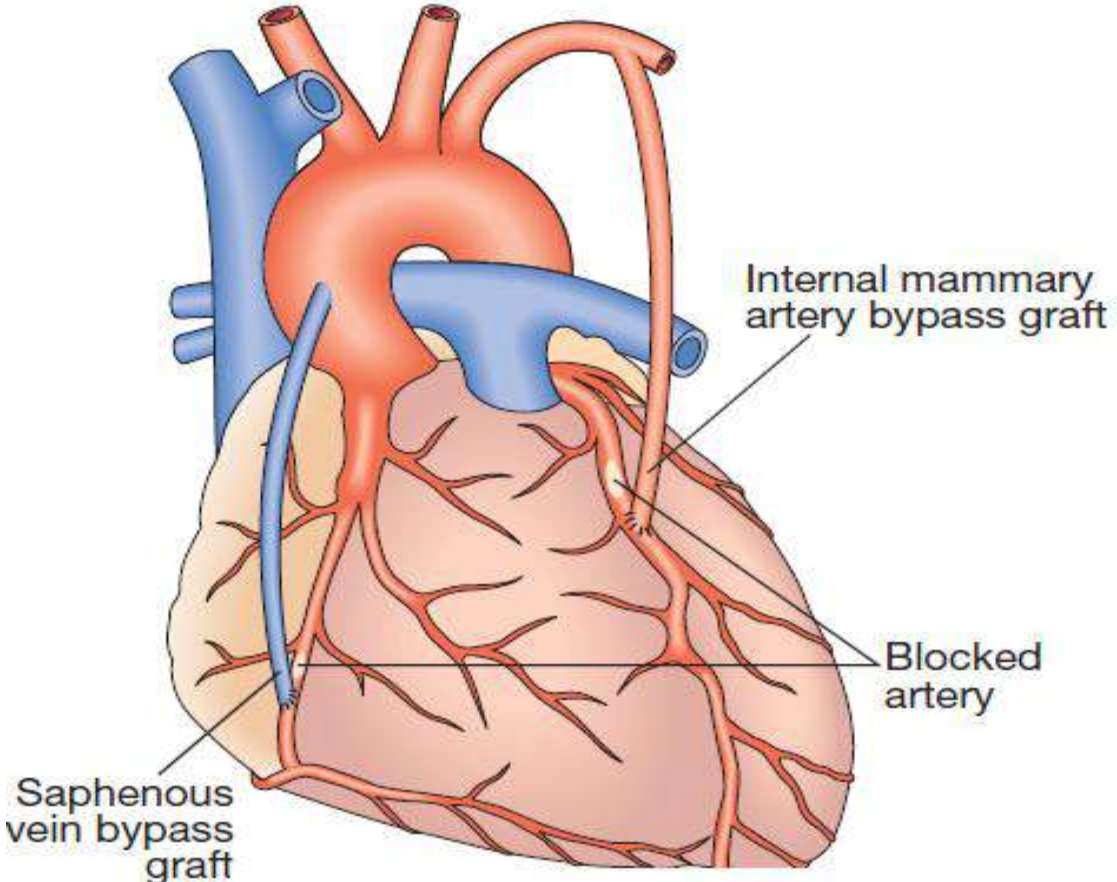
College of Pharmacy / University of Baghdad

Manual of Internal Medicine



Coronary artery bypass graft surgery.

Fourth Edition.2019-2020

خاص بطلبة كليات الصيدلة /المرحلة الخامسة

(تدريب مستشفيات / ردهة الباطنية)

إعداد

فرع الصيدلـــــــة السريـــــــريـــــــة

Lists of Contents

A-Cardiovascular Disorders

1-Hypertension (HTN)

Definitions :

1-**Hypertension** : is a condition where the BP is **consistently** above **130/80 mmHg** [1]

.

2-**Essential HTN : ** Most patients (90–95% of cases**)** with hypertension have essential hypertension , in **which there is no identifiable cause for their chronically elevated BP** [2].

3-**Secondary HTN:** Patients with secondary hypertension have a specific identified cause for elevated BP. The **most common causes** are :
Chronic kidney disease, Renovascular disease, Coarctation of the aorta, Primary aldosteronism ,Cushing syndrome ,Pheochromocytoma and Obstructive sleep apnea. [3]

4-**Hypertensive crises**: are situations in which measured BP values are markedly elevated[2] (BP >180/120 mm Hg) [4].

5-**Resistant HTN**: defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic). [5]

Clinical Presentation and complications:

1-Patients with uncomplicated primary hypertension are usually **asymptomatic** [4]
2- The most common and important cardiovascular complications associated with hypertension are **stroke** and **myocardial infarction** [6].

Diagnosis

1-The diagnosis of hypertension is made only after the average of two or more measurements, taken on separate occasions [7](Repeated after weeks) [6].

Treatment

Desired Outcome

Goal blood pressure values are **less than 140/90 for uncomplicated hypertension** and **less than 130/80** for patients with **chronic kidney disease**, **coronary artery disease** (myocardial infarction [MI] or angina), or **stroke** [4].
Note : the current recommendation of American diabetic association is stated that: People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of ,<130 mmHg. Lower systolic targets, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. Patients with diabetes should be treated to a diastolic blood pressure (DBP) ,<80 mmHg [8].

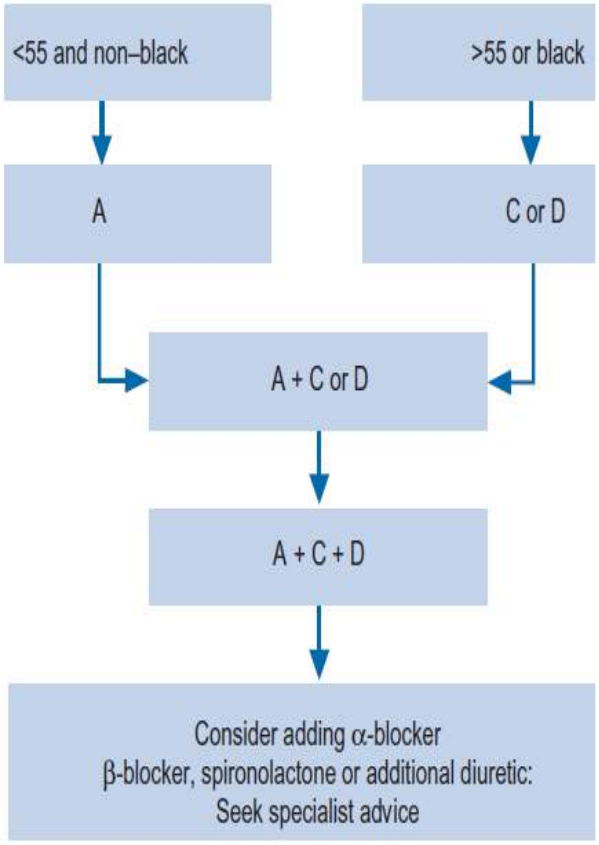
A-Nonpharmacologic Therapy [2]

- Weight reduction - BMI should be < 25 kg/m^2
- Low-fat and saturated fat diet, Low-sodium diet 6 g sodium chloride per day.
- Dynamic exercise - at least 30 minutes per day.
- Reduce cardiovascular risk by stopping smoking .

B-Pharmacologic Therapy:

1-Initial drug selection depends on the degree of BP elevation and the presence of **comorbid conditions** [4].

2-Primary antihypertensive agents that are acceptable as *first-line* options include **thiazide-type diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs),** and **calcium channel blockers (CCBs)** [4]. (figure 1) [5].



A = ACE inhibitor; C = calcium channel blocker; D = diuretic

Fig. 1 Algorithm for drug sequencing in hypertension.

3-**β-blockers are no longer recommended as 1st line agent for any patient group unless there is a compelling indication** (e.g. angina). β-blockers were found to **be less effective in reducing the major cardiovascular events, especially stroke**, than other antihypertensives [7].

4-All patients with diabetes and hypertension should be treated with either an **ACE inhibitor or an ARB.** Both classes provide **nephroprotection** and reduced CV risk [4].

5-Thiazides are the preferred type of diuretic for treating hypertension [1]. Loop diuretics are no more effective at lowering BP than thiazides unless renal function is significantly impaired (eGFR) <30 mL/min per 1.73 m2). They are also a suitable choice if heart failure is present [5].

6-**Methyldopa** is the most suitable drug choice for use in pregnancy because of its long-term safety record. **Calcium channel blockers**, and **hydralazine** are also used. β-Blockers, particularly atenolol, are used less often as they are associated with intrauterine growth retardation [5].

Major contraindications and side effects of antihypertensive drugs[3]

DRUG CLASS	Major contraindications	Side effects
Diuretics Thiazides	Gout	Insulin resistance, new-onset type 2 diabetes, Hypokalemia, hyponatremia,Hypertriglyceridemia Hyperuricemia, precipitation of gout.
Loop diuretics	Hepatic coma	Interstitial nephritis, Hypokalemia Potentiate aminoglycoside ototoxicity and nephrotoxiciy.
Potassium-sparing diuretics	Serum potassium concentration > 5.5 mEq/L,GFR < 30 mg/mL/1.73 m2	Hyperkalemia, gynecomastia .
ACE inhibitors ,ARBs	Pregnancy, Bilateral renal artery stenosis, Hyperkalemia	Dry Cough(only for ACE inhibitors), Hyperkalemia, Angioedema. Leukopenia, Cholestatic jaundice
Dihydropyridine CCBs	significant aortic stenosis , unstable angina	Headache, Flushing,Ankle edema Gingival hyperplasia Esophageal reflux disease
Nondihydropyridine CCBs	Heart block Bradycardia Systolic heart failure	AV block (especially with verapamil)Constipation (often severe with verapamil) Worsening of systolic function, heart failure, Gingival edema or hypertrophy
β-Adrenergic blockers	Asthma (nonselective and selective at high doses)Heart block Depression	Heart block, New-onset type 2 diabetes (especially in combination with a thiazide) , acute decompensated heart failure Bronchospasm Depression, nightmares, fatigue Cold extremities, claudication .

Central sympatholytics	Orthostatic hypotension	Depression, dry mouth, lethargy Erectile dysfunction (dose dependent) Rebound hypertension with clonidine withdrawal
Direct vasodilators	Orthostatic hypotension	Reflex tachycardia Fluid retention Hirsutism, pericardial effusion with minoxidil Lupus with hydralazine

Comorbidities can help guide choice of antihypertensive medication: [9]

- CKD: ACEI or ARB.
- Heart failure: ACEI or ARB, β-blocker, aldosterone antagonist, diuretics.
- Myocardial infarction: β-blocker, ACEI, aldosterone antagonist.
- Migraines: β-blockers, CCBs.
- Benign prostatic hypertrophy: α-blockers.
- Essential tremor: β-blockers.
- Hyperthyroidism: β-blockers (nonselective).
-Asthma : CCBs

Hypertensive Urgency and Emergency [5] [9]

Hypertensive urgency (severely elevated BP without acutely progressive end-organ damage)
- Need prompt but gradual control of BP using an **oral agents**.
-Outpatient follow-up is appropriate, but needs BP assessment at least weekly.
- Rapidly acting oral agents, such as **Labetalol ,captopril** , a short-acting ACE inhibitor, which lowers blood pressure within 15 to 30 minutes of oral dosing and **clonidine**. are used.

Hypertensive emergency (severely elevated BP with acutely progressive end-organ damage).
- BP must be brought down rapidly but in a controlled fashion in an intensive care unit by administering **intravenous antihypertensive medications**, which have a rapid effect and are easily titratable like :Nicardipine, Labetalol, Clevidipine, Esmolol ,Hydralazine , Nitroglycerin (intravenous), sodium Nitroprusside. And enalaprilate.

Note:- manifestations of acute end organ damage in hypertensive emergency are: Hypertensive encephalopathy, Intracranial hemorrhage , Unstable angina , Acute myocardial infarction, Left ventricular failure with pulmonary edema, Acute aortic dissection and Eclampsia. [8]

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2-Heart Failure

Definition

• Heart failure (HF) is a condition caused by the **inability of the heart to pump sufficient blood to meet the metabolic needs of the body** [1].

Classification

With systolic failure(problem in **contraction**): there is a decreased ejection of blood from the heart during systole. **With diastolic failure** (problem in the **filling of ventricles**), filling of the ventricles during diastole is reduced [2].

Etiology:

The common underlying etiologies in patients with heart failure are coronary artery disease and hypertension [3].

Clinical Manifestations

A-Left-sided failure. If blood cannot be adequately pumped from the left ventricle to the peripheral circulation, the blood will backs up into the pulmonary alveoli. The result is the **development of pulmonary congestion and edema** [4].
Patients can experience a variety of symptoms [**Dyspnea** (difficult breathing), or **shortness of breath (SOB)**], related to buildup of fluid in the lungs [5].

1-Exertional dyspnea occurs when patients describe breathlessness induced by physical activity [5].

2-Orthopnea : Orthopnea is present **if a patient is unable to breathe while lying flat on a bed (i.e., in the recumbent position)**[5].

3-Paroxysmal nocturnal dyspnea (PND)occurs when patients awaken suddenly with a feeling of breathlessness and suffocation [5].

B-Right -sided failure.
When blood is not pumped from the right ventricle, the blood backs up throughout the body producing **systemic** congestion **and edema** [4]. Edema is especially noticeable in the **legs (ankles edema)because gravity pulls the fluid into the lower half of the body** [6].

Heart Failure Symptoms' Classification

(table1)[7].

Table 1

New York Heart Association Classification of Heart Failure

Class I	No symptoms with ordinary activity
Class II	Symptoms with ordinary activity
Class III	Symptoms with less than ordinary activity
Class IV	Symptoms at rest

Investigations

1-Echocardiogram: Used to assess LV size, and ejection fraction (EF) (the fraction of the blood pushed during systole from the volume of blood that present at the end of diastole : normally it is more than 50 %) [5].

2-Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions [4].

3-ECG: To assesses the presence of any other cardiac problems, such as arrhythmias [5, 8].

Treatment

Nonpharmacologic Interventions

Nonpharmacologic treatment involves:

1-**Dietary modifications** in HF consist of sodium restriction and sometimes fluid restriction [5]. Patients should routinely practice moderate salt restriction (2–2.5 g sodium or 5–6 g salt per day) [9]. Patients should be educated to avoid cooking with salt and to limit intake of foods with high salt content [5]. . Fluid restriction may not be necessary in many patients. When applicable, a general recommendation is to limit fluid intake from all sources to less than 2 liters per day [5].

2-Exercise, while discouraged when the patient is acutely decompensated (Acute heart failure), is recommended when patients are stable. Regular low intensity, aerobic exercise that includes walking, swimming, or riding a bike is encouraged, while heavy weight training is discouraged [5]. .

3-Modification of classic risk factors, such as **tobacco** and **alcohol** consumption, is important to minimize the potential for further aggravation of heart function [5].

Pharmacologic Treatment

A-Systolic Heart Failure

Agents with proven benefits in **improving symptoms**, **slowing disease progression**, and **improving survival** (**reduce mortality)** in chronic HF include:

ACE inhibitors, ARBs, β-adrenergic blockers [1], **aldosterone antagonists** (in select patients) [1, 5] and most recently the combination of angiotensin-receptor/neprilysin inhibitor (ARNI) [(sacubitril/valsartan (Entresto®)] [10].

A-Neprilysin inhibitors [10].

1-Neprilysin is an enzyme that involved in degradation of many peptides including natriuretic peptides, bradykinin and adrenomedullin. Inhibition of neprilysin increased the availability of these peptides which **exert favorable effects in heart** failure (e.g. vasodilatation and natriuretic actions).

2-Because neprilysin also degrades angiotension II, a neprilysin inhibitor must be combined with agent that blocks rennin-angiotension system. Since ACE and neprilysin each breakdown bradykinin, inhibiting both enzyme lead to significant increase **in the risk of angioedema**. For that reason the neprilysin inhibitor-ARB (Sacubitril/Valsartan) combination was developed.

3-The updated American College of Cardiology/American Heart Association (ACC/AHA)guideline in 2016 recommend using an ACE inhibitor, ARB, or ARNI in combination with background therapy, including beta-blockers and aldosterone antagonists, to reduce morbidity and mortality.

4-For patients with **chronic symptomatic class II or III HF** with reduced ejection fraction who tolerate an ACE inhibitor or ARB, the guidelines recommend **replacing** the **existing ACE inhibitor or ARB with an ARNI to reduce morbidity and mortality**.

B-Angiotensin-Converting Enzyme(ACE) Inhibitors:

1-The updated (ACC/AHA)guideline in 2016 recommend using an ACE inhibitor (like captopril, lisinopril, enalapril,…..), ARB, or ARNI in combination with background therapy, including beta-blockers and aldosterone antagonists, to reduce morbidity and mortality [10].

2-ACE inhibitors should be initiated at low doses, followed by increments in dose if lower doses have been well tolerated [9].

C-β-Blockers:

1-The ACC/AHA guidelines state that *β*-blockers should be prescribed to **all patients with stable systolic HF** unless they have a C/I. **Extended-release metoprolol** succinate, **carvedilol**, and **bisoprolol** are FDA approved for use in HF. Metoprolol and bisoprolol are both partially selective *β*1-lockers, and carvedilol is a mixed *α*1- and nonselective *β*-blocking agent [1].

2- *β*-Blockers should be initiated **in stable patients** who have **no or minimal evidence of fluid overload**. Because of their negative inotropic effects, *β*-blockers

should be started in very low doses with slow upward dose titration [1](**in a 'start low, go slow' fashion**) [11] to avoid symptomatic worsening [1].

D-Angiotensin II Receptor Blockers (ARBs):

Although some data suggest that ARBs produce equivalent mortality benefits when compared with ACE inhibitors, **the ACC/AHA guidelines recommend use of ARBs only in patients who are intolerant of ACE inhibitors** [1].

E-Aldosterone Antagonists:

There is evidence that aldosterone mediates some of the major effects of RAAS activation, **such as myocardial remodeling and fibrosis**, as well as sodium retention and potassium loss at the distal tubules [9].
Currently low-dose aldosterone antagonists (e.g. 25 mg/day spironolactone) should be added for:
(1) Patients with symptoms of **moderate to severe heart failure (**NYHA class II-IV**) who are receiving standard therapy**; and
(2) **Those with LV dysfunction early after MI** (where heart failure occurs in the first 4 weeks after an acute myocardial infarction [1, 11]).
(3)in patients with a left ventricular ejection fraction **≤ 35%.**[12].

F-Diuretics:

1-Loop and thiazide diuretics have not been shown to improve survival in heart failure [11]. Consequently, diuretic therapy (in addition to sodium restriction) is recommended in all **patients with clinical evidence of fluid retention** (peripheral and pulmonary edema) [1, 13]. Patients who do not have fluid retention would not require diuretic therapy [1].

2-Loop diuretics (furosemide, bumetanide, and torsemide) are the most widely used diuretics in HF [5].

J-Nitrates and Hydralazine:

1-Nitrates (e.g., ISDN) and Hydralazine are combined in the treatment of HF because of their complementary hemodynamic actions [1]. Hydralazine is a potent arterial dilating agent that decrease afterload. Nitrates have venous dilating properties that decrease preload [14].

2-The combination may be reasonable **for patients with persistent symptoms despite optimized therapy with an ACE inhibitor (or ARB) and β-blocker**. The combination also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs [1].

H-Digoxin

1-Digoxin does not improve survival in patients with HF but does provide **symptomatic Benefits** only [1] .

2-Current recommendations are for the addition of digoxin for **patients who remain symptomatic despite an optimal HF regimen consisting of an ACE inhibitor or ARB, β-blocker, and diuretic** [5].

3-Digoxin is also prescribed routinely in patients with HF and concurrent atrial Fibrillation (AF) [14] to slow ventricular rate regardless of HF symptoms [2].

Ivabradine is approved by FDA for symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, with sinus rhythm and a heart rate of greater than or equal to 70 bpm at rest to reduce the risk of hospitalization for worsening HF in adults. [14].

B-Heart Failure Caused by Diastolic Dysfunction

Diastolic dysfunction, an inadequacy of ventricular relaxation and impaired LV filling. Diastolic dysfunction is characterized by a normal **or near-normal LVEF** [15](40% to 60%)[5]. For symptomatic patients, diuretics in conjunction with salt restriction are indicated initially to relieve congestive symptoms. Thereafter, **β-adrenergic blockers**, **calcium channel blockers** (e.g., **verapamil**), or **ACE inhibitors**, and **ARBs**, may be **beneficial** [15].

Note :

1-Unlike in systolic HF, nondihydropyridine calcium channel blockers (**diltiazem** and **verapamil**) may be useful in heart failure caused by diastolic dysfunction [5].

2-A recent study did not find favorable effects with digoxin in patients with mild to moderate diastolic HF. Therefore, the role of digoxin for symptom management and HR control in these patients is not well established [5].

Pulmonary edema[16].

Immediate treatment for acute pulmonary edema:

- Patient should be placed in the **semisitting position** to decrease venous return.

-Supplemental **oxygen** should be administered, **mechanical ventilation** is indicated if oxygenation is inadequate or hypercapnia occurs.

-**Morphine sulfate** reduces anxiety and dilates pulmonary and systemic veins; 2-4 mg can be given intravenously over several minutes and can be repeated every 10-25 minutes until an effect is seen.

-**Furosemide** is a venodilator that decreases pulmonary congestion within minutes of IV administration, well before its diuretic action begins. An initial dose of 20-

80 -mg IV should be given over several minutes and can be increased based on response.
- **IV nitroglycerin** or nitroprusside can be used if systolic BP is > I 00.
- **inotropic** drugs like dopamine or dobutamine in patients with concomitant hypotension or shock. (if systolic BP< 90).

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3-Chronic Stable Angina

Definitions

1-Angina pectoris is a discomfort in the chest and/or an adjacent area resulting from myocardial ischemia (1).
2-Stable angina: is defined as **a predictable occurrence** of chest discomfort with physical exertion (2) and is predictably resolved with rest or administration of sublingual nitroglycerin (3).
3-Angina caused by **spasm** of the coronary arteries is known as **Variant or (Prinzmetal) angina** (4).
4-Unstable angina : angina which *increases rapidly in severity and occurs at rest* (5).

Pathophysiology

1-**Angina pectoris typically occurs when myocardial oxygen demand exceeds myocardial oxygen supply** (perfusion).

2-The underlying pathologic condition is the presence of **atherosclerosis** in one or more of the coronary arteries (6).

Table 1

Precipitating Factors
Mild, moderate, or heavy exercise, depending on patient
Effort that involves use of arms above the head
Cold environment
Walking against the wind
Walking after a large meal
Emotions: fright, anger, or anxiety
Coitus

Precipitating Factors:

Precipitating factors for **stable angina pectoris** are summarized in table 1 [6].

Clinical Findings

The diagnosis of angina pectoris depends principally upon the history, which should specifically include:

1. Circumstances that precipitate and relieve angina: Angina occurs most commonly **during activity and is relieved by resting** [7].

2. Characteristics of the discomfort: **Patients** often do not refer to angina as "pain" but as a sensation of **tightness**, , **burning**, or **pressing** [7].

3. Location and radiation: In most cases, the discomfort is **felt behind** or slightly to the left of **the mid sternum**. It **radiates** most often to the **left shoulder and upper arm**, frequently **moving down the arm**.
It may also radiate to the **right shoulder or arm**, the **neck**, or **even the back** [7].

4. Duration of attacks:
Duration of attack is usually **0.5–30 minutes** [6].

5-Nitroglycerin Relief: Relief of pain occurring **within 45 seconds to 5 minutes of taking Nitroglycerin** [6].

Diagnosis

1-The **resting ECG** is **normal in about one half** of patients with angina who are not experiencing an acute attack [8].
2-S**tress ECG Testing** [9].
3-Coronary angiography: Coronary angiography is regarded as the definitive test as it demonstrates the **presence of occlusions**, their **position** and their **severity** [4].

Treatment

1-Risk factors Modification

Alterable risk factors include **smoking**, **hypertension**, **hyperlipidemia**, **obesity**, and **sedentary lifestyle**. These factors should be identified and treated when possible [8]

2-Pharmacologic Therapy:

The current national guidelines recommend that all patients be given the following unless contraindications exist :
(1)-Sublingual nitroglycerin for immediate relief of angina.
(2)-Aspirin (or Clopidogrel in patients with aspirin hypersensitivity or intolerance).
(3)-β- blockers.
(4)-Calcium antagonists or **long-acting nitrates** [isosorbide dinitrate(ISDN) or isosorbide mononitrate (ISMN)]for reduction of symptoms when β-blockers are

contraindicated (or they may be used in combination with β-blockers when initial treatment with β-blockers is not successful).
(5)-LDL-lowering therapy: for patients with coronary artery disease (CAD) and a high LDL concentration (to be lowered to less than 100 mg/dL) [8]**.**

A-Aspirin therapy: (81–325 mg daily) should be prescribed for all patients with angina. **Clopidogrel**, 75 mg daily is a good alternative in aspirin-intolerant patients [8].
B-β-Adrenergic Blocking Agents: They reduce heart rate and force of contraction, **allowing greater time for perfusion and decreased demand for oxygen.** Cardioselective beta-blockers, such as atenolol and metoprolol, are preferred [4].
Note: β-Blockers have little or no role in the management of **variant angina** as they may induce coronary vasoconstriction and prolong ischemia [2].

C-Nitrates :1-Nitrate therapy may be used to terminate an acute anginal attack, to prevent effort- or stress-induced attacks, or for long-term prophylaxis.
Sublingual, **buccal**, or **spray** nitroglycerin products are preferred for **alleviation of anginal attacks** because of rapid absorption [8].

Current recommendations are if the pain persists or is unimproved 5 minutes **after the first dose of NTG**, the patient should contact their physician or be transported to an emergency room as they may be experiencing an MI. If patient needs more than one tablet, he can take a maximum of three tablets in 15 minutes [6, 7].

2-Chewable, oral, and transdermal products are acceptable for **long-term prophylaxis** of angina.
The main limitation to long-term nitrate therapy is **tolerance**, which can be limited by using a regimen that includes a minimum 8- to 10-hour period per day without nitrates (**nitrate-free interval**) [7].

D-Calcium Channel Antagonists:1-Good candidates for calcium channel antagonists include patients with contraindications or intolerance to β-blockers, Prinzmetal's angina, and peripheral vascular disease [8].
2-Because calcium channel antagonists may be more effective, some authorities consider them the agents of choice for ***variant angina***. A patient unresponsive to calcium channel antagonists alone may have nitrates added [8].

E-Statins: Statins lower cholesterol but are also thought to have **antithrombotic and anti-inflammatory properties**. They have benefits even in those with 'normal' cholesterol [3].

F-Others antianginal agents include: **Ranolazine** which is especially useful in patients who cannot tolerate further decreases in heart rate and blood pressure secondary to the use of traditional antianginal agents. [6]

3-Nonpharmacological therapy

In those who fail to respond to drug therapy, or where there is occlusion of numerous coronary arteries, coronary artery bypass graft (**CABG**) surgery or percutaneous coronary intervention (**PCl**) should be considered [4].
In PCl, a balloon attached to a catheter is used to open the patient's coronary vessels , which may also be held open with **a metal stent** [4].

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4-Acute Coronary Syndrome (ACS)

1-ACS is an umbrella term that includes either unstable angina (**UA**) or acute myocardial infarction (AMI) [consisting of ST segment elevation MI (**STEMI**) or non–ST segment elevation MI (**NSTEMI**)] [1].

2-Unstable angina is characterized by rapidly worsening angina, angina on minimal exertion or angina at rest in **the absence of myocardial damage** [2].

3-MI occurs when symptoms occur at rest and there is **evidence of myocardial necrosis** [causing elevation in cardiac **biomarkers** (enzymes)][2, 3].

	ST segment elevation	**Elevation of cardiac enzymes**
STEMI	Yes	Yes
NSTEMI	No	Yes
UA	No	No

4-UA and NSTEMI present without persistent ST segment elevation and are managed differently from STEMI [4].

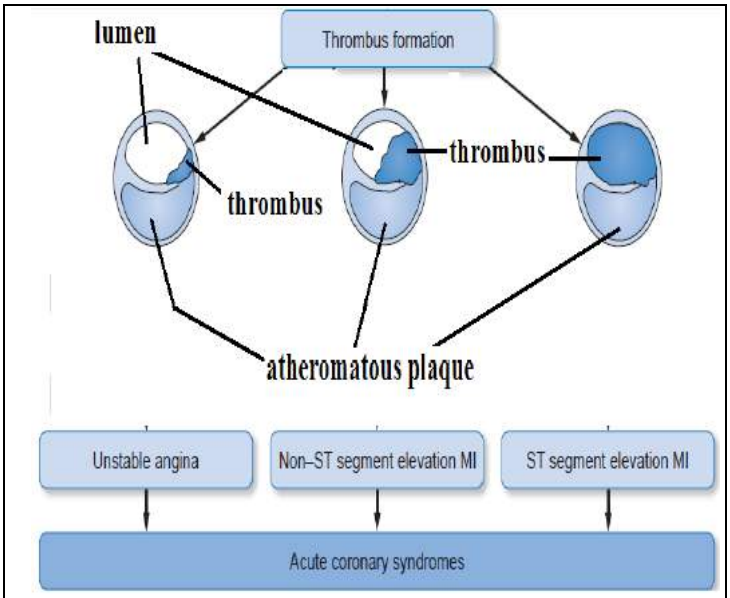

Figure1: Thrombus formation in ACS.

Pathophysiology

1- The majority of ACS results from **occlusion of a coronary artery secondary to thrombus formation**[1].

2-In patients with **UA**, there is **little thrombotic occlusion**. In patients with **NSTEMI**, there is **partial thrombotic occlusion**. For **STEMI**, there is **total thrombotic occlusion** [1].

Risk Factors

Risk factors for an ACS may be **modifiable or nonmodifiable**. Nonmodifiable risk factors include age, male gender , and **family history**.
Modifiable risk factors include smoking, alcohol intake, physical inactivity, hypertension, type 2 diabetes, dyslipidemias, obesity …….[5, 6].

Clinical Presentation

1-**Central chest pain** similar to that occurring in angina is the most common presenting symptoms .**Unlike angina** it is usually **occurs at rest** , is more **severe and last for longer duration** (e.g. some hours) .Accompanying symptoms may include **nausea**, **vomiting**, **diaphoresis**, or **shortness of breath (SOB)** [6].
2-Sudden death, **from arrhythmias** [like **ventricular fibrillation** (**VF**)], may occur immediately and often within the first hour [2].

Diagnosis

A-ECG :

1-The ECG should be obtained within 10 minutes of patient presentation.[1, 3].
2- The ECG is also helpful in determining the **location of an infarction** [1, 3] (Fig. 3) [1].

3-Infarctions are located in a specific region of the heart (e.g.,

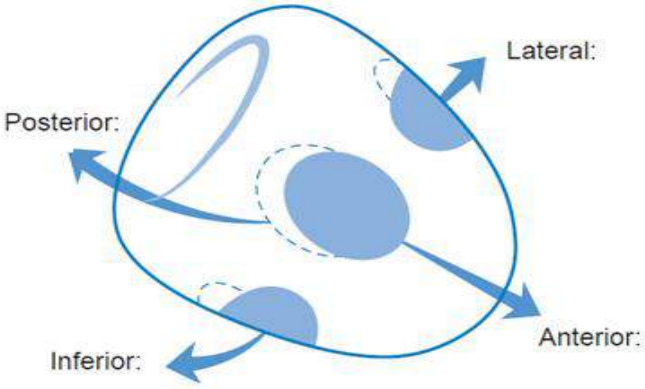

Figure 3: Location of an anterior, lateral, inferior, or posterior infarction

anterior, **lateral**, **inferior**, **posterior**). **An anterior wall infarction carries a worse prognosis** than an inferior or lateral wall infarction because it is more commonly ***associated with development of left ventricular failure and cardiogenic shock*** [(1)].

4-Some patients with myocardial ischemia have no ECG changes, so biochemical markers should be assessed [(3)].

B-Biochemical markers

1-Whena cardiac cell is injured, enzymes [Troponins T and I , creatine kinase myocardial band (CK-MB)**]** are released into the circulation [(1)].
2-Troponins T and I are highly specific for myocardial injury and are preferred for the diagnosis of an acute MI [(5)].

Complications [(1)]

1-Heart failure 2-Arrhythmias. 3-Reinfarction.

Treatment

The primary strategy for patients with an **occluded coronary artery** (**STEMI**) is the restoration of coronary flow with either a **fibrinolystic agent or percutaneous coronary intervention**(**PCI**). **If the coronary artery is patent (UA and NSTEMI), then fibrinolysis is unnecessary and probably harmful, although PCI may still be appropriate** [(4)].

A-Nonpharmacological Therapy

1-Nonpharmacological Therapy for STEMI

For patients with STEMI, primary **PCI** (with either **balloon** angioplasty or **stent placement**) is the treatment of choice when the patient with STEMI presenting **within 12 hours of the onset of chest discomfort** [(3, 7)].

2-Nonpharmacological Therapy for NSTEMI

In patients with NSTEMI, it is recommended either **PCI or coronary artery bypass grafting (CABG)** revascularization as an early treatment [(3)].

B-Pharmacological Therapy

Early Pharmacotherapy for STEMI

1-Oxygen: (if oxygen saturation is <90%)[(3, 7)].

2-Morphine: Morphine is administered as an analgesic and a venodilator that lowers preload, but it does not reduce mortality [(3)].

3-Sublingual followed by intravenous (IV) nitroglycerin: Immediately upon presentation, sublingual nitroglycerin (NTG) tablet should be **administered**. Intravenous NTG should be initiated in all patients with an ACS who have **persistent ischemic symptoms** (i.e. not controlled by SL nitroglycerin), **heart**

failure, or **uncontrolled high blood pressure**. Treatment should be continued for **about 24 hours after ischemia is relieved** [3].

4-Fibrinolytic Therapy: A fibrinolytic agent (**alteplase**, **reteplase**, **tenecteplase**) should be given to patients with **STEMI presenting within 12 hours of the onset of chest discomfort** when it is anticipated that primary **PCI cannot be performed** [7] [8].

Alteplase is found as two **50 mg** vials each reconstituted with 50 ml water for injection .its dose is **100** mg given as below :
15 m1 direct intravenous injection.(bolus)
50 ml by intravenous infusion during **30** minutes.
35 ml intravenous infusion during **1** hour.

5-Antiplatelet and anticoagulant Therapy

A-Aspirin: Aspirin should be administered within the first 24 hours of hospital admission [initially 160 to 325 mg **of aspirin** then a daily maintenance dose of 75 to 162 mg indefinitely] [3].

B-P2Y12 receptor inhibitor (Clopidogrel, Prasugrel, Ticagrelor) : P2Y12 inhibitor therapy should be given for all patient with STEMI in addition to aspirin [3, 7]. hey are usually given as **loading dose followed by maintenance dose** [3, 7].
Clopidogrel : loading dose 300mg, maintenance dose 75 mg once daily
Prasugrel : loading dose 60mg, maintenance dose 5 -10 mg once daily.
Ticagrelor :loading dose 180 mg, maintenance dose 90 mg twice daily.

C-Anticoagulants [unfractionated heparin (UFH), **bivalirudin** (Direct thrombin inhibitor) , **enoxaparin** (a LMWH)] : Anticoagulant therapy should be initiated in the emergency department and continued for 48 hours or longer in some patients [8].

The dose of **unfractionated heparin** is 60 units/kg IV bolus(max 4,000 units) followed by 12 units/kg/hour (max1,000 units/hour) for 48hours or until revascularization.

The dose of **enoxaparin** is 1mg /kg twice daily by subcutaneous injection maximum dose is **100mg** twice daily.

D-Glycoprotein IIb/IIIa Receptor Inhibitors: In patient undergoing PCI in STEMI **and receive UFH as anticoagulant**, a GP IIb/IIIa inhibitor (e.g. **abciximab)** should be added to UFH [3].

6-β-Adrenergic Blockers : A β-blocker should be administered early for patients with STEMI **(within the first 24 hours),** and then an oral β-blocker should be continued indefinitely[3].

7-ACE inhibitors: An ACE inhibitor (or ARBs) should be started **within 24 hours of presentation**, in the absence of contraindications [3, 7].

8- Statins: a high-intensity statin such as **atorvastatin** 40 to 80 mg or **rosuvastatin** 20-40 mg daily should be given. [1]

Early Pharmacotherapy for NSTEMI

Early pharmacotherapy for UA/ NSTEMI is similar to that for STEMI except that: **Fibrinolytic therapy is never administered to NSTEMI** [3].

Long-term therapy Following MI .

Those who have experienced MI have an increased risk of further attacks so secondary prevention is important. After MI (STEMI or NSTEMI), patients should receive indefinite treatment with **aspirin**, a **β-blocker**, and an **ACE inhibitor** [3].

1-Aspirin: All patients should receive aspirin indefinitely (or clopidogrel if aspirin is C/I) [3].

2-ACE Inhibitors and Angiotensin Receptor Blockers: ACE inhibitors should be initiated in **all patients after MI** to prevent the development of heart failure [3].

3-β-Blockers: After an ACS, patients should received a β-blocker indefinitely. A calcium channel blocker can be used in patients who cannot use β-blocker [3].

4- Nitrates: All patients should be prescribed a short-acting **sublingual NTG or lingual NTG spray** to relieve anginal symptoms when necessary [3].

5- P2Y12 receptor inhibitor (Clopidogrel, Prasugrel, Ticagrelor) : P2Y12 receptor inhibitor should be prescribed to all patients with MI [STEMI or NSTEMI] [3, 7].

6-Aldosterone Antagonists : should be considered within the first 2 weeks after MI to reduce mortality in all patients who **experienced HF symptoms** .The drugs are continued **indefinitely** [3].

7-Lipid-Lowering Agents: All patients with CAD should receive dietary counseling and pharmacotherapy in order to reach an LDL **cholesterol concentration <100 mg/dl** (and an optional LDL goal of <70 mg/dL) [3]. **Statins** are the preferred agents for lowering LDL cholesterol and should be prescribed in **most patients** [3].

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5-Venous Thromboembolism

1-Venous thromboembolism (VTE) results from clot formation in the venous circulation and is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE) (1).

2-**About 90% of the DVT involve the legs**, about 5% involve the upper extremities (e.g., axillary, or jugular veins), and the remaining 5% involve other veins of the body (e.g., internal iliac, renal) (2).

Pathophysiology (2).

Factors that may contribute to the formation of a thrombus include the following (Virchow triad): **1. Stasis of blood**. **2. Damage to blood vessels**. **3. Hypercoagulability of blood** .

Clinical Presentation: (1)

A-Symptoms of DVT include **unilateral leg swelling**, **pain**, tenderness, erythema, and **warmth**.
B-Symptoms of PE include dyspnea, tachypnea, pleuritic chest pain, tachycardia, palpitations, cough, diaphoresis, and hemoptysis.

Diagnosis(3)

blood test : The quantitative plasma d-dimer level rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin . But the d-dimer assay is not a specific test since Levels are increased in conditions other than DVT or PE **.**

Imaging tests

- **Doppler ultrasonography** of the deep-venous system is the primary Diagnostic test for DVT.

- computed tomography pulmonary angiography (CTPA) with intravenous contrast is the principal imaging test for the diagnosis of PE.

Classification of pulmonary embolism [3]

-Massive PE characterized by extensive thrombosis affecting at least half of the pulmonary vasculature.
-Submassive PE characterized by right ventricular dysfunction despite normal systemic arterial pressure.
-Low-risk PE which has an excellent prognosis.

Classification of Deep Venous Thrombosis[3]

Lower extremity DVT and upper extremity DVT With Leg DVT is about 10 times more common than **upper extremity DVT,** which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or central venous catheters.

Treatment[3] [4]

There are **three major treatment strategies**: **(1)** the use of parenteral anticoagulation with unfractionated heparin(UFH), low-molecular-weight heparin (LMWH), or fondaparinux "bridged" to warfarin as follow:

initially a low molecular weight heparin or **unfractionated heparin** is given. LMWH is now preferred over UFH for the initial treatment of VTE. **warfarin** is started at the same time as UFH or LMWH. Treatment with **UFH or LMWH should continue for at least 5 days** and until that the international normalized ratio (**INR**) **be therapeutic (between 2.0 and 3.0.) for 2 days** before stopping UFH or LMWH.
UFH is dosed to achieve a target activated partial thromboplastin time (**aPTT**) that is 2–3 times the upper limit of the laboratory normal. This is usually equivalent to an aPTT **of 60–80 seconds** .

(2) parenteral therapy switched after 5 days to a novel oral anticoagulant such as **dabigatran** or **edoxaban** .

(3) oral anticoagulation monotherapy with **rivaroxaban or apixaban** with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose **without parenteral anticoagulation.**

Management of massive pulmonary embolism [3]

For patients with massive PE and hypotension volume repletion with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates right ventricular wall stress.

Fibrinolysis

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE .

100 mg of recombinant tissue plasminogen activator (tPA) alteplase given as a continuous intravenous infusion over 2 h.

Pulmonary embolectomy by surgical process can also be used.

Advantages of LMWHs (e.g. Enoxaparin, Dalteparin, Tinzaparin) include: (1) more predictable anticoagulation (SC dosage regimens are based on body weight); (2) improved SC bioavailability; (3) longer half-life; (4) lower incidence of thrombocytopenia; and (5) less need for routine laboratory monitoring [(1)].

Duration of anticoagulation therapy

Anticoagulation therapy is continued for a **minimum of 3 months** [(5)] to prevent recurrent thrombosis but should be given longer depending on the underlying etiology of the VTE and the patient's risk factors [(6)](some patient may require **an indefinite anticoagulation**) [(6)].

Complications of Anticoagulants[(3)]

1-The most serious adverse effect of anticoagulation is **hemorrhage**. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered.

2-Major bleeding from warfarin is best managed with prothrombin complex concentrate. With less serious bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

3- Idarucizumab is a monoclonal antibody fragment used to reverse dabigatran Anticoagulation.

4-**Heparins**, particularly UFH, may also cause **thrombocytopenia** (low platelet count). This may occur in two forms [(7)].

A-Heparin-associated thrombocytopenia (HAT) is a benign, transient, and mild that usually occurs within the first few days of treatment [(7)].

B-**Heparin-induced thrombocytopenia (HIT)**, a more severe immune-mediated reaction which is usually develops 5 to 10 days after the initiation of heparin therapy (however, immediate-onset HIT can occur rapidly within hours of UFH initiation in patients previously exposed to heparin) [(7)].

5-During pregnancy, warfarin should be avoided if possible because of warfarin embryopathy. However, women can take warfarin postpartum and breast-feed safely. Warfarin can also be administered **safely during the second trimester** [4].

New oral anticoagulants (Target-specific oral anticoagulants):

1-These currently include two categories, **direct thrombin (factor IIa) inhibitor** (DTI) (dabigatran) and **direct Xa inhibitors** (rivaroxaban, apixaban, and edoxaban) [8].
2-As compared to warfarin, these oral anticoagulants have a **more rapid onset**, **shorter half-life**, **wider therapeutic window**, and **more predictable pharmacokinetics** [8].
3- They have few drug and food interactions with no need for laboratory monitoring.
4-Compared to warfarin, the target-specific anticoagulants have **a lower risk of intracranial hemorrhage** and a higher risk of gastrointestinal bleeding[8] .
5-Issues of concern include the **lack of antidote (except dabigatran)** and a relatively high cost. [9]

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6-Stroke

1-A stroke, or cerebrovascular accident (CVA), is defined as an abrupt onset of a neurologic deficit that lasts at least 24 hours and is presumed to be of vascular origin [1, 2].
2-Transient ischemic attacks (TIAs) are ischemic neurologic deficits lasting less than 24 hours and usually less than 30 minutes [1].

3-Stroke can be either **ischemic or hemorrhagic** in origin [1]. Approximately 85% of strokes are **ischaemic** and 15% **haemorrhagic** [3].

Risk Factors for Stroke

1-Nonmodifiable risk factors for stroke include increased age, male gender, and heredity [1].
2-Modifiable risk factors include hypertension and cardiac disease (e.g., CAD) diabetes mellitus, dyslipidemia, and cigarette smoking [1].

Pathophysiology

A-Ischemic Stroke:

Ischemic strokes are due either to **local thrombus formation or to emboli** where the clot forms elsewhere in the body before it is transported to the brain to occlude a cerebral artery [1, 3]. The final result is decreasing cerebral blood flow causing ischemia and infarction [1].

B-Hemorrhagic Stroke:

A haemorrhagic stroke occurs when there is bleeding from the vessels within the brain (**intracranial**) or the vessels on the surface of the brain into the space between the skull and the brain (**subarachnoid**) [3].
The presence of blood in the brain causes damage to the tissue through a mass effect and the neurotoxicity of blood components [1]

Symptoms of stroke

The signs and symptoms of stroke are summarized in (table 1) [4]:

Investigations [2]

1-The priority is usually to determine the **type of stroke suffered** .This is achieved through the use of **CT** scan or **MRI** of the brain. This will establish the **type** of stroke and the **size** and **location** of any haemorrhage or infarct.

Table 1: signs and symptoms

Sudden weakness, numbness, or paralysis of the face, arm, or leg (especially on one side of the body)
Loss of speech or trouble talking or understanding language
Sudden loss of vision
Sudden severe headache
Unexplained dizziness or loss of balance or coordination

2-Further tests are done to establish **risk factors** for the stroke event (such as **BP** for hypertension, blood **glucose** for diabetes and **ECG** for the presence of arrhythmias).

Pharmacologic Therapy of Ischemic Stroke

1-Thrombolysis: All patients with an ischemic stroke **within 4.5 hours** of onset should receive thrombolytic treatment with intravenous tissue plasminogen activator (**alteplase**) because it is effective in improving stroke outcome [1, 5, 6].

Endovascular mechanical thrombectomy used as an alternative or adjunctive treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who failed to achieve vascular reperfusion with IV thrombolytics. **[2]**

2-**Brain edema** develops between the second and third day after stroke onset**[2]** , with symptoms and signs of increasing intracranial pressure (ICP). Elevated ICP is managed by head elevation and osmotic agents such as **mannitol** [5, 6].

3-Maintenance of an adequate cerebral perfusion pressure helps prevent further ischemia. **Attempts to lower the blood pressure of hypertensive patients during the acute phase (i.e., within 2 weeks) [6] (first 7 days) [1] of a stroke should generally be avoided**, as lowering the blood pressure may further compromise ischemic areas [6]. However, the pressure should be lowered if it exceeds 220/120 mm Hg, if there is malignant hypertension, concomitant myocardial ischemia, or if blood pressure is >185/110 mmHg and thrombolytic therapy indicated [short-acting parenteral agents (e.g., labetalol, nicardipine, and nitroprusside) are preferred] [1].

4- **Aspirin is the only antiplatelet agent that has been proven effective for the acute treatment of ischemic stroke**; there are several antiplatelet agents proven for the secondary prevention of stroke (see below) [2]. Aspirin should be started between 24 and 48 hours after completion of alteplase [1]. In patients not eligible for thrombolytic therapy, the immediate administration of aspirin 325 mg orally daily is indicated [6].

5-Anticoagulant drugs should be started in the setting of **atrial fibrillation** or other source of cardioembolism. Treatment is with **warfarin** (target INR 2.0–3.0) or **dabigatran** [6].

6-The increase in body temperature is associated with worse outcomes after an acute stroke, so a reduction in body temperature can be beneficial in stroke patients. Use of antipyretics, such as **acetaminophen** are advised to maintain normal or slightly subnormal body temperatures. [7]

7-hyperglycemia may adversely affect ischemic infarction outcomes and increased mortality . If hyperglycemia is detected, appropriate insulin therapy should be initiated to keep the serum glucose concentration less than 140 mg/dL without causing hypoglycemia. [7]

Secondary prevention

Those who have experienced an ischaemic stroke have an increased risk of a further stroke so secondary prevention is important [3].

1-Antiplatelets : Aspirin, **clopidogrel**, and the **combination of aspirin plus extended-release dipyridamole** are the antiplatelet agents most commonly used for this purpose [2].

2-Anticoagulant: In patients with **atrial fibrillation** and a presumed cardiac source of embolism, oral anticoagulation with either vitamin K antagonism (**warfarin**), **apixaban**, **dabigatran**, or **rivaroxaban** is recommended for secondary stroke prevention [1].

3-Statins: treatment with statins reduces the risk of recurrent stroke. Statins is used in ischemic stroke patients to achieve a LDL cholesterol concentration of less than 100 mg/dL [1].

4-Elevated blood pressure is common after ischemic stroke, and its treatment is associated with a decreased risk of stroke recurrence. **ACE inhibitor and a diuretic** are usually considered for reduction of blood pressure in patients with stroke or TIA after the acute period (first 7 days) [(1)].

B- Pharmacologic Therapy of Hemorrhagic Stroke:

1-There are currently no proven pharmacologic strategies for treating intracerebral hemorrhage [(1)].

2-**Subarachnoid hemorrhage** is associated with a high incidence of delayed cerebral ischemia after the bleeding episode. Vasospasm of the cerebral vasculature is thought to be responsible for the delayed ischemia and occurs between 4 and 21 days after the bleed. The calcium channel blocker **Nimodipine (60 mg every 4 hours for 21 days**) is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia [(1)].

Complications of stroke

Complications of stroke are summarized in (table 2) [(7)]

Table 2: Complications of stroke and their prevention and treatment [(7)]

Complication	Prevention	Treatment
Chest infections	Nurse Care	Antibiotics
Seizure	Maintain cerebral oxygenation	Anticonvulsants
DVT / PE	S.C. heparin	Anticoagulant
Hyperglycemia	Treat diabetes	Insulin if necessary
Pressure sore	Frequent turning, monitor pressure area	Nursing care, special matter
Urinary infection	Use penile sheath, avoid catheterization if possible	Antibiotics
Constipation	Appropriate laxative and diet	Appropriate laxative

Rehabilitation

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy [(2)]and is effective in reducing long-term disability [(1)]

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7-Atrial fibrillation (AF) (irregular irregularity):

1-**AF is one of the most common arrhythmias** and it is a major cause of morbidity and mortality. AF incidence increases with age and is more common in patients with **hypertension**, **coronary artery disease** and **heart failure**. Other causative factors include **hyperthyroidism** and high alcohol consumption [(1)].

2-During episodes of AF, the atria beat **rapidly but in an uncoordinated manner**. The ventricles are activated irregularly. This produces the characteristic 'irregularly irregular' pulse [(2)].

3-One of the most important consequence of AF is **embolic stroke** [(3)]. (During AF, atrial contraction is absent. Therefore, due to the fact that atrial contraction is responsible for approximately 30% of ventricular filling, this blood that is not ejected from the left atrium to the left ventricle pools in the atrium, and facilitates the formation of a **thrombus**) [(4)].

Notes:

A-Because the frequency of right atrial thrombosis is less than that of left atrial thrombosis in AF patients, the risk of stroke is enhanced much more than the risk of pulmonary embolism [(3)].

B- The risk of stroke increases after restoration of normal sinus rhythm [by drugs or by **direct current cardioversion** (DCC)]which allows more efficient cardiac contractility and expulsion of the thrombus [(3)].

Clinical presentation :

1-Patients with atrial flutter or AF may be **asymptomatic** [(5)].

2-Patients may experience **symptoms of heart failure** [(6)]. Symptoms including **shortness of breath, fatigue, dizziness and syncope** (Congestive heart failure develops when the atria do not effectively pump blood into the ventricles)[(7)].
Patients commonly complain of **palpitations**; often the complaint is "I can feel my heart beating fast" or "It feels like my heart is going to beat out of my chest."[(8)].

Diagnosis:

The electrocardiogram (ECG) is the cornerstone of diagnosis for cardiac rhythm disturbances [(6)].

Treatment

Hemodynamically Unstable AF

1-For patients who present with an episode of AF that is hemodynamically unstable (patients with shock or severe hypotension, pulmonary edema, or ongoing

myocardial infarction or ischemia), emergent conversion to sinus rhythm is necessary using **direct current cardioversion** (DCC) [8, 9].

Hemodynamically stable AF patient
Rate Control Versus Rhythm Control
A-Ventricular Rate Control is achieved by inhibiting the proportion of electrical impulses conducted from the atria to the ventricles through the AV node. Therefore, drugs that are effective for ventricular rate control are those that inhibit AV nodal impulse conduction: β-blockers, diltiazem, verapamil, and digoxin [8].

B-Rhythm Control (Restoration of sinus rhythm) can be achieved with DCC or with antiarrhythmic agents (pharmacological cardioversion) (type Ic, and III agents are effective) [6, 10]. DCC is generally more effective than drug therapy [8].

Table 2
Vaughn Williams Classification System

Ia: Quinidine, procainamide, disopyramide
Ib: Lidocaine, mexiletine, tocainide
Ic: Flecainide, propafenone, moricizine
II: Beta-blockers
III: Amiodarone, bretylium, sotalol, ibutilide, dofetilide
IV: Verapamil, diltiazem

C-The treatment strategy for most patients should be **a rate control strategy**. However, rhythm control is necessary when patients experience symptoms despite adequate rate control, or if patients cannot tolerate the adverse effects of rate-controlling medications **[3].**

Conversion To Normal Sinus Rhythm

1-The cardioversion decision strategy depends greatly on the duration of AF. If the AF is less than 48 hours in duration, then the likelihood of atrial clot formation is low and conversion to sinus rhythm is safe and may be attempted with elective DCC or specific drug therapy [3, 8].
2-However, if the duration of the AF episode is longer than 48 hours or if there is uncertainty regarding the duration of the episode, two strategies for conversion may be considered [8].
A-Anticoagulate patients with warfarin, maintaining a therapeutic International Normalized Ratio (INR) for 3 weeks, after which cardioversion may be performed [8].
B-Alternatively, **a transesophageal echocardiogram** (TEE) can be used to determine whether atrial clots have formed. If no clot is observed on TEE, then there is low risk for stroke with cardioversion of AF. However, if an atrial clot is evident on TEE, the patient need to be adequately anticoagulated for 3 weeks before cardioversion to prevent embolization of the clot and stroke [3].

3-If cardioversion is successful, patients should **remain on warfarin for at least 4 weeks after cardioversion** because normal atrial contraction may not return for up to 3 weeks, and patients may be at risk of late embolization [3].

Stroke Prevention

1-Patients with AF have an increased risk for stroke compared with patients without AF [3].

2- Decision strategy for assigning patients to **receive anticoagulation** for prevention of thromboembolism in AF is presented in Table 9-10 [8].

3- The landscape of anticoagulation for stroke prevention in AF has changed with the availability of **dabigatran**, **rivaroxaban**, and **apixaban** [8].

4- **Dabigatran**, approved by the (FDA) in 2010, is a direct thrombin inhibitor for stroke prevention in patients with **nonvalvular AF**.

Advantages of dabigatran include the fact that INR monitoring is not required, and the drug's onset of action is rapid, eliminating the need for bridging with unfractionated or low molecular weight heparins. In addition, there is a lower likelihood of drug interactions with dabigatran than with warfarin.

Table 9–10

American Heart Association/American College of Cardiology/Heart Rhythm Society Recommendations for Prevention of Thromboembolism in Patients with Nonvalvular AF[a,17]

CHA_2DS_2-VASc Score	Recommended Stroke Prevention Strategy
0	Antithrombotic therapy is not recommended
1	No antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered
≥ 2	Oral anticoagulation recommended. Options include: Warfarin (INR: 2.0–3.0) Dabigatran Rivaroxaban Apixaban

CHA_2DS_2-VASc score calculated as follows:[28]

Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 points
Diabetes mellitus	1 point
History of **s**troke, TIA or thromboembolism	2 points
Vascular disease (prior MI, PAD or aortic plaque)	1 point
Age 65–74 years	1 point
Female **s**ex	1 point
Maximum score	9 points

a Patients with AF who have mechanical heart valves should receive warfarin titrated to an INR of 2.0–3.0 or 2.5–3.5 depending on the type and location of the prosthetic heart valve.
AF, atrial fibrillation; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

6-**Rivaroxaban**, an oral factor Xa inhibitor, was approved by the FDA in 2011 for prevention of stroke or systemic embolism in AF. Rivaroxaban was shown to be non inferior to warfarin for prevention of stroke or systemic embolism in patients

with AF, and compared with warfarin, rivaroxaban was associated with a **lower risk of intracranial and fatal bleeding** [8].

7-**Apixaban**, another oral factor Xa inhibitor, was approved by the FDA in 2012 for prevention of stroke and systemic embolism. Apixaban may be **superior to warfarin for prevention of stroke or systemic embolism in patients with AF,** with **lower bleeding risk** [8].

8-For patients for whom **warfarin is preferred over other oral anticoagulants** (such as in patients with mechanical prosthetic heart valves, those with valvular AF, and patients with end-stage renal disease), **specific genetic tests to guide the initiation of therapy** have been approved by the FDA [8].

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.B-Gastroenterology

1-Cirrhosis and Portal Hypertension

Definitions:

Cirrhosis,can be defined as **fibrosis of the hepatic parenchyma (hepatocytes) resulting in nodule formation and altered hepatic functions** [1].

Etiology:

World-wide, the most common causes of cirrhosis are **chronic viral hepatitis (types B and C) and prolonged excessive alcohol** consumption [2, 3].

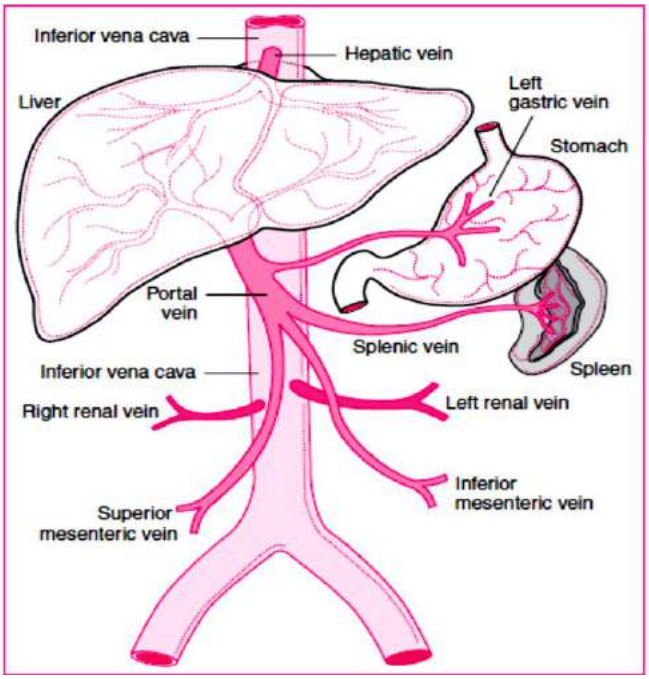


Figure -1-The portal venous system

Pathophysiology:

The main pathophysiologic abnormalities that resulted from cirrhosis are [2]:

A-Ascites:

1- Ascites is the **accumulation of an excessive amount of fluid within the peritoneal cavity**. [2].

2-The development of ascites is related to **hypoalbuminemia** and the **activation of the renin-angiotensin-aldosterone system (RAAS), with sodium and water retention** [1, 2, 4].

B-Portal hypertension and esophageal varices:

1-Portal hypertension is a consequence of **increased resistance to blood flow through the portal vein** [2] **because of fibrotic changes** [2].

The most important sequelae of portal hypertension are the **development of varices** [2].

2-The varices develop in the **esophagus**, **stomach**, and **rectum** [5]. Varices are **weak vessels**, and any increase in pressure can cause **rupture and bleeding** [5].

C-Hepatic encephalopathy (HE):

HE is an **alteration in mental status and cognitive function occurring in the presence of liver failure** [4]. The symptoms of HE **range from forgetfulness, mental confusion to coma** [6]. HE may result from an accumulation of **gut-derived nitrogenous substances** in the systemic circulation which then enter the CNS [2].

D-Spontaneous Bacterial Peritonitis (SBP)

1-SBP is defined as the **spontaneous infection of the ascitic fluid in the absence of an identified intra-abdominal source of infection** [1, 4].

E-Abnormalities in Coagulation

Most coagulation factors are created in the liver, and the levels of these factors can be significantly reduced in chronic liver disease **leading to bleeding tendency** [2].

F- Hepatorenal syndrome

The hepatorenal syndrome (HRS) **is a form of renal failure without renal pathology that occurs in about 10% of patients with liver cirrhosis** [4].

Signs and Symptoms

Cirrhosis is ***often asymptomatic until the late stages of disease*** [4]. The presenting signs and symptoms of cirrhosis are: [2]

- Hepatomegaly, splenomegaly .
- Pruritis, jaundice, palmar erythema, hyperpigmentation.
- Gynecomastia, reduced libido.

- Ascites, edema.
- Encephalopathy.

Laboratory abnormalities [2].

- **Hypoalbuminemia**
- Elevated **prothrombin time**, **alkaline phosphatase, AST**, **and ALT.**

Treatment

A-General approach:

Identify and eliminate the causes of cirrhosis (e.g., alcohol abuse) [2].

B-Hepatic Encephalopathy:

1-Durig episode of acute HE, temporary protein restriction can be useful. Long term protein restriction is not recommended [4].

2- **The use of lactulose is standard therapy for HE** [7]. **Antibiotic** therapy with **metronidazole** (250 mg orally three times daily)or **neomycin** is reserved for patients who have not responded to lactulose [2].

The nonabsorbable agent **rifaximin**, 550 mg orally twice daily or 400 mg three times daily , is preferred and has been shown to maintain remission of and reduce the risk of re hospitalization for hepatic encephalopathy over a 24-month period, with or without the concomitant use of lactulose. [8]

C-Spontaneous Bacterial Peritonitis (SBP):

1-Antibiotics: **Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy** [2] [**Third-generation cephalosporins like** cefotaxime, 2 g every 8–12 hours for at least 5 days ceftriaxone 1 gm once daily **,** Fluoroquinolones (ciprofloxacin or ofloxacin) may be used] [2, 7, 8].

2-**Albumin**: Plasma volume expansion with albumin **decreases the incidence of HRS** and improves survival [8].

3-**Prophylactic antibiotics**:

A- **Primary prevention** (prevention of SBP in patients who never develop SBP previously) (e.g. for those who experience a **variceal** hemorrhage) [2,7]. Oral **norfloxacin** or I.V **ceftriaxone** reduces the risk of bacterial peritonitis [9].

B-**Secondary prevention**: (prevention of SBP in patients who develop SBP) : Antibiotics **used indefinitely** [8]. Examples of antibiotic used for secondary prevention are **Norfloxacin**, **Trimethoprim-sulfamethoxazole** and **Ciprofloxacin** [4, 9, 10].

D-Management of Portal hypertension and Variceal Bleeding:

1-Primary Prophylaxis (prevention of a first variceal bleeding)

All patients with cirrhosis and portal hypertension **with varices** should receive primary prophylaxis with β-Adrenergic blockers to reduce portal pressure [(2)].

2-Acute Variceal Hemorrhage

A-**Fluid resuscitation.**

B-**Combination pharmacologic therapy plus endoscopic variceal ligation (EVL)** is the most rational approach to treatment [(2)].

C-**Vasoactive drug therapy** [**octreotide** (a synthetic analogue of somatostatin), or **terlipessin**]. These agents decrease splanchnic blood flow and reduce portal and variceal pressures [(5)].

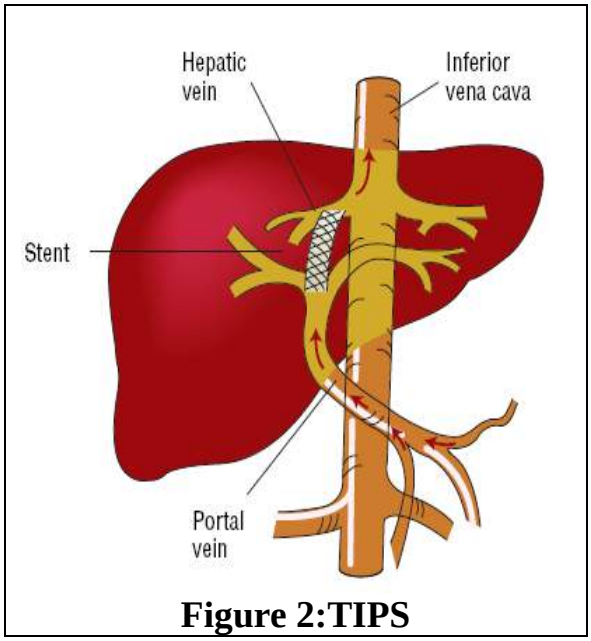


Figure 2:TIPS

D-If standard therapy fails to control bleeding, an invasive procedure such **transjugular intrahepatic portosystemic shunt** (**TIPS**) is necessary. The TIPS involves the placement of one or more stents between the hepatic vein and the portal vein (figure 2) [(1)].

3-Prevention of rebleeding (secondary prophylaxis):

A combination of **EVL and nonselective β-blockers** (Propranolol or nadolol) is considered the most effective regimen [(7)].

E-Ascites:

1-The treatment of ascites includes **abstinence from alcohol**, **sodium restriction**, and **diurectics**. Sodium chloride should be restricted to 2 g/day [(2)].
If sodium restriction alone fails to result in diuresis and weight loss, diuretics should be prescribed [(5)] with a goal of **0.5-kg maximum daily weight loss** [(2)].

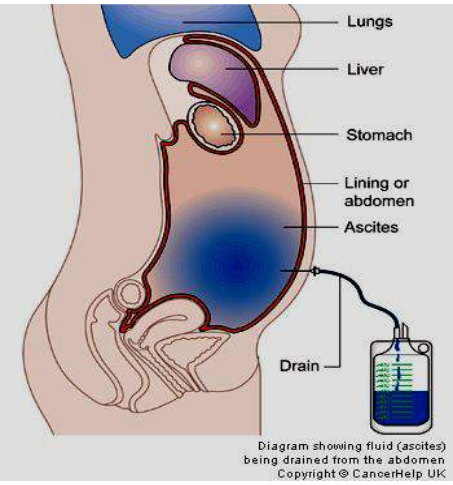
2-Because of the role of hyperaldosteronism in ascites, **spironolactone** is the drugs of choice [(5)].
Loop diuretics (**furosemide**) may be added to the regimen [(1, 9)]. Diuretic therapy in cirrhosis is typically lifelong [(5)].

The dose of spironolactone is initially **100** mg orally daily and may be increased by 100 mg every 3–5 days up to a maximum dose of **400 mg/day**, The dose of oral furosemide ranges from **40** mg/day to maximum **160** mg/day. [(8)]

3-In patients with **pronounced** ascites, **paracentesis** (removal of ascitic fluid from the abdominal cavity with a needle or a catheter) has proven to be an effective treatment [10]. **Concomitant albumin** replacement by I.V infusion is given to avoid depleting the intravascular space and precipitating hypotension [5].

F-Pruritis:

1-Antihistamines are not very effective for pruritis in liver disease. If given, non-sedating antihistamines would be preferable (e.g. **loratidine**), as **sedating antihistamines could mask the effects of hepatic encephalopathy** [10].



2-Anion exchange resins (**colestyramine**) bind to the bile acids that cause itching and is **first-line therapy** [10].

G-Clotting disorders:

Treatment is vitamin K (phytomenadione), 10 mg given IV for 3 days. The patient's INR and prothrombin time are monitored [5].

H-Hepatorenal syndrome:

1- ***The definitive treatment for HRS is liver transplantation*** [1]. **Diuretic therapy must be stopped** because this can worsen the kidney disease [1].

2-Management of HRS also includes **expanding the intravascular volume with I.V albumin** [2] **plus vasoconstrictors** [e.g. terlipressin] [8].

Liver Transplantation

Liver transplantation in cirrhosis is considered in patients **with severe, irreversible liver disease** [1].

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2 -Upper gasrtrointestinal bleeding (UGIB)

Definitions[1]

1-**Hematemesis** : vomiting of bright red blood or "coffee-grounds" material.

2-**Melena**: the passage of black, tarry stool.

3-**Hematochezia** : the passage of bright red or maroon blood from the rectum.: Usually suggests a lower GI source, but can be from a massive upper GI bleeding.

Etiology: [2]

-**Peptic Ulcer Disease** (the most common cause of UGIB)
-Portal Hypertension and varices.
-Mallory-Weiss Tears
-Vascular Anomalies
-Drugs
-Gastric Neoplasms
-Erosive Gastritis.
-Erosive Esophagitis

Diagnosis[3]

The definitive method of diagnosis is by **O**eseophago—**G**astro-**D**uodenoscopy (OGD)(endoscopy) .it is also used in the treatment of bleeding by cautery, injection, endoclips or thermocoagulation .

Initial Evaluation [2]

A. Stabilization

The initial step is measurement of blood pressure and heart rate which reflect the degree of blood loss.
Intravenous fluids 0.9% saline or lactated Ringer ,blood transfusion are administered according to the hemodynamic state of the patient.
Endoscopy must be done during the **first 24 hour of presentation**, and during the **first hour in patient with massive bleeding.**

B-Acute Pharmacologic Therapies

1. Acid inhibitory therapy:

Intravenous proton pump inhibitors (ppi) (**esomeprazole or omeprazole , 80 mg bolus, followed by 8 mg/h continuous infusion for 72 hours**) designed to sustain intra gastric pH >6 and enhance clot Stability thus reduce the risk of re bleeding in patients with peptic ulcers with high-risk features (active bleeding, visible vessel, or adherent clot) after endoscopic treatment.
Administration of continuous intravenous proton pump inhibitor **before** endoscopy results in a decreased number of ulcers with lesions that require endoscopic therapy so It therefore is standard clinical practice to administer intravenous ppi before endoscopy in patients with significant upper gastrointestinal bleeding. (2) (4)

2.Octreotide: Continuous intravenous infusion of **octreotide (100 mcg bolus, followed by 50–mcg/h)** reduces splanchnic blood flow and portal blood pressures and is effective in the initial control of bleeding related to portal hypertension. It is administered to all patients with active upper gastrointestinal bleeding and evidence of liver disease or portal hypertension until the source of bleeding can be determined by endoscopy. (2)

Prevention of re-bleeding(5)

After endoscopic hemostasis of ulcer bleed, treatment with PPIs is recommended for **6–8 weeks**. Long term acid reduction treatment is required for patients on continuing aspirin, NSAID or warfarin therapy. H. pylori positive patients should receive antibiotic therapy.
patients requiring antiplatelet or anticoagulant therapy for secondary cardiovascular prophylaxis should restart them **7 days** or as soon as cardiovascular risk outweigh gastrointestinal risks.
all variceal bleed patients should receive secondary prophylaxis with repeated sessions of EVL at 3–4 weeks interval, Usually 2–4 endoscopic sessions are required. Concomitant use of oral nonselective beta blockers such as **propranolol**, **nadolol** or **carvedilol** is recommended toreduce portal pressure.

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C-Endocrine Disorders

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [(1)].

Pathophysiology

There are two main types of diabetes: type 1 and type 2.

1-Type 1 diabetes (accounts for <10%), is caused by destruction of the insulin-producing β-cells of the pancreas [(2)] (leading to absolute deficiency of insulin secretion) [(3)].

2-Type 2 diabetes (accounts for about 90%), results from lack of sufficient insulin production and/or lack of sensitivity to the effects of insulin (**insulin resistance)** [(2)].

Table 1: Differences between type 1 and type 2 diabetes [(4, 5)].

	Type 1	**Type 2**
Endogenous insulin	Absent(Absolute insulin deficiency)	Present(relative or partial insulin deficiency)
Age at onset	Usually <30 yr	Usually >40 yr
Body weight	Patients usually not overweight	Patients usually overweight
Acute complication	Extreme hyperglycaemia causes diabetic ketoacidosis (DKA)	Extreme hyperglycaemia causes hyperosmolar hyperglycaemic state

Clinical presentation

1. Symptom severity and onset help differentiate type 1 from type 2 DM.

a. **Type 1 DM** typically presents with an **abrupt onset** and an acute presentation [(3)].

b. Symptoms in individuals with **type 2 DM** generally develop **gradually**, with some patients being asymptomatic or having only mild symptoms upon diagnosis [(3)].

2. Classic signs and symptoms of DM include **polydipsia** (excessive thirst) , **polyuria** (excessive urination) , **polyphagia** (excessive hunger) [(3)] .

3. Individuals with type 1 DM may additionally present with unintentional **weight loss** [(3)],(significant weight loss is less common in **type 2 DM)** [(5)].

Diagnosis [(5, 6)]

Criteria for the diagnosis of DM include any one of the following:

1. Hemoglobin **A1C ≥6.5%.**
2. Fasting (defined as no caloric intake for at least 8 hours) plasma glucose **≥126** mg/dL (7.0 mmol/L).
3. Two-hour plasma glucose **≥200 mg/** dL (111.1 mmol/L) during an oral glucose tolerance test (OGTT) .

4. A random plasma glucose concentration ≥200 mg/dL (111.1 mmol/L) in a patient with classic symptoms of diabetes (Polyuria, polydipsla, unexplained weight loss).

Note: The diagnosis must be confirmed by repeating the test, preferably the same test [7].

Treatment

1- There are three major components to the treatment of diabetes: **diet**, **drugs** (insulin and antidiabetic agents), and **exercise** [7].

2-Appropriate treatment requires **goal setting** for **glycemia**, **blood pressure**, and **lipid levels** [5]. The American Diabetes Association (ADA) metabolic goals for adults with diabetes mellitus are listed in Table 2 [8].

Table 2
American Diabetes Association Metabolic Goals[a] for Adults With Diabetes Mellitus

Glycemic goals	
• A1C	<7.0% (normal, 4%–6%)
• Preprandial plasma glucose	70–130 mg/dL
• Postprandial plasma glucose	<180 mg/dL
Blood pressure	<140/80 mm Hg
Lipids	
• Low-density lipoprotein cholesterol	<100 mg/dL
• Triglycerides	<150 mg/dL
• High-density lipoprotein cholesterol	
– Men	40 mg/dl
– Women	50 mg/dl

Note: Lower systolic targets, such as ,<130 mmHg, may be appropriate for certain individuals, such as younger patients,if it can be achieved without undue treatment burden [8].

Pharmacotherapy of type 1 diabetes mellitus [9].

All patients with type I DM require insulin, Two regimens are commonly used: **basal-bolus and twice daily**.

A-Basal-bolus regimens The dose of insulin is 0.5-1 unit/kg /day , 50% given as basal insulin(long- or intermediate-acting insulins) once or twice daily and 50% as fast-acting insulin (**regular insulin, lispro, aspart,** or **glulisine)** divided into 3 equal doses and administered prior to meals. This provides a pattern of insulin delivery similar to that in normal individuals.

B-Twice daily injections (before breakfast and before the evening meal) of pre-mixed preparations of short- and intermediate-acting insulin provide a convenience for many patients. **Two-thirds of the daily dose given in the morning** (with about two thirds given as long-acting insulin and one-third as

short-acting) and **one-third in the evening** (with approximately one-half given as long-acting insulin and one-half as short-acting).

Table 3: Types of insulins [7].

Insulin	Onset (hours)	Peak (hours)	Duration (hours)	Appearance
Rapid-acting (insulin aspart, glulisine, and lispro)	5–15 minutes	30–90 minutes	<5	Clear
Regular	0.5–1	2–4	5–7	Clear
NPH	2–4	4–12	12–18	Cloudy
Insulin glargine	1.5	No pronounced peak	20–24	Clear[b]
Insulin detemir	0.8–2	Relatively flat	5.7–23.2	Clear[b]

[a]The onset, peak, and duration of insulin activity may vary considerably from times listed in this table.
[b]Should not be mixed with other insulins. Some patients require twice-daily dosing.

Note : Supplemental doses of rapid-acting insulin are administered to acutely lower glucose concentrations that exceed the target glucose concentration. These doses must be individualized for each patient . [7] A general approach is to give an additional 1 to 2 units of supplemental rapid-acting insulin for each to 50-mg/dL elevation above the target level. or using the equation:
[body weight in kg] × [(measured blood glucose level – desired glucose level in mg/dL)/1500]. [9]

Hypoglycemia[7]

Definition

Blood glucose concentration <60 mg/dL: Patient may or may not be symptomatic
Blood glucose <40 mg/dL: Patient is generally symptomatic
Blood glucose <20 mg/dL: Can be associated with seizures and coma

urgent treatment of hypoglycemia[9]

If the patient is able to eat, **oral** treatment with or glucose-containing fluids, candy, or food is appropriate. A reasonable initial dose is 15–20 g of glucose. If the patient is unable to to take carbohydrates orally, **parenteral** therapy is used . IV administration of glucose **25 g (mL of 50% dextrose for 1–3 minutes**) should be followed by a glucose infusion with serial plasma glucose measurements. If IV therapy is not practical, SC or IM **glucagon** (1 mg in adults) can be used, particularly in patients with T1DM.
The somatostatin analogue **octreotide** can be used to suppress insulin secretion in sulfonylurea-induced hypoglycemia. These treatments raise plasma glucose concentrations only transiently, and patients should eat as soon as is possible to replete glycogen stores.

Diabetic Ketoacidosis(DKA) [9]

Definitions

Is a condition characterized by hyperglycemia (serum glucose > 250 mg/dL, ketosis, and metabolic acidosis (serum bicarbonate <15 mmol/L with increased anion gap).

Precipitating events [9]

Inadequate insulin administration, Infection ,Infarction and stressful conditions .

Management Of Diabetic Ketoacidosis [9]

1-initially fluid replacement: **2–3 L** of 0.9% saline over first 1–3 h (10–20 mL/kg per hour); subsequently,0.9 %or 0.45% saline at 250–500 mL/h; change to5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches **250 mg/dL**

2-Administeration of short-acting regular insulin: IV (0.1 units/kg) bolus , then 0.1 units/kg per hour by continuous IV infusion .If the initial serum potassium is <3.3 mmol/L, insulin should not be administered until the potassium is corrected.

3-Measurement of capillary glucose every 1–2 h; measure electrolytes (especially K+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h,Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.

4-potassium Replacement : 20–40 meq/L of infusion fluid, with monitoring of ECG and urine output.

5-if the patient is stable, glucose level is 150–200 mg/dL, and acidosis is resolved. Insulin infusion may be decreased, long-acting insulin is given as soon as patient is able to eat. Allow for a 2–4 hour overlap in insulin infusion and SC long-acting insulin injection..

6-treatment of the underlying cause that precipitate DKA like infection , myocardial infraction or trauma.

Pharmacotherapy of type 2 diabetes mellitus

1-In patients with type 2 diabetes, first-line therapy involves advice about dietary and lifestyle modification. Oral anti-diabetic drugs are usually added in those who do not achieve glycaemic targets as a result, or **who have severe symptomatic hyperglycaemia at diagnosis and a high HbA1c** [8].

2-However, the guidelines in some countries are to introduce medication immediately upon diagnosis of diabetes [8].

3-Table 4 lists classes of drugs for type 2 DM [6].

3-A reasonable treatment algorithm for initial therapy **uses metformin** as initial therapy because of its efficacy, known side-effect profile, and relatively low cost **(Fig. 1)**. Metformin has the advantage that **it promotes mild weight loss**, and improves the lipid profile slightly [9]. However, type 2 DM is a progressive disorder and ultimately requires multiple therapeutic agents and often insulin [9].

Table 4 :classes of drugs for type 2 DM	
Drug Type	**Examples**
Biguanides	Metformin
Sulfonylureas	Glipizide , Glimepiride, Glibenclamide
Dipeptidyl peptidase IV (DPP-IV) inhibitors	Sitagliptin , Saxagliptin, Linagliptin, Alogliptin, vildagliptin
Thiazolidinediones	Pioglitazone
Glinides	Nateglinide, Repaglinide
α-Glucosidase Inhibitors	Acarbose, Miglitol
Incretins	Exenatide, Liraglutide,semaglutide
Amylin agonist	Pramlintide
Bile Acid Sequestrant	Colesevalem
Dopamine Agonist	Bromocriptine
sodium-glucose cotransporter 2 (SGLT-2) Inhibitor	Canagliflozin, empagliflozin ,dapagliflozin

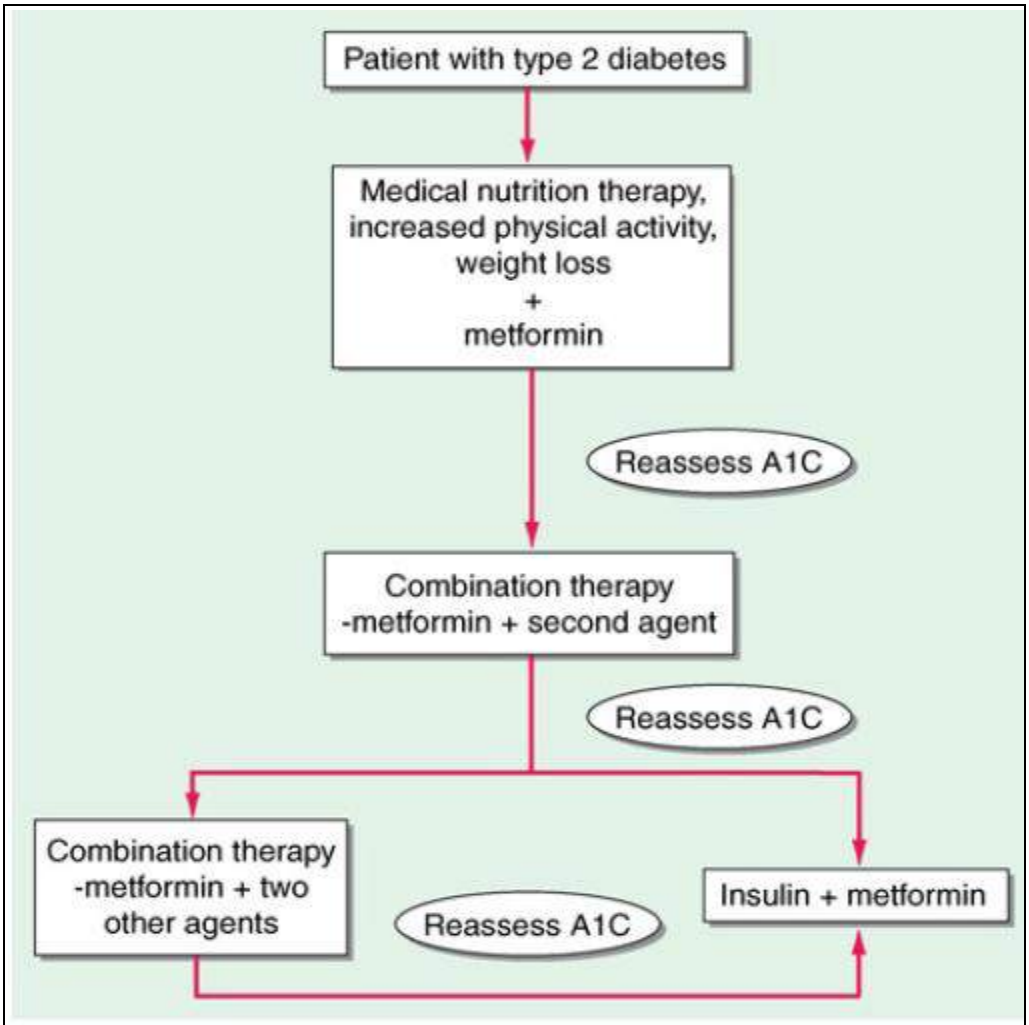

Figure 1 : Glycemic management of type 2 diabetes. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, and GLP-1 receptor agonists.

Treatment of complications

1-Retinopathy

• Early retinopathy may reverse with improved glycemic control. More advanced disease may requires laser therapy [(4)].

2-Neuropathy [(4)].

A- Peripheral neuropathy is the most common complication in type 2 DM outpatients. Paresthesias, numbness, or pain may be predominant symptoms. Pharmacologic therapy include **duloxetine(the preferred one),** low-dose **TCAs,** anticonvulsants (e.g., **gabapentin, pregabalin**), **, topical capsaicin,** and various analgesics, , including **tramadol** and **NSAIDS**.

B- Gastroparesis : use of **metoclopramide** may be helpful.
C- Patients with **orthostatic hypotension** may require mineralocorticoids (**fludrocortisone**)
D- Diabetic diarrhea: is commonly nocturnal and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**.
Octreotide may be useful in unresponsive cases.

E-Erectile dysfunction: is common, and initial treatment should include one of the oral medications (e.g., **sildenafil, vardenafil, tadalafil**).

3-Nephropathy [4].

• Glucose and blood pressure control are most important for prevention of nephropathy.
• **ACE inhibitors and ARBs** have shown efficacy in preventing the clinical progression of renal disease in patients with type 2 DM.

4-Peripheral Vascular Disease and Foot Ulcers [4].

• Claudication and nonhealing foot ulcers are common in type 2 DM. Smoking cessation, correction of dyslipidemia, and antiplatelet therapy are important treatment strategies.
• **Cilostazol** may be useful in selected patients.

5-Coronary Heart Disease [4, 10].

• Multiple-risk-factor intervention [treatment of dyslipidemia (usually with a **statin**) and hypertension (a goal BP of <140/80 mm Hg), smoking cessation, antiplatelet therapy] reduces macrovascular events.

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D-Renal disorders

1-Acute kidney injury (acute renal failure)

Acute kidney injury (AKI), previously known as acute renal failure, is characterized by the **sudden and often reversible** impairment of kidney function which develops over a period of hours to days resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys [1-3].

Pathophysiology [4, 5].

AKI can be classified into three main types:

A-Pre-renal (resulting from decreased renal perfusion) for example hypotension, and hypovolaemia .

B-Renal (resulting from structural damage to the kidney) occurs in diseases such as acute tubular necrosis (ATN).

C-Post-renal resulting from obstruction of urine flow (e.g. by renal stones).

Signs and Symptoms of Uremia [6, 7]

1-Neurological: weakness, fatigue, Mental status changes (coma and seizure may occur with severe uremia).

2-Skin symptoms include: Pruritus.

3-Gastrointestinal: Nausea, vomiting and anorexia

Complications [1]

The kidney plays a central role in the control of volume status, blood pressure, electrolyte balance, acid-base balance, and for excretion of nitrogenous and other waste products. Complications associated with AKI are:

1- Uremia: Buildup of nitrogenous waste products, manifested as an elevated BUN concentration, is a hallmark of AKI. At higher concentrations, mental status changes and bleeding complications can arise [1].

2-Intravascular volume overload [1].

3-Hyperkalemia (Higher levels may trigger arrhythmias**)** [1].

4-Hyperphosphatemia [1]. **5-Hypocalcemia** [1]. **6-Metabolic acidosis** [1].

7-Hematologic complications of AKI include **anemia** and **bleeding**. Uremia causes decreased erythropoiesis and platelet dysfunction [1].

8-Malnutrition: AKI is often a severely hypercatabolic state, and, therefore, malnutrition is a major complication [1].

9-Infection: Patients with AKI are at substantial risk of infection because humoral and cellular immune mechanisms are depressed [2].

Investigations [6, 7]:

A-Physical examinations

B-Laboratory Tests (serum creatinine , BUN(blood urea nitrogen) , Blood count, serum Ca , K+, Na , phosphate,….)

C-Renal Ultrasound and pyelography.

D-Histological investigations: renal biopsy.

Treatment

Currently, there is no definitive therapy for AKI. **Supportive care is the mainstay of AKI management regardless of etiology**. The ultimate goal is to have the patient's renal function restored to pre-AKI baseline [4].

A-Hemodynamic status

1-If hypovolaemia is present, it should be corrected by replacement of intravenous fluid or blood; excessive administration of fluid should be avoided, since this can cause pulmonary oedema [2].

2-**Volume overload can complicate ARF**. Diuretics (usually high-dose **loop diuretics**) may be used . Volume overload causing **respiratory compromise** that is refractory to medical management is an indication for urgent **dialysis** [8].

B-Dietary measures

Adequate nutritional support should be ensured. **Enteral or parenteral nutrition** may be required [2].

C-Hyperkalemia

1-Hyperkalemia is the most common and serious electrolyte abnormality in AKI [4].

2-The condition may be life-threatening **causing cardiac arrhythmias** and, if untreated, can result in cardiac arrest [9].

3-If serum K+ concentration is > 6.5 mmol/L (normal range 3.5–5.5 mmol/L), this should be treated immediately(table 1) to prevent **life-threatening cardiac arrhythmias** [2].

Table 1: Treatment of severe hyperkalaemia

Objective	Therapy
Stabilise cell membrane potential[1]	IV calcium gluconate (10 mL of 10% solution)
Shift K into cells	Inhaled β_2-adrenoceptor agonist (e.g. salbutamol) IV glucose (50 mL of 50% solution) and insulin (5 U Actrapid®) IV sodium bicarbonate[2]
Remove K from body	IV furosemide and normal saline[3] Ion-exchange resin (e.g. Resonium®) orally or rectally Dialysis

[1]If ECG changes suggestive of hyperkalaemia (K typically > 7 mmol/L)
[2]If acidosis present. [3]If adequate residual renal function.

E-Hypocalcaemia [4. 10].

1-Hypocalcemia is prevented and treated using oral calcium supplementation with calcium carbonate is usually adequate.

2-For **symptomatic hypocalcemia**, **i.v calcium is used** (e.g. as calcium gluconate).

F-Hyperphosphataemia

1-Hyperphosphataemia can occur in AKI but **rarely requires treatment** [9].

2-If it become necessary to treat, phosphate-binding agents may be used to retain phosphate ions in the gut. The most commonly used agents are calcium containing such as **calcium carbonate and are given with food** [9].

G-Infection

1-Patients with AKI are at substantial risk of infection because **humoral and cellular immune mechanisms are depressed** [2].

2-Ptients with pyrexia must be immediately investigated and treated with appropriate antibiotic therapy if infection is discovered [2, 9].

H-Acidosis

1-Metabolic acidosis can be treated by **infusions of sodium bicarbonate** (8.4%) [1, 2].

2-If elevation of serum sodium or fluid overload precludes the use of sodium bicarbonate, extreme acidosis is best treated by **dialysis** [9].

I-Uraemic gastro-intestinal erosions

These are a recognized consequence of AKI, probably as a result of reduced mucosal cell turnover owing to high circulating levels of uraemic toxins [9]. **GI prophylaxis with PPI or H2RA is required**. Uremic bleeding may respond to **desmopressin** [1].

J-Anemia

1-The anemia seen in AKI is usually multifactorial and is **not improved by erythropoiesis stimulating agents**, due to their delayed onset of action and the presence of bone marrow resistance in critically ill patients [1].

2-**Blood transfusion** is appropriate for patients with **symptoms attributable to anemia** [8].

Renal Replacement Therapy

Renal replacement therapy (RRT) may be required on a temporary basis in patients with AKI or on a permanent basis for those with chronic kidney disease (CKD) [2].

The common types of renal replacement therapy used in clinical practice are: • **Haemodialysis** • **Peritoneal dialysis** [9].

Indications for dialysis are summarized by (**table 2**) [4].

Table 2: The AEIOUs That Describe the Indications dialysis [4].

Indication for Renal Replacement Therapy	Clinical Setting
A Acid–base abnormalities	Metabolic acidosis resulting from the accumulation of organic and inorganic acids
E Electrolyte imbalance	Hyperkalemia, hypermagnesemia
I Intoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O fluid Overload	Postoperative fluid gain
U Uremia	High catabolism of acute renal failure

A-Haemodialysis

1-In haemodialysis, the blood is removed from the patient and is returned to the patient after passing through a dialyser [9].

2-**Heparin is added** to the blood as it leaves the body to prevent the dialyser clotting [9].

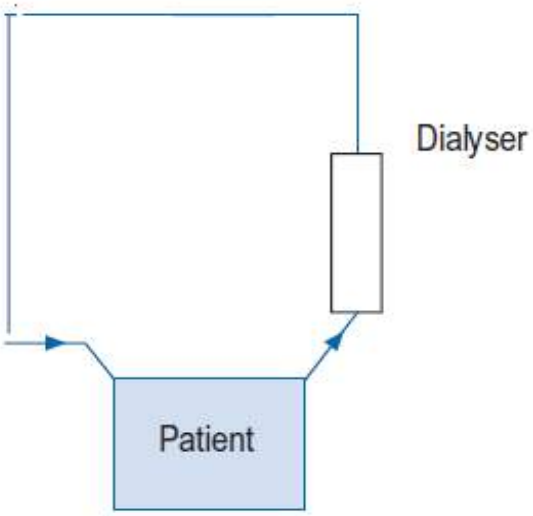

Figure 1: haemodialysis

B-Peritoneal dialysis

1-Peritoneal dialysis is rarely used now for AKI except in circumstances **where haemodialysis is unavailable** [9].

2-Warmed sterile peritoneal dialysis fluid (typically 1–2 L) is instilled into the abdomen, left for a period of about 30 min (dwell time) and then drained into a collecting bag (**Fig. 2**). The process may be repeated up to 20 times a day, depending on the condition of the patient [9].

3-It is associated with a high incidence of **peritonitis** and **permits protein** loss, as albumin crosses the peritoneal membrane [9].

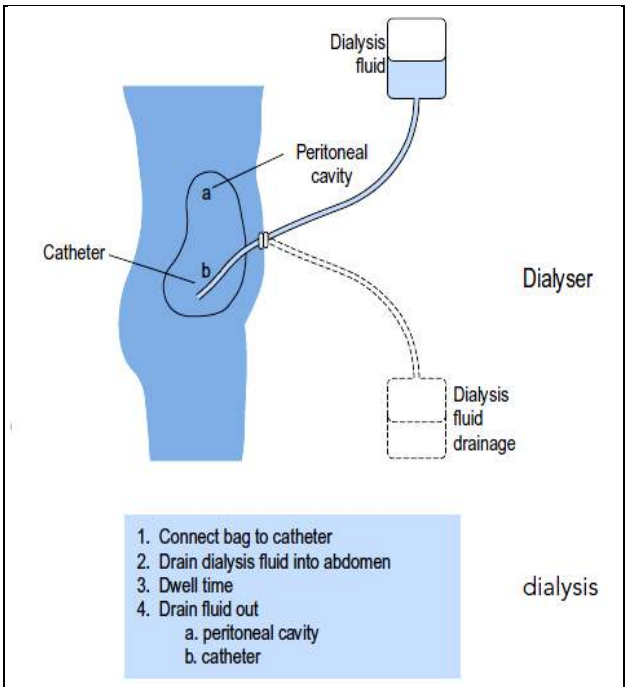

Figure 2: Procedure for peritoneal dialysis.

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2-Chronic kidney disease

Chronic kidney disease (CKD), previously termed chronic renal failure, refers to an **irreversible** deterioration in renal function which usually develops over a **period of months to years** [1, 2].

Etiology [2]

Many disorders can cause CKD. However, epidemiologic studies indicate that **diabetes mellitus and hypertension** account for the majority of cases (>60%) [2].

Metabolic and Systemic Consequences of CKD

A- Uraemia

1-Uraemia results from the accumulation of urea and other nitrogenous toxins [3].

2-The symptoms of uraemia include **anorexia**, **nausea**, **vomiting**, and an increased tendency to bleed (**uremic bleeding**) due to impaired platelet adhesion [4]. Patient may also experience **itching** and peripheral neuropathies [5].

B-Cardiovascular Complications

1-The risk of cardiovascular disease is substantially increased and represent an important cause of death in patients with CKD [1, 6].

2-**Hypertension** is the most common complication of CKD. As kidney disease progresses, hypertension due to salt and water retention usually develops [6].

3-**Dyslipidemia** may be associated with kidney disease [5]. Dyslipidaemia results in a raised**, atherogenic lipid profile** [3].

4-Patients with CKD are at higher risk for **Coronary artery disease** and **heart failure** [6].

C-Hematologic Complications

1-Anemia: The anemia of CKD is primarily due to decreased erythropoietin production [6].

2-Coagulopathy: The coagulopathy of CKD is mainly caused by platelet dysfunction. Clinically, patients can have petechiae, purpura, and an increased tendency for bleeding during surgery [6].

D-Calcium, Phosphorus, and Bone Homeostasis

1-Declining GFR leads to reduced excretion of phosphate and, thus, **hyperphosphataemia**; which stimulates increased synthesis of parathyroid hormone (PTH) [7].

2-Failing kidneys are not able to convert vitamin D to the active form 1,25-dihydroxycholecalciferol [8].This will impair intestinal absorption of calcium, thereby **causing hypocalcaemia** which also stimulate PTH production [1, 7].

3-**Hyperparathyroidism stimulates bone turnover** [7] (**renal osteodystrophy**) [8] (increased bone reabsorption to maintain adequate calcium levels) [4].

E-Electrolyte, and acid-base disorders

1-Patients with CKD often develop **hyperkalemia** and **metabolic acidosis** [1, 7].

F-Immune dysfunction

Cellular and humoral immunity is impaired in advanced CKD and there is **increased susceptibility to infections** [1].

G-Neurological and muscle function

1-Muscle symptoms are probably caused by general nutritional deficiencies and electrolyte disturbances(especially hypocalcaemia) [4].

2-**Muscle cramps** are common. The '**restless leg syndrome'**, in which the patient's legs are jumpy during the night, may be troublesome [1].

3-The neurological changes are non-specific and include **inability to concentrate**, **memory impairment**, and **irritability** probably caused by uraemic toxins [4].

H-Endocrine function

1-In both genders, there is **loss of libido** related, at least in part, to hypogonadism as a consequence of hyperprolactinaemia. [1]

2-The half-life of **insulin** is prolonged in CKD [1] (because of decreased renal insulin clearance) [6], but there is also **insulin resistance** [1]. Because of this, insulin requirements are **unpredictable** in diabetic patients in advanced CKD [1].

Diagnostic test result [9]

A- Blood tests typically show:

(1) Elevated BUN and serum creatinine concentration.
(2) Reduced arterial pH and bicarbonate concentration (metabolic acidosis).
(3) Reduced serum calcium level.
(4) Increased serum potassium and phosphate levels.
(5) Normochromic, normocytic anemia.

B-Urinalysis may reveal glycosuria, proteinuria.

Differentiation ARF from CRF:

Distinction between ARF and CRF depend on history , and duration of symptoms.
A Normochromic anemia and the presence of renal osteodystrophy are suggestive of CRF [10].

Treatment

The goal is to delay the progression of CKD, minimizing the development or severity of complications [5].

A-Anemia:

1-**Erythropoiesis-stimulating agents** (ESAs) (e.g., recombinant erythropoietin [**epoetin**] and **darbepoetin**) are FD Aapproved for CKD-anemia. [epoetin is given once or twice a week. Darbepoetin can be administered every 2–4 weeks]. These agents usually given subcutaneously [6].

2-The recommended target hemoglobin in patients receiving ESAs **is 11 to 12** g/dL[5] for optimal safety; studies show that targeting a higher Hgb **increases risk of stroke** and possibly other cardiovascular events [6].

3-**Iron supplementation** is necessary to replete iron stores. Iron is usually given parenterally (oral therapy is limited by poor absorption and adverse effects) [5].

B-Hypertension

1-The target blood pressure **is less than 130/80** mm Hg for patients **with CKD**; a goal of **125/75 mm** Hg is recommended for patients with **proteinuria** [6].
2-Salt and fluid intake should be restricted [5].
3-Most patients require three or more antihypertensive agents to achieve target blood pressure. ACEIs, ARBs, and dihydropyridine calcium channel blockers are the preferred agents [5].

C-Volume Overload

1-Patients with evidence of fluid retention should have a restriction of salt and fluid intake [1, 4].

2-**Loop diuretics**, such as furosemide (Lasix) are generally indicated to treat fluid overload [1, 2].

D-Hyperlipidemia

Hyperlipidemia should be managed aggressively in patients with CKD to a LDL- cholesterol goal <100 mg/dL . **Statins** are the drugs of first choice [5].

E-Osteodystrophy

The osteodystrophy of CKD is due to three factors: hyperphosphataemia, vitamin D deficiency and hyperparathyroidism [4].

1-**hyperphosphataemia** should be treated by **dietary restriction** of foods with high phosphate content (milk, cheese, eggs and protein-rich foods) and by the **use**

of phosphate-binding drugs. Various drugs are available, including **calcium carbonate**, and polymer phosphate binders such as **sevelamer** [1].

2-Vitamin D deficiency may be treated with the synthetic vitamin D analogues **1α-hydroxycholecalciferol** (alfacalcidol) at 0.25–1 μcg/day. The serum calcium level should be monitored, and the dose adjusted accordingly.

3-**Cinacalcet** targets the calcium-sensing receptors of the parathyroid gland and suppresses PTH production. Cinacalcet, 30–90 mg orally once a day, can be used if elevated serum phosphorus or calcium levels prohibit the use of vitamin D analogs; cinacalcet can cause serious hypocalcemia , and patients should be closely monitored for this complication. [6].

4-The rise in Vitamin D and calcium levels that result from starting vitamin D therapy usually suppresses the production of PTH by the parathyroids. If vitamin D therapy does not correct PTH levels then parathyroidectomy, to remove part or most of the parathyroid glands, may be needed [4].

F-Potassium homeostasis

See Treatment of hyperkalemia in AKI.

G-Metabolic acidosis

Metabolic acidosis can be corrected by the administration of sodium bicarbonate [8].

H-Neurological problems

1-Neurological changes are generally caused by uraemic toxins and improve on the treatment of uraemia by dialysis or diet [4].

2-**Muscle cramps** are common and are often treated with **quinine sulphate**. **Restless legs** may respond to low doses of **clonazepam** or **co-careldopa** [4].

I-Pruritus

Itching associated with CKD failure can be extremely severe, and difficult to treat. Non-sedating antihistamines such as loratidine are generally less effective than **sedating antihistamines such as chlorphenamine** which may be useful, particularly at night [4].

J-Uremic bleeding

Abnormal bleeding time and coagulopathy in patients with CKD may be **reversed temporarily** with **desmopressin**. Optimal dialysis will usually correct a prolonged bleeding time [7].

Treatment of End-Stage Renal Disease

When GFR declines to 5–10 mL/min/1.73 m^2 , **renal replacement therapy** (hemodialysis, peritoneal dialysis, or kidney transplantation) **is required** [6].

Rejection of Kidney Transplant

Immunosuppression in kidney transplantation [7]

Immunosuppressive treatment can be divided into three phases:
1-induction: consists of antilymphocyte antibodies given within the first week after transplantation.
2-Maintenance immunosuppression refers to medications given daily for the long term prevention of renal allograft rejection. the standard maintenance therapy is a three-drug regimen(**tacrolimus or sirolimus , mycophenolate, and prednisone**)
3- Antirejection therapy is given to treat acute rejection episodes when they occur.

Adverse Effects of Immunosuppressant Used In Renal Transplantion [11]

1-Infection

patients are exposed to opportunistic infection or reactivation of latent infections. Prophylaxis for cytomegalovirus (CMV) infection with **gancyclovir** ,and Pneumocystis *Jirovecci* pneumonia wth **trimethoprim-sulfamethoxazole** is given. **oral nystatin** used to prevent oral candidiasis, **fluconazole** and **amphotericin** are used for systemic fungal infections

2-Malignant Neoplasia

There are an increased risks to develop some malignant neoplasms like Kaposi sarcoma , cervical , anal ,gastrointestinal tract and lung carcinomas. Treatment usually involves a reduction in immunosuppression along with chemotherapy.

3-Calcineurin Inhibitor–Induced Nephrotoxicity

cyclosporine and tacrolimus can cause an acute reversible nephrotoxicity in patients who experience sudden elevations in drug blood levels and resolved when the dose is reduced. But long term , nephrotoxicity , which can cause allograft failure can occur . careful monitoring of blood calcineurin inhibitor levels is essential.

Rejection after kidney transplantation[12]

-**Hyperacute rejection** occurs within minutes to hours after transplantation of the allograft, it is the result of preformed cytotoxic antibodies against donor-specific antigens. This type of rejection is rare because of ABO matching and improved HLA typing before transplant, but it remains associated with a poor prognosis.

-Acute rejection occurs within the first year with most episodes occurring within the first two months after kidney transplantation. Treatment include the use high-dose corticosteroid (usually IV infusion of **methylprednisolone 500 -1000 mg Daily for three days**) is considered first-line therapy because it works very quickly in decreasing lymphocyte responsiveness, easy to administer and reverses at least 75% of acute rejection episodes.

-Chronic rejection is a major cause of long-term kidney graft loss after the first year. It occurs slowly in most cases over several years. Characterized by a progressive decline in renal function. no specific treatment exists and therapy is supportive. Ultimately, retransplantation is needed. some patients may benefit from mycophenolate and sirolimus.

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Manual of Surgery

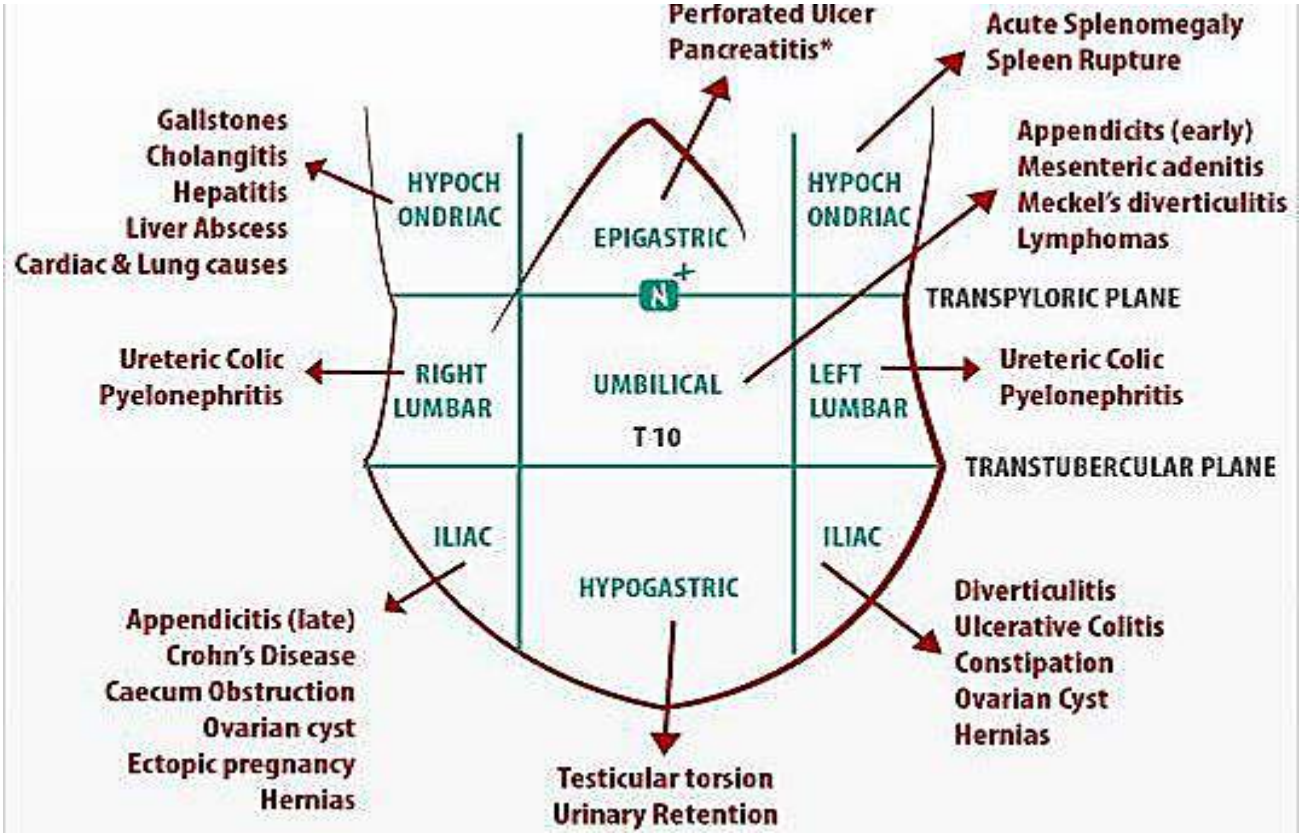
خاص بتدريب طلبة كلية الصيدلة \ المرحلة الخامسة \ ردهة الجراحية

أعداد : -

فرع الصيدلة السريرية

2019

1-1: Language of Surgery (1)



Abdominal area

1 **Right upper quadrant (RUQ) or hypochondrium**
2 **Epigastrium**
3 **Left upper quadrant (LUQ) or hypochondrium**
4 **Right flank (merges posteriorly with right loin)**
5 **Periumbilical or central area**
6 **Left flank (merges posteriorly with left loin)**
7 **Right iliac fossa (RIF)**
8 **Suprapubic area**
9 **Left iliac fossa (LIF)**

-ectomy	**Cutting something out.**
-gram	**A radiological image.**
-pexy	**Anchoring of a structure to keep it in position.**
-plasty	**Surgical refashioning in order to regain good function /cosmesis.**
-scopy	**Procedure with instrumentation for looking into the body.**
-stomy	**An artificial union between a conduit and the outside world or another conduit.**
-tomy	**Cutting something open to the outside world.**
-tripsy	**Fragmentation of an object.**

epi-	**Upon**	**Per-**	**Going through**
End-	**Inside**	**peri-**	**Around**
mega-	**Enlarged**	**Sub-**	**Beneath**
Pan-	**Whole**	**trans-**	**Across**
para-	**Alongside**		

abscess	**A cavity containing pus. Remember: *if there is pus about, let it out.***
cyst	**Fluid-filled cavity lined by epi/endothelium.**
fistula	**An abnormal connection between two epithelial surfaces. Fistulae often close spontaneously, but will not do so in the presence of malignant tissue, distal obstruction, foreign bodies, chronic inflammation, and the formation of a muco-cutaneous junction (eg stoma).**
hernia	**The protrusion of a viscus/part of a viscus through a defect of the wall of its containing cavity into an abnormal position.**
colic	**Intermittent pain from over-contraction/obstruction of a hollow viscus.**
ileus	**Used in this book as a term for adynamic bowel.**
sinus	**A blind-ending tract, typically lined by epithelial or granulation tissue, which opens to an epithelial surface.**
stent	**An artificial tube placed in a biological tube to keep it open.**
stoma	**An artificial union between conduits or a conduit and the outside.**
ulcer	**Interruption in the continuity of an epi/endothelial surface.**
volvulus	**Twisting of a structure around itself. Common GI sites include the sigmoid colon and caecum, and more rarely the stomach.**

angio-	**Tube or vessel**	**lith-**	**Stone**
appendic-	**Appendix**	**mast/mammo**	**Breast**
chole-	**Relating to gall/bile**	**meso-**	**Mesentery**
colp-	**Vagina**	**Nephr-**	**Kidney**
cyst-	**Bladder/fluid-filled sac**	**Orchid-**	**Testicle**
-doch-	**Ducts**	**oophor-**	**Ovary**
enter-	**Small bowel**	**Phren-**	**Diaphragm**
eschar-	**Dead tissue, eg from burn**	**pyloromy-**	**Pyloric sphincter**
gastr-	**Stomach**	**pyel-**	**Renal pelvis**
hepat-	**Liver**	**proct-**	**Anal canal**
Hyster-	**Uterus**	**salping-**	**Fallopian tube**
lapar-	**Abdomen**	**splen-**	**Spleen**
		thoraco-	**Chest**

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1-2: Surgical Prophylaxis

Definition

Antibiotics administered before contamination of previously sterile tissues or fluids are considered prophylactic. The goal of prophylactic antibiotics is to prevent an infection from developing [(1)].

Common surgical pathogens

*****The predominant organisms causing SSIs after clean procedures are skin flora, including S. aureus and coagulase-negative staphylococci (e.g., Staphylococcus epidermidis)

*In clean-contaminated procedures, including abdominal procedures and heart, kidney, and liver transplantations, the predominant organisms include gram negative rods and enterococci in addition to skin flora [(6)]

Antimicrobial selection

• The choice of the prophylactic antimicrobial depends on the type of surgical procedure, most likely pathogenic organisms, safety and efficacy of the antimicrobial, current literature evidence supporting its use and cost.

• Typically, gram-positive coverage is included in the choice of surgical prophylaxis because organisms such as *S. aureus* and *S. epidermidis* are common skin flora.

• Parenteral antibiotic administration is favored because of its reliability in achieving suitable tissue concentrations.

• First-generation cephalosporins (particularly cefazolin) are the preferred choice.

Antianaerobic cephalosporins (eg, cefoxitin or cefotetan) are appropriate choices when broad-spectrum anaerobic and gram negative coverage is desired.

• Vancomycin may be considered for prophylactic therapy in surgical procedures involving implantation of a prosthetic device in which the rate of methicillin-resistant *S. aureus* (MRSA) is high. If the risk of MRSA is low and a β-lactam hypersensitivity exists, clindamycin can be used instead of cefazolin in order to limit vancomycin use. Current literature evidence supporting its use and cost [(1)].

1-3: Types of Surgical Operations

Surgical operations are classified as clean, clean -contaminated, contaminated, or dirty. Antimicrobial prophylaxis is appropriate for clean, clean-contaminated, and contaminated operations. [(3)]. (Table 1).

Table -1. Wound Classification, Risk of SSI[b], and Indication for Antibiotics [(1,3,6)]

Classification	Description	SSI risk	Antibiotics
Clean	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entereddrainage.	**Low**	**Not indicated unless high-risk procedure**
Clean-contaminated	Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category.	**Medim**	**Prophylactic antibiotics indicated**
Contaminated	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) Technique break during clean- contaminated. procedure.	**High**	**Prophylactic antibiotics indicated**
Dirty	Obvious preexisting infection present (abscess, pus, or necrotic tissue present).	_____	**Therapeutic antibiotics required**

Principles of Antimicrobial Prophylaxis

1-Route of Administration

Intravenous administration is preferred because it produces a more reliable and predictable serum and tissue concentration than intramuscular administration [(4)].

Oral administration is also used in some bowel operations. Non-absorbable compounds like erythromycin base and neomycin are given up to 24 hours prior to surgery to reduce microbial concentrations in the bowel. Note that oral agents are used adjunctively and do not replace IV agents [(3)].

2-Timing of First Dose

For prevention of SSIs, correct timing of antimicrobial administration is imperative so as to allow the persistence of therapeutic concentrations in the blood and wound tissues during the entire course of the operation. The National Surgical Infection Prevention Project recommends infusing antimicrobials for surgical prophylaxis within 60 minutes of the first incision [(3)]. (A single dose of antibiotic should be administered within 30 minutes to one hour before incision [(4)]) (They are given 15-60min prior to the procedure)[(5)]. (وكلها معناها واحد تقريبا)

Exceptions to this rule are fluoroquinolones and vancomycin, which can be infused 120 minutes prior to avoid infusion-related reactions. Beginning the infusion after the first incision is of little value in preventing SSI [(3)].

3-Dosing and Redosing

The goal of antimicrobial dosing for surgical prophylaxis is to maintain antibiotic concentrations above the MIC of suspected organisms for the duration of the operation [(3)].

If an operation exceeds two half-lives of the selected antimicrobial, then another dose should be administered. Repeat dosing has been shown to lower rates of SSI.

4-Duration

The National Surgical Infection Prevention Project and published evidence suggest that the continuation of antimicrobial prophylaxis beyond wound closure is unnecessary. The duration of antimicrobial prophylaxis should not exceed 24 hours (48 hours for cardiac surgery) [(3)].

Combination antimicrobial therapy

• Combinations of antimicrobials are generally used to broaden the spectrum of coverage for empiric therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.

Disadvantages of Combination Therapy

• including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria [(3)].

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TABLE 2. Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis [2] . للاطلاع

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen[a]	Comments
Gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Cefazolin 1 g x 1 (see text for recommendations for percutaneous endoscopic gastrostomy)	High-risk patients only (obstruction, hemorrhage, malignancy, acid suppression therapy, morbid obesity)
Biliary tract	Enteric gram-negative bacilli, anaerobes	Cefazolin 1 g x 1 for high-risk patients Laparoscopic: None	High-risk patients only (acute cholecystitis, common duct stones, previous biliary surgery, jaundice, age >60, obesity, diabetes mellitus)
Colorectal	Enteric gram-negative bacilli, anaerobes	PO: Neomycin 1 g + erythromycin base 1 g at 1 P.M., 2 P.M., and 11 P.M. 1 day preop plus mechanical bowel prep. IV: Cefoxitin or cefotetan 1 g x 1	Benefits of oral plus IV is controversial except for colostomy reversal and rectal resection
Appendectomy	Enteric gram-negative bacilli, anaerobes	Cefoxitin or cefotetan 1 g x 1	A second intraoperative dose of cefoxitin may be required if procedure lasts longer than 3 hours
Urologic	*E. coli*	Cefazolin 1 g x 1	Generally not recommended in patients with sterile pre-op urine cultures
Cesarean section	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefazolin 2 g x 1	Give after cord is clamped
Hysterectomy	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Vaginal: Cefazolin 1 g x 1 Abdominal: Cefotetan 1 g x 1 or Cefazolin 1 g x 1	Antibiotic prophylaxis should not exceed 24 hours
Head and neck	*S. aureus*, streptococci oral anaerobes	Cefazolin 2 g or clindamycin 600 mg at induction and q8h x 2 more doses	Addition of gentamicin to clindiamycin is controversial
Cardiothoracic	*S. aureus, S. epidermidis, Corynebacterium*, enteric gram-negative bacilli	Cefazolin 1 g q8h x 48h	Second-generation cephalosporins also have been advocated In areas with high prevalence of *S. aureus* resistance, vancomycin should be considered
Vascular	*S. aureus, S. epidermidis*, enteric gram-negative bacilli	Cefazolin 1 g at induction and q8h x 2 more doses	Abdominal and lower extremities have the highest infection rates
Orthopedic	*S. aureus, S. epidermidis*	Joint replacement: Cefazolin 1 g x 1 preop, then q8h x 2 more doses Hip fracture repair: Same as above except continue for 48 hours	Open fractures assumed contaminated with gram-negative bacilli; aminoglycosides often used—see text
Neurosurgery	*S. aureus, S. epidermidis*	CSF shunt procedures: Cefazolin 1 g x 1 or ceftriaxone 2 g x 1 Craniotomy: Cefazolin 1 g x 1 or cefotaxime 1 g x 1 or trimethoprim-sulfamethoxazole (160/800) IV x 1	No agents have been shown better than cefazolin in randomized control comparative trials.

[a]One-time doses are optimally infused at induction of anesthesia except as noted. Repeat doses may be required for long procedures. See text for references.

1-4: Thromboprophylaxis

Deep venous thrombosis (DVT) is most common in patients over 40 years of age who undergo major surgery. **A <u>postoperative increase in platelets</u>** coupled with **<u>venous endothelial trauma</u> and <u>stasis</u>** all contribute. If no prophylaxis is given, 30% of these patients will develop DVT and 0.1-0.2% will die from pulmonary thromboembolism (PTE) [(1)].

<u>Types of thromboprophylaxis</u> [(1)].

1-Mechanical devices: Thromboembolic deterrent stockings (TEDS).
2-Drugs acting on the clotting cascade: Heparin and Low molecular weight heparin (LMWH).

<u>Regimen</u>

heparin 5000U SC 2h pre-op, then every 8-12h SC for 7d or until ambulant. **Low molecular weight heparin** (**LMWH, eg enoxaparin** 20mg/24h SC, increased to 40mg for high-risk patients, starting 12h pre-op) [(2)].
Fondaparinux (a factor Xa inhibitor) reduces risk of DVT over LMWH without increasing the risk of bleeding. [(2)].

<u>Risk groups</u> [(1)]

All patients are -at risk of developing deep vein thrombosis just as is the general population. National requirements for VTE prophylaxis require all patients to be assessed for risk factors on admission and after 24h in hospital. Risk is judged according to:

• **Procedure factors.** Prolonged anesthetic time, lower limb or pelvic surgery.
• **Patient factors.** Immobility, malignancy, age, dehydration, obesity, diabetes, cardiorespiratory disease, inflammatory pathologies, oral contraceptive pill or hormone replacement therapy (HRT), past or family history of thromboembolic disease.

Balanced against:
• **Bleeding risks.** Active bleeding, stroke, invasive procedures, bleeding disorders (liver disease, thrombocytopenia, inherited disorders).

• **Risks of compression devices.** Peripheral vascular disease (PVD).

<u>References:</u>
1-McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition. Copyright 2014 © Oxford University Press.
2-Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

1-6: Preoperative bowel preparation
A-Elective colon operation:

The human colon and distal small intestine contain a numerous reservoir of aerobic and anaerobic bacteria that are excluded from the body by a mucous membrane barrier, if this barrier is disturbed by disease, trauma, or if the colon is opened to the peritoneal cavity during operation, bacteria may escape into adjacent tissues and causes serious infection, this risk can be minimized by two ways:

<u>1-Mechanical preparation:</u> This is done by one or both of the following procedures:
A-Whole gut lavage with an electrolyte solution, mannitol 10%, or poly ethylene glycol the day before surgery.

B-Standard mechanical cleansing, which utilizes dietary restriction, catheters, and sometimes enemas 1- 2 days before the operation.

2-Antibiotic preparation:

Either oral or parenteral antibiotic

Two oral regimens are now used**:**

A- An aminoglycoside with erythromycin base.

B- An aminoglycoside with metronidazole.

Parenteral regimen

That is now used is cefoxitin IV before induction of anesthesia.

Combination of parenteral and oral antibiotics show low incidence of infection.

B-Emergency colon preparation:

The following is recommended:

1-Intraoperative lavage performed by introducing of saline in the colon through balloon catheter.

2-Parenteral antibiotic, they should be given IV shortly before operation and continues for 1-7 days postoperatively.

1-7: Intravenous fluid therapy

Intravenous fluids

Are given if sufficient fluids cannot be given orally. About 2500mL fluid containing roughly 100mmol Na+ and 70mmol K+ per 24h are required.

Special cases

Acute blood loss Resuscitate with colloid or 0.9% saline via large-bore cannulae until blood is available.

Children Use dextrose-saline for fluid maintenance: 100mL/kg for the first 10kg, 50mL/kg for the next 10kg, and 20mL/kg there after—all per 24h.

Elderly More prone to fluid overload, so use IV fluids with care.

GI losses (diarrhoea, vomiting, NG tubes, etc) Replace lost K+ as well as lost fluid volume.

Heart failure Use IV fluids with care to avoid fluid overload.

Liver failure Patients often have a raised total body sodium, so use salt-poor albumin or blood for resuscitation, and avoid 0.9% saline for maintenance.

Acute pancreatitis Aggressive fluid resuscitation is required due to large amounts of sequestered 'third space' fluid.

Poor urine output Aim for >1 mL/kg/h; the minimum is >0.5mL/kg/h. Give a fluid challenge, eg 500mL 0.9% saline over 1h (or half this volume in heart failure or the elderly), and recheck the urine output. If not catheterized, exclude retention; if catheterized, ensure the catheter is not blocked!

Post-operative Check the operation notes for intraoperative losses, and ensure you chart and replace added losses from drains, etc.

Shock Resuscitate with colloid or 0.9% saline via large-bore cannulae. Identify the type of shock.

Transpiration losses (fever, burns) Beware the large amounts of fluid that can be lost unseen through transpiration. Severe burns in particular may require aggressive fluid resuscitation [(1)].

Types of fluid according to isotonicity

A- Isotonic: Isotonic crystalloids have a tonicity equal to the body plasma. When administered to a normally hydrated patient, isotonic crystalloids do not cause a significant shift of water between the blood vessels and the cells. Thus, there is no (or minimal) osmosis occurring [(4)].

B-Hypertonic: crystalloids have a tonicity higher than the body plasma. The administration of a hypertonic crystalloid causes water to shift from the extravascular spaces into the bloodstream, increasing the intravascular volume.

C-Hypotonic: crystalloids have a tonicity lower than the body plasma. The administration of a hypotonic crystalloid causes water to shift from the intravascular space to the extravascular space, and eventually into the tissue cells. Because the IV solution being administered is hypotonic, it creates an environment where the extravascular spaces have higher concentrations of electrolytes [(4)].

Types of IV fluid

A-Crystalloids: Crystalloids are composed of water and electrolytes [(3)].

1- 5% glucose

(=dextrose) is isotonic, but contains only a small amount of glucose (50g/L) and so provides little energy (~10% daily energy per litre). The liver rapidly metabolizes all the glucose leaving only water, which rapidly equilibrates throughout all fluid compartments. It is, therefore, useless for fluid resuscitation (only 1/9 will remain in the intravascular space), but suitable for maintaining hydration. Excess 5% glucose IV may lead to water overload and hyponatraemia [(1)].

2- Hypertonic glucose (10% or 50%)

may be used in the treatment of hypoglycaemia. It is irritant to veins, so care in its use is needed. Infusion sites should be inspected regularly, and flushed with 0.9% saline after use [(3)].

3- 0.9% saline (normal saline)

has about the same Na+ content as plasma (150mmol/L) and is isotonic with plasma. 0.9% saline will equilibrate rapidly throughout the extracellular compartment only, and takes longer to reach the intracellular compartment than 5% glucose. It is, therefore, appropriate for fluid resuscitation, as it will remain predominantly in the extracellular space (and thus ⅓ of the given volume in the intravascular space), as well as for maintaining hydration [(1)].

4- Half-Normal Saline (0.45% NaCl or ½ NS)

Half-normal saline is a hypotonic fluid that provides free water in relative excess when compared with the sodium concentration. This crystalloid is typically used to treat patients who are hypertonic due to primary depletion of the ECF. Because half normal saline is hypotonic, serum sodium must be closely monitored during administration [(3)].

5- Hypertonic Saline (3% NaCl)

Hypertonic saline is obviously hypertonic and provides a significant sodium load to the intravascular space. This solution is used very infrequently given the potential to cause significant shifts in the water balance between the ECF and the ICF. It is typically used to treat patients with severe hyponatremia who have symptoms attributable to low serum sodium [(3)].

6- 5% Dextrose/Half-Normal Saline (D5 ½ NS)

D5 ½ NS is a hypotonic fluid that is commonly used as a maintenance fluid. This crystalloid is typically used once fluids deficits have been corrected with normal saline or lactated Ringer's solution. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration [(3)].

7- Dextrose-saline (one-fifth normal saline)

is isotonic, containing 0.18% saline and 4% glucose . It has roughly the quantity of Na+ required for normal fluid maintenance, when given 10-hourly in adults, but is now most commonly used in a pediatric setting [(1)].

Intravenous 0.18% saline/4% glucose solution ('hypotonic saline'regarding to sodium content) in children: reports of fatal hyponatraemia – do not use in children aged 16 years or less, except in specialist settings under expert medical supervision such as renal, cardiac, liver, high dependency and intensive care units.[(5)]

8- Hartmann's solution

contains Na+ 131mmol, Cl– 111mmol, lactate 29mmol, K+ 5mmol, HCO_3^- 29mmol, and Ca^{2+} 2mmol per litre of fluid. It is an alternative to 0.9% saline, and some consider it more physiological [(1)].

9-Ringer's lactate solution

technically the closest fluid to serum composition although theoretical advantages are of limited practical value [(2)]. Lactated Ringer's solution is often used for fluid resuscitation after a blood loss due to trauma, surgery, or a burn injury. [4] It has been used to induce urine output in patients with renal failure [(4)].

Lactated Ringer's solution is used because the by-products of lactate metabolism in the liver counteract acidosis, which is a chemical imbalance that occurs with acute fluid loss or renal failure [[4]]. Lactated Ringer's solution should also not be used in patients with a pH level above 7.5 (alkalosis) and in anuria or renal failure due to accumulation of K [(4)].

Potassium in IV fluids:

•Potassium ions can be given with 5% glucose or 0.9% saline, usually 20mmol/L or 40mmol/L.

• K+ may be retained in renal failure, so beware giving too much IV.

• Gastrointestinal fluids are rich in K+, so increased fluid loss from the gut (eg diarrhoea, vomiting, high-output stoma, intestinal fistula) will need increased K+ replacement.

•The maximum concentration of K+ that is safe to infuse via a peripheral line **is 40mmol/L,** at a maximum rate of **20mmol/h**. Fluid-restricted patients may require higher concentrations or rates in life-threatening hypokalaemia. Faster rates risk cardiac dysrhythmias and asystole, and higher concentrations thrombophlebitis, depending on the size of the vein, so give concentrated solutions >40mmol/L via a central venous catheter, and use ECG monitoring for rates over >10mmol/h [(1)] .

B-Colloids

Resuscitation fluids that restore and/or increase the intravascular oncotic pressure [(3)]. Colloids (especially blood) produce a more lasting expansion of intravascular volume than crystalloid, which rapidly enters the interstitial tissues [(2)].

1-Gelofusine is succinylated gelatin (a bovine collagen).

2-Dextran is a glucose polymer mixture; it has been associated with anaphylactic reactions and profound coagulopathy.

3-HES preparations are derived from hydroxyethyl starch.

4-Albumin is a naturally occurring plasma protein, sterilized by ultrafiltration: 5% albumin is isotonic; 20% albumin is hypertonic. Indications for use of albumin as a volume expander are very limited [(2)].

5-Blood, platelets, FFP (fresh Frozen Plasma), and cryoprecipitate.

Intravenous Fluid Packaging

Most IV fluids are packaged in soft plastic or vinyl bags of various sizes (10, 50, 100, 250, 500, 1,000, 2,000, and 3,000 milliliters).

IV fluids on the surgical ward

Notes:

1* Fluid required = pre-existing deficit + normal maintenance + ongoing losses

3*Too many fluids can lead to [(4)]:

-Lungs stiffer - > gas exchange impaired
-Cardiac failure
-Peripheral oedema
-Inhibition of wound healing

4*Not enough fluid can lead to:

-Renal damage
-Cardiovascular damage
-Tissue hypoperfusion

What fluids to use

1-Haemorrhagic/hypovolaemic shock:

Insert 2 large IV cannulae, for fast fluid infusion. Start with crystalloid (eg 0.9% saline) or colloid (eg Gelofusine®) until blood is available. The advantage of crystalloids is that they are cheap but they do not stay as long in the intravascular compartment as colloids, as they equilibrate with the total extracellular volume (dextrose is useless for resuscitation as it rapidly equilibrates with the enormous intracellular volume). In practice, the best results are achieved by combining crystalloids and colloids. Aim to keep the haematocrit at ~0.3, and urine flowing at >30mL/h. Monitor pulse and BP often [(1)].

2- Septicemic shock: e.g. Gelofusine like substance

3-Heart or liver failure:

Avoid sodium loads: use 5% dextrose [(1)]. Or one-fifth normal saline [(4)].

4-Excessive vomiting:

Use 0.9% saline: replace losses, including K^+ [(1)].

Risks of intravenous therapy [(6)]

1-Infection infection of IV sites is usually local, causing easily visible swelling, redness, and fever. If bacteria do not remain in one area but spread through the bloodstream, the infection is called septicemia and can be rapid and life-threatening. An infected central IV poses a higher risk of septicemia, as it can deliver bacteria directly into the circulation.

2-Phlebitis is irritation of vein that is not caused by infection, but from the mere presence of a foreign body (the I.V catheter) or the fluid or medication being given . Symptoms are swelling, pain and redness around the vein site.

3-Infiltration this occurs when the tip of the IV catheter withdraws from the vein or pokes through the vein into surrounding tissue, or when the vein wall becomes permeable and leaks fluid. It requires replacement of the IV at different location.

4-Fluid overload this occurs when fluids are given at higher rate or in larger volume than the system can absorb or excrete. Possible consequences includes Hypertension, heart failure, and pulmonary edema.

5-Embolism a blood clot or other solid mass, or an air bubble, can delivered into the circulation through an IV line and end up with blocking vessel. Peripheral I.V has a lower risk of embolism. This risk is greater with a central I.V line.

References:

1- Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

2- McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition .Copyright 2014 © Oxford University Press.

3- Marie A. Chisholm-Burns, Terry L. Schwinghammer, Barbara G. Wells, Patrick M. Malone, Joseph T. DiPiro. Pharmacotherapy principles and practice, Fourth Edition. Copyright © 2016.

4-Harold Ellis, Sir Roy Calne, Christopher Watson. General Surgery, 11th Edition. Blackwell publishing2006.

5- Drug safety update.Volume 6, Issue 3 October 2012.

6- Nicolae Sfetcu, Health & Drugs: Disease, Prescription & Medication, 1st Edition, February 22, 2014.

1-8: Blood transfusion and blood products (1)

1-Whole blood

Rarely used e.g. for exchange transfusion: use crossmatched blood if possible, but if not, use universal donor group (O Rh-ve blood) changing to crossmatched blood as soon as possible. Blood >2d old has no effective platelets.

2-Red cells

(packed to make haematocrit ~70%) Use to correct anaemia or blood loss. 1U Hb by 1-1.5g/dL. In anaemia, transfuse until Hb ~8g/dL.

3-Platelets

Not usually needed if not bleeding or count is >20 x 10^9/L. 1U should platelet count by >20 x 10^9 /L. Failure to do so suggests refractoriness.

4-Fresh frozen plasma (FFP)

Use to correct clotting defects: e.g. DIC (disseminated intravascular coagulation); warfarin overdosage where vitamin K would be too slow; liver disease; thrombotic thrombocytopenic purpura . It is expensive and carries all the risks of blood transfusion. Do not use as a simple volume expander.

5-Human albumin solution

is produced as 4.5% or 20% protein solution and is for use as protein replacement. 20% albumin can be used temporarily in the hypoproteinaemic patient (eg liver disease; nephrosis) who is fluid overloaded, without giving an excessive salt load. Also used as replacement in abdominal paracentesis.

6-Others

Cryoprecipitate (a source of fibrinogen); coagulation concentrates **(self-injected in haemophilia); Immunoglobulin (anti-D).**

Complications of transfusion:

• Early (within 24h):
Acute haemolytic reactions (eg ABO or Rh incompatibility); anaphylaxis; bacterial contamination; febrile reactions; allergic reactions (itch, urticaria, mild fever); fluid overload; transfusion-related acute lung injury.

• Delayed (after 24h):
Infections; iron overload; graft-versus-host disease; post-transfusion purpura.

Transfusing patients with heart failure

If Hb ≤ 5g/dL with heart failure, transfusion with packed red cells is vital to restore Hb to safe level, eg 60–80g/L, but must be done with great care. Give each unit over 4h with furosemide (eg 40mg slow IV/PO; don't mix with blood).

References:
1- Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

1-5: Preoperative prophylaxis against aspiration pneumonia (1)

Patients at greatest risk for regurgitation and aspiration include those with increased gastric acid, elevated intragastric pressure, gastric or intestinal hypomotility, digestive structural disorders, neuromuscular incoordination, and depressed sensorium. These can include pregnant women, obese patients, and patients with diabetes, as well as patients with a hiatal hernia, gastroesophageal reflux, esophageal motility disorders, or peptic ulcer disease.

A- Antacid agents

should be given as a single dose (30 mL) approximately 15 to 30 minutes before induction of anesthesia, antacids has two major **advantages**:
1-Rapid onset of activity.
2-Effective on the fluid already present in the stomach.

The major **disadvantages** are:
1-a short-acting buffering effect that is not likely to last as long as the surgical procedure.
2-the potential for emesis (owing to their lack of palatability);
3-the possibility of incomplete mixing in the stomach; and
4-their administration adds fluid volume to the stomach.

B- Gastric motility stimulants (prokinetic agents)

The gastric motility stimulant, metoclopramide, has no effect on gastric pH or acid secretion, this agent reduces gastric volume by promoting gastric emptying. Metoclopramide should be administered 60 minutes before induction of anesthesia when given orally. When given by the IV route, metoclopramide should be slowly administered 15 to 30 minutes before induction of anesthesia.

C- H2 receptor antagonists

H2-receptor antagonists reduce gastric acidity and volume by decreasing gastric acid secretion. Unlike antacids, the H2-receptor antagonists do not produce immediate effects. Onset time for these agents when administered orally is 1 to 3 hours; good effects will be seen in 30 to 60 minutes when administered IV. After IV administration, the cimetidine dose should be repeated in 6 hours if necessary, whereas therapeutic concentrations of ranitidine and famotidine persist for 8 and 12 hours, respectively.

D- Proton pump inhibitors

Act at the final site of gastric acid secretion, making these agents very effective in suppressing acid secretion.

References:

1- Alldredge, Brian K.; Corelli, Robin L.; Ernst, Michael E.; Guglielmo, B. Joseph; Jacobson, Pamala A.; Kradjan, Wayne A.; Williams, Bradley R., Applied Therapeutics: The Clinical Use of Drugs, 10th Edition. 2013.

1-9: The control of pain [1]

Guidelines for success:

1-Give regular doses rather than on an as required basis.

2-Choose the best route: PO, PR, IM, epidural, SC, inhalation, or IV.

A-Non-narcotic (simple) analgesia

Paracetamol 0.5-1.0g/4h PO (up to 4g daily) :Caution in liver impairment.

NSAIDs, eg ibuprofen 400mg/8h PO . or diclofenac 50mg/8h PO, or 100mg PR/IM ; these are good for musculoskeletal pain and renal or biliary colic.

CI: peptic ulcer, clotting disorders, anticoagulants. Cautions: asthma, renal or hepatic impairment, pregnancy, and the elderly. Aspirin is contraindicated in children due to the risk of Reye's syndrome.

B-Opioid drugs for severe pain

Morphine (eg 10-15mg/2-4h IV/IM) or diamorphine (5-10mg/2-4h PO, SC, or slow IV, but you may need much more) are best.

Side-effects of opioids: These include nausea (so give with an antiemetic, eg prochlorperazine 12.5mg stat IM), respiratory depression, constipation, cough suppression, urinary retention, and sedation (do not use in hepatic failure or head injury). Dependency is rarely a problem. Naloxone may be needed to reverse the effects of excess opioids.

C-Epidural analgesia

Opioids and anesthetics are given into the epidural space by infusion or as boluses.

D-Adjuvant treatments e.g.

1-Anticonvulsants, antidepressants, gabapentin or steroids for neuropathic pain.

2-Antispasmodics, eg hyoscine butylbromide (Buscopan20-10 ®mg/8h PO/IM/IV) for intestinal, renal tract colic.

References:

1-Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

1-10: Nausea and vomiting [1]

This affects up to 75% of patients. It predisposes to increased bleeding, incisional hernias, aspiration pneumonia, low absorption of oral medication, poor nutrition, and low K+.

Causes include:

• Prolonged surgery; anaesthetic agents;

• Post-operative ileus; bowel obstruction; constipation; gastric reflux; peptic ulceration or bleeding; medications, and hyponatraemia.

Classification of antiemetics

Combining two different types of antiemetic increases efficiency.

A-Antidopaminergic agents

1-Good against opioid nausea and vomiting, sedative, extrapyramidal side-effects
2-e.g. prochlorperazine 12.5mg IM, metaclopramide 10mg IV/IM/PO tds.

B-Antihistamines

1-Sedation, tachycardias, hypotension with IV injection
2-e.g. cyclizine 50mg IM/IV/PO tds.

C-Anticholinergics

1-Active against emetic effect opioids, sedation, confusion, dry mouth
2-e.g. hyoscine (scopolamine) 0.3-0.6mg IM.

D-Antiserotonergics

1-Lowest side-effect profile of all antiemetics
2-Ondansetron 1-8mg PO/IV/IM tds, granisetron 1mg PO/IV td.

1-11: Constipation

Failure to pass stool is common. Caused by lack of privacy, immobility, pain from wounds or anal fissures, dehydration, poor nutrition, low dietary fiber, opiates, iron supplements, and spinal anaesthesia.

Treat with:

1-Bulking agents, e.g. Fybogel 1 sachet PO bd.
2-Stool softeners, e.g. sodium docusate 30-60mg od PO.
3-Osmotic agents, e.g. lactulose 5-10mL bd.
4-Stimulants, e.g. senna 1 tablet bd PO, bisacodyl 5-20mg nocte PO.

References:

1- McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition. Copyright. 2014 © Oxford University Press.

2-1: Peri-operative care and diabetes

Surgery causes considerable stress in patients. In response, the neuro-endocrine system stimulates glycogenolysis (breakdown of glycogen to glucose) and gluconeogenesis (glucose synthesis from non-carbohydrate sources) via counter-regulatory hormones such as catecholamines, cortisol, growth hormone and glucagon. These hormones can antagonise the effects of insulin and cause insulin resistance [(1)].also this stress decrease the absorption of oral hypoglycemic drugs

Note: In general if the diabetic patient is well control have no infection or complication and undergo minor surgery we can convert him to an appropriate iv regimen - e.g., an infusion consisting of glucose, insulin and potassium (referred to as GLIK or sometimes) or a sliding-scale insulin regimen[(1)] but if the patient is not well control with many complication related to poor glycemic control or have infection like diabetic foot we have to ensure tight glycemic control by converting him to intensive insulin therapy.

Intravenous Insulin, Glucose, Potassium, and Fluids:-

1-Insulin

2- Glucose

3- Potassium

Diabetic foot

Approximately 25% of diabetic patients report a history of skin and soft tissue infection and 5%-15% of diabetic patients undergo limb amputation.

Etiology:

1--Poor glycemic control lead to an increase in blood viscosity which becomes a good media for the growth of bacteria, the causative agent include one or more of the following bacteria:
Staphylococcus aureus, Staphylococcus epidermis., Enterococcus faecalis., Bacteroid species. Pseudomonas aerogenosa., and Klebseilla species.
2--Peripheral vascular disease which decreases blood flow to extremities.
3--Somatic neuropathy: which decreases pain perception.
4--Autonomic neuropathy: which decreases sweating, and subsequently dry, scaly skin.

Management:

A-Non-pharmacological:
1-Inspect feet for cuts, blisters, or scratches.
2--Wash feet daily in taped water and dry thoroughly.
3--Apply lotion to the feet to prevent calluses and cracking.
4--Ensure shoes fit properly.
5--Trim nails regularly.
6--Do not use chemical agents to remove corns or callus.

Pharmacological:

A-Tight glycemic control:

This can be achieved by intensive insulin therapy as follows:
Starting dose of insulin is **1-1.5U/kg/day** which is given as follows:
¼of total daily dose before each meal as soluble insulin SC.
¼of total daily dose at 11pm as intermediate insulin SC.
Monitor therapy by making FBS which should be less than 120mg/dl.
If the patient develops morning hyperglycemia, the patient should be asked about signs of hypoglycemia at 2:00-3:00am and measure glucose level at this time.
If this reveals hypoglycemia, the morning hyperglycemia is rebound type (Somogi effect) which can be managed by ensuring that the patient take intermediate insulin at the specified time and reduce the dose of intermediate insulin.
If this reveals hyperglycemia, the morning hyperglycemia is due to down phenomena, and can be managed by increasing the dose of intermediate insulin.
Make 2h. Postprandial glucose level and the result should be less than 180mg/dl, if we did not get this target, give 2U soluble insulin IV for each 50mg/dl of glucose above the goal.
If the patient stabilize on this regimen, we can convert him to a less frequent regimen, and on discharge, **the following regimen is given:**
2/3of total daily dose is given before breakfast as 30% soluble insulin and 70% of intermediate insulin.

1/3of total daily dose is given before dinner as 30% soluble insulin and 70% of intermediate insulin.

B-Antibiotic therapy:

Effective combination should cover most potential pathogens (G+ve, G-ve, and anaerobes). This can be achieved by giving :
Clindamycin 600mg q 8h + gentamicin 2mg/kg q 8h.
In patients with poor renal function, gentamicin could be replaced by:

1-A quinolone (ciprofloxacin 200mg IV infusion q 12h), or
2-A 3rd generation cephalosporine (cefotaxim 1g q 8h, or cefotriaxone 1g q 24 h)
3-Piperacillin 1g q 6hr, or 2g q 4hr in severe cases.
4-Cefazoline 1g q 6h + metronidazole 500mg q 8h IV infusion.

The treatment should continue for 3-4 days after all signs of infection are absent. Drainage and surgical debridement of necrotized tissue are essential; also it is necessary to change dressing twice daily.

References:
1-Mohamed H. Rahman and James Anson . Peri-operative care and diabetes. The Pharmaceutical Journal .13 March 2004 (Vol 272) 323-325.
2-Samuel Dagogo-Jack and K. George M.M. Alberti. Management of Diabetes Mellitus in Surgical Patients. Diabetes Spectrum 15:44-48, 2002.

2-2-1: Perioperative medication management:

In general, one should stop any medication that may prove harmful around the time of surgery e.g., (MAO inhibitors, anticoagulants), continue any medications that are necessary for the patient's health (e.g., steroids, anti-arrhythmic agents, beta-blockers, transplant meds).

Common drugs that have been associated with withdrawal symptoms when discontinued Preoperatively include selective serotonin reuptake inhibitors (SSRIs), beta-blockers, clonidine, statins, and corticosteroids.

In general, most nonsteroidal anti-inflammatory drugs should be stopped at least 3 days before surgery**.** Herbal medications should be stopped at least 7 days before surgery, owing to the uncertainly over their actual contents [(1)].

2-2-2: Peri-operative medication in patients with cardiovascular disease [(2)]

When a patient with cardiovascular disease (CVD) is to undergo surgery, we need to consider whether or not any of the drugs used to treat his or her cardiovascular problems need to be stopped

Table 1. Outline of Perioperative Drug Management of Patients with Coronary Artery Disease

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure
Nitroglycerin	**Usual dose**	**Usual dose**	**IV infusion if frank ischemia**	**Continue IV dose if needed or until medication can be taken PO**
Beta-blockers	**Usual dose**	**Usual dose plus beta-blocker protocol**	**Usual dose plus beta-blocker protocol**	**Usual dose plus beta-blocker protocol**

Calcium channel blockers	**Usual dose**	**Usual dose morning of surgery**	**Usual dose morning of surgery**	**Continue IV dose until medication can be taken PO**
Aspirin	**Discontinue 1 week before surgery**			**Restart postoperatively at discretion of surgeon**
Ticlopidine	**Discontinue 1 week before surgery**			**Restart postoperatively at discretion of surgeon**
Warfarin	**Discontinue 3-4 days**			

Table 2. Perioperative Drug Management for Patients With Hypertension

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure
Beta-blockers	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**IV bolus or infusion (usually not required)**	**Continue IV dose until medication can be taken PO**
Calcium channel blockers	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**IV bolus or infusion (usually not required)**	**Continue IV dose until medication can be taken PO**
ACE inhibitors	**Stop day before**	**Do not take day of surgery**	**IV formulations (usually not required)**	**Continue IV dose until medication can be taken PO**
Diuretics	**Stop day before**		**IV beta-blockers/IV calcium channel blockers**	**Restart when patient on oral liquids**
Potassium supplements	**Stop day before; consider checking potassium level**			**Restart when patient on oral liquids**
Central-acting sympatholytics	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**Transdermal clonidine/IV methyldopa**	**Restart when patient on orals liquids**
Peripheral sympatholytics	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**Any IV formulation (usually not required)**	**Restart when patient on oral liquids**
Alpha-blockers	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**Any IV formulation (usually not required)**	**Restart when patient on oral liquids**
Vasodilators	**Usual dose**	**Usual dose on morning of surgery with sip of water**	**IV formulation (usually not required)**	**Continue IV dose until medication can betaken PO**

References:
Nafisa K Kuwajerwala, MD; Chief Editor: William A Schwer, MD. Perioperative Medication Management. Nov 11, 2015.

2-3: Surgery in those on steroids [1]

Patients on steroids may not be able to mount an appropriate adrenal response to meet the stress of surgery due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Extra corticosteroid cover may be required, depending on the type of surgery. Consider cover for any patient taking >5mg/d of prednisolone (or equivalent) for more than 2 weeks or any patient who has had their long-term steroid reduced in the last 2–4 weeks. There is also potential for HPA suppression in patients taking long-term high-dose inhaled or topical corticosteroids. Patients should take their normal morning steroid dose.

• **Minor procedures:** under local anaesthetic: No supplementation required.
• **Moderate procedures:** (eg joint replacement) Give 50mg hydrocortisone before induction and 25mg every 8h for 24h. Resume normal dose thereafter.
• **Major surgery:** Give 100mg hydrocortisone before induction and 50mg every 8h for 24h. After 24h, halve this dose each day until the level of maintenance. Patients with primary adrenal insufficiency will need extra cover. The major risk with adrenal insufficiency is hypotension, so if this is encountered without an obvious cause, consider a stat dose of hydrocortisone.

References:

1- Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

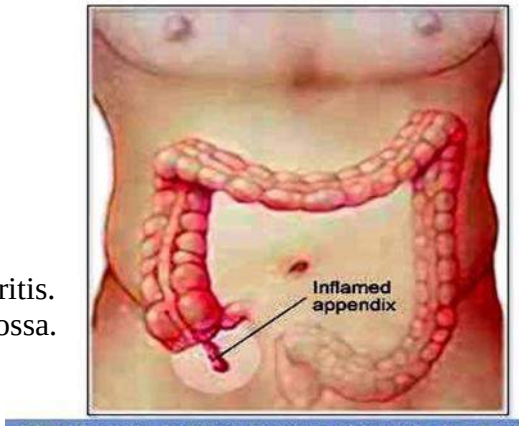
2-4: Surgery and the contraceptive pill [1]

Oestrogen-containing contraceptive pills increase the risk of thromboembolic disease in women taking them prior to surgery. Progesterone-only contraceptives appear to pose little or no additional risk and may be continued during surgery. The increase in risk is related to the size of the operative procedure and the existing co-morbidity; the advice is adjusted accordingly.

References: 1- McLatchie, Greg; Borley, Neil; Chikwe, Joanna Oxford Handbook of Clinical Surgery, 4th Edition. Copyright 2014 © Oxford University Press.

3-1: Acute appendicitis

This is the most common surgical emergency. in which Gut organisms invade the appendix wall [1].



Clinical features

A-Symptoms [2]
1-malaise, anorexia, and fever;
2-diarrhoea common and may be mistaken for acute (gastro)enteritis.
3-abdominal pain starts centrally and localizes to the right iliac fossa.
4-abdominal pain caused by coughing and moving.
B-Signs [2]
1-fever, tachycardia; 2-abdominal tenderness.
C-Investigations may be normal and none are diagnostic or exclusive [2].

Establish a diagnosis

The diagnosis is a clinical one in all but exceptional cases and investigations are usually unnecessary [2].

Complications [1]

1-**Perforation**
2-**Appendix mass** may result when an inflamed appendix becomes covered with omentum.
3-**Appendix abscess** may result if an appendix mass fails to resolve.

Management

A-Acute appendicitis

1- Appendicectomy [2].
2- IV antibiotics on induction; continued antibiotics only indicated for perforation.

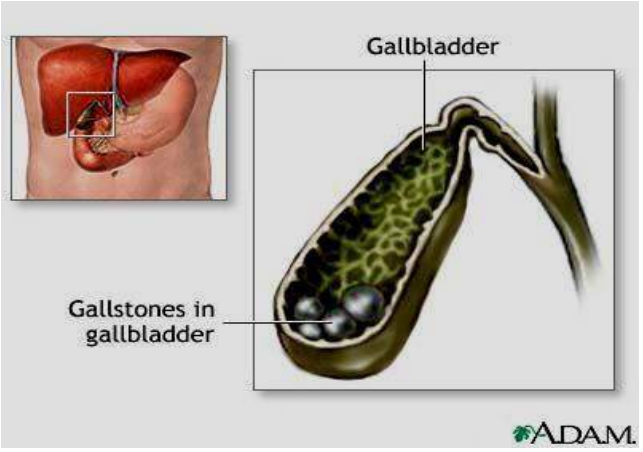
B-Appendix mass or appendix abscess [2]

1-IV antibiotics (e.g. cefuroxime 750mg tds + metronidazole 500mg tds),
2-If symptoms settle: delayed (interval) appendicectomy after 6 weeks,
3-If symptoms fail to settle: may need acute appendicectomy.
4-Appendix abscess may be amenable to drainage.

References

1-Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.
2-McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition. Copyright. 2014 © Oxford University Press.

3-2: Gallstones:



Pathological features [1]

Bile has three major constituents:
1-bile salts (primary: cholic and chenodeoxycholic acids; secondary: deoxycholic and lithocholic acids).
2-Phospholipids (90% lecithin).
3-cholesterol.
Bile containing excess cholesterol relative to bile salts and lecithin is predisposed to gallstone formation.

Types of gallstones [1]

1-Pure cholesterol (10%).
2-Pure pigment (bile salts; 10%).
3-Mixed (80%). Most common; usually multiple.

Predisposing conditions [1]

1-Increasing age.
2-Female (pregnancy and use of the oral contraceptive).
3-Obesity.
4-Multiparity.
5-Chronic haemolytic disorders (only for pigment stones).

Clinical features (common presentations) [1]

A-Biliary colic

Intermittent severe epigastric and right upper quadrant; usually associated with nausea and vomiting. Resolves after a few hours.

Acute cholecystitis[1]

Severe continuous right upper quadrant pain; often radiates to right flank and back; associated with anorexia and pyrexia.

Complications of acute cholecystitis include [1]

1-formation of an empyema or abscess of the gallbladder (rare)
2-perforation with biliary peritonitis (very rare);
3-jaundice due to compression of the adjacent common bile duct by pressure.

Chronic cholecystitis [1]

Repeated episode of infection causes thickening and fibrosis of gall bladder.

Diagnosis and investigations[1,2,3]

1-WCC 2-ultrasound (Ultrasound is the investigation of choice for diagnosing gallstones)
3-Abdominal x-ray (AXR) only shows ~10% of gallstones.

Treatment:

Asymptomatic gallstones found incidentally are not usually treated because the majority will never give symptoms. Symptomatic gallstones are best treated surgically [3].

A-Surgical treatment

Cholecystectomy

This is the treatment of choice for all patients fit for GA (general anesthesia) [1]. If delayed, relapse occurs in 18% and may be associated with more complications, so early surgery is generally recommended [2].

B-Non-surgical treatments [1, 3]

1-Dissolution therapy (chenodeoxycholic or ursodeoxycholic):

• Rarely used. Requires a functioning gall bladder, small stones.
• Problems—requires prolonged treatment, <70% response, high rate of recurrence of stones, side effects of medication (diarrhoea, pruritus).

2-Extracorporeal shock wave lithotripsy (ESWL) [1].

Hardly ever used. Risk of visceral injury and high risk of stone recurrence.

References:

1- McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition. Copyright. 2014 © Oxford University Press.

2- Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

3-Walker, Brian R.; Colledge, Nicki R.; Ralston, Stuart H.; Penman, Ian D. Davidson's Principles and Pracrtice of Medicines. 22 th Edition 2014.

3-3: Common bile duct stones

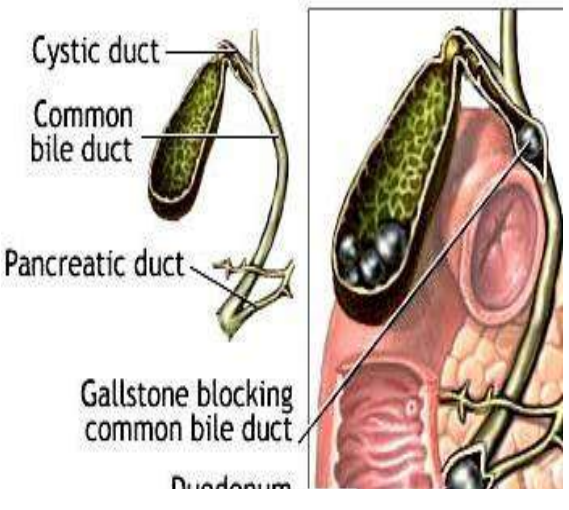
Key facts

Types of stones as per gallbladder stones.
Common bile duct (CBD) stones about 10% of patients with gallstones. Most pass from the gallbladder into the CBD (secondary duct stones).Rarely form within the CBD (primary duct stones); almost always associated with partial duct obstruction.

Diagnosis and investigations

1- (WCC in cholangitis and pancreatitis), LFTs (conjugated bilirubin and alkaline phosphatase), serum amylase (in pancreatitis).

2-The most convenient method of demonstrating obstruction to the common bile duct is by transabdominal ultrasound [2].



Management

Cholangitis should be treated with analgesia, intravenous fluids and broad-spectrum antibiotics, such as cefuroxime and metronidazole. Patients also require urgent decompression of the biliary tree and stone removal.

Endoscopic Retrograde Cholangio-Pancreatography (ERCP)with biliary sphincterotomy and stone extraction is the treatment of choice and is successful in about 90% of patients. If ERCP fails, other approaches include percutaneous transhepatic drainage and combined endoscopic procedures, extracorporeal shock wave lithotripsy (ESWL) and surgery.

Surgical treatment of choledocholithiasis is performed less frequently than ERCP because it carries higher morbidity and mortality.

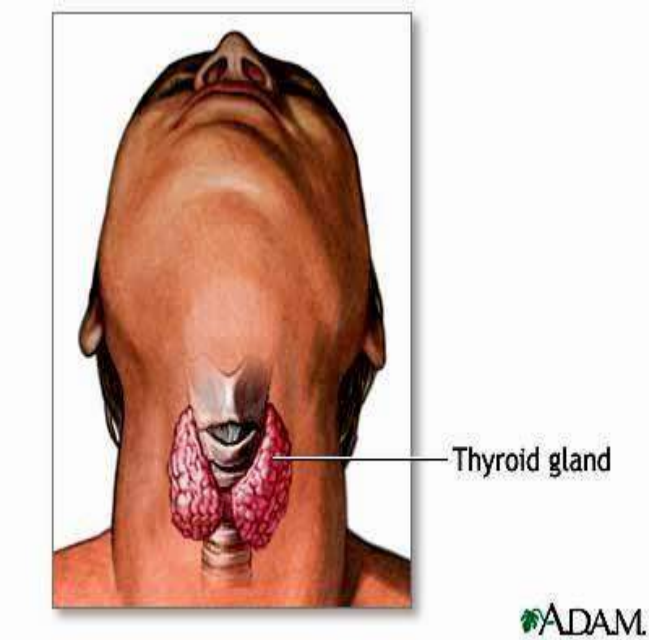
References:

1- **McLatchie, Greg; Borley, Neil; Chikwe, Joanna. Oxford Handbook of Clinical Surgery, 4th Edition. Copyright. 2014 ©Oxford University Press.**

2-Walker, Brian R.; Colledge, Nicki R.; Ralston, Stuart H.; Penman, Ian D. Davidson's Principles and Pracrtice of Medicines. 22 th Edition 2014.

3-7: Thyroidectomy

The surgical removal of part or all of the thyroid gland, thyroidectomy allows treatment of hyperthyroidism, respiratory obstruction from goiter, and thyroid cancer.



Subtotal thyroidectomy used to correct hyperthyroidism when drug therapy fails or radiation therapy is contraindicated, reduces secretion of thyroid hormone. It also effectively treats diffuse goiter. After surgery, the remaining thyroid tissue usually supplies enough thyroid hormone for normal function.

Total thyroidectomy may be performed for certain types of thyroid cancers, such as papillary, follicular, medullary, or anaplastic neoplasms. After this surgery, the patient requires lifelong thyroid hormone replacement therapy.

Indications

Pressure symptoms, relapse hyperthyroidism after >1 failed course of drug treatment, carcinoma, cosmetic reasons, symptomatic patients planning pregnancy.

Pre-operative management:

• Treat hyperthyroidism pre-operatively with antithyroid drugs until the patient is euthyroid (p210), eg carbimazole up to 20mg/12h PO or propylthiouracil 200mg/12h PO. Potassium iodide also has a role.

• Propranolol up to 80mg/8h PO can be used to control tachycardia or tremor associated with hyperthyroidism (continue for 5d post-op).

Complications

1-Early
Hoarseness, hemorrhage, hypoparathyroidism, thyroid storm (symptoms of severe).

2-Late
Hypothyroidism, recurrent hyperthyroidism.

References:
1-Longmore, Murray; Wilkinson, Ian B; Baldwin, Andrew: Wallin, Elizabeth. Oxford Handbook of Clinical Medicine, 9th Edition. Copyright 2014 © Oxford University Press.

3-8: Bowel Obstruction

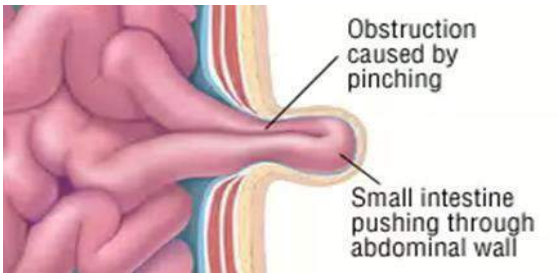
*A blockage prevents the contents of the intestines from passing normally through the digestive tract. The problem causing the blockage can be inside or outside the intestine. Inside the intestine, a tumor or swelling can fill and block the inside passageway of the intestine. Outside the intestine, it is possible for an adjacent organ or area of tissue to pinch, compress or twist a segment of bowel.
* A bowel obstruction can occur in the small bowel (small intestine) or large bowel (large intestine or colon). Also, a bowel obstruction can be total or partial, depending on whether any intestinal contents can pass through the obstructed area.

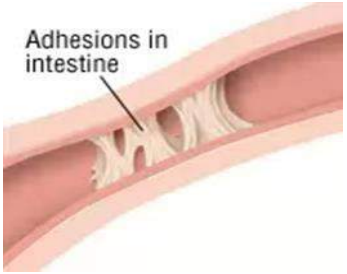
*** In the small intestine, the most common causes of bowel obstruction are:**

1- Adhesions —Adhesions develop on the outside of injured intestine or pelvic organs as they heal after surgery or infection. Gynecological surgeries and surgery involving the appendix or colon are particularly likely to result in adhesions.

2- Hernia

3- Tumors – Cancerous tumors





***In the large intestine, the most common causes of bowel obstruction are:**

1-Colorectal cancer

2-Volvulus – Volvulus is an abnormal twisting of a segment of bowel around itself. This twisting motion typically produces a closed loop of bowel with a pinched base, leading to intestinal obstruction. In Western countries, volvulus is most common among people over age 65, and these patients often have a history of chronic (long-lasting) constipation.

3-<u>Diverticular disease</u> – In the large bowel, diverticula are small, balloon-shaped pouches that protrude from the wall of the intestine. If diverticula become infected this is called diverticulitis. During healing from infection, scars may form in the wall of the colon as it.

Symptoms

Symptoms of small-bowel obstruction can include:

1-Cramping abdominal pain, generally coming in intense waves that strike at intervals of five to 15 minutes and sometimes center either on the navel or between the navel and rib cage (Pain that becomes constant may be a symptom of bowel strangulation)
2-Nausea and vomiting
3-No gas passing through the rectum
4-A bloated abdomen, sometimes with abdominal tenderness
5-Rapid pulse and rapid breathing during episodes of cramps

Symptoms of large-bowel obstruction can include:

1-A bloated abdomen.
2-Abdominal pain, which can be either vague and mild, or sharp and severe, depending on the cause of the obstruction
3-Constipation at the time of obstruction, and possibly intermittent bouts of constipation for several months beforehand.

Exams and Tests

Tests that show obstruction include:
1-Abdominal CT scan
2-Abdominal x-ray
3-Ultrasound

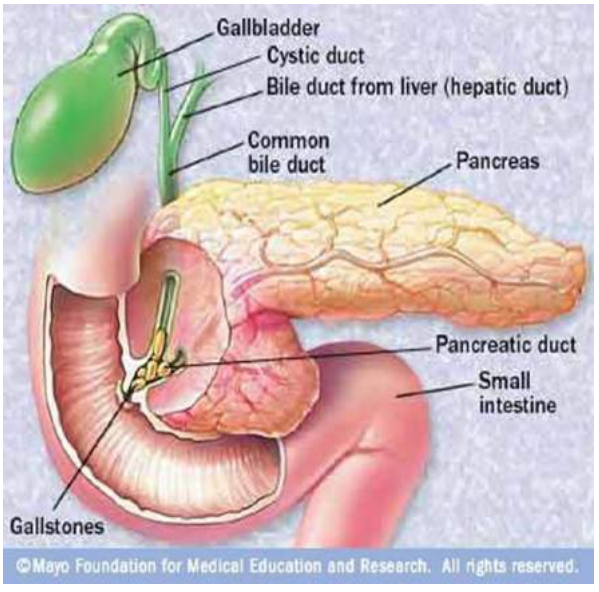
Treatment

Treatment involves placing a tube through the nose into the stomach or intestine to help relieve abdominal swelling (distention) and vomiting. Volvulus of the large bowel may be treated by passing a tube into the rectum. Surgery may be needed to relieve the obstruction if the tube does not relieve the symptoms, or if there are signs of tissue death.

<u>References:</u>
1- McKenzie S, Evers BM. Small intestine. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, eds. Sabiston Textbook of Surgery. 19th ed. St. Louis, Mo: WB Saunders; 2012: chap 50.
2- Fry RD, Mahmoud N, Maron DJ, Bleier JIS. Colon and rectum. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, eds. Sabiston Textbook of Surgery. 19th ed. St. Louis, Mo: WB Saunders; 2012: chap 52.

3-9: Pancreatitis

Pancreatitis is an inflammation of the pancreas. It has several causes and symptoms and requires immediate medical attention. It occurs when pancreatic enzymes (especially trypsin) that digest food are activated in the pancreas instead of the small intestine. It may **be <u>acute</u>—beginning suddenly and lasting a few days, or <u>chronic</u>— occurring over many years. Chronic pancreatitis can lead to diabetes or pancreatic cancer** [(1)].



Causes

Ethanol use accounts for 30% of cases and gallstones about 30% to 40% of cases. Other common

causes include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), pregnancy, and auto-digestion due to early activation of pancreatic enzymes [2].

Pathophysiology

1. Ethanol abuse may cause precipitation of pancreatic enzymes in pancreatic ducts, leading to chronic inflammation and fibrosis or may be directly toxic to the pancreatic cells.

2. Gallstones can cause obstruction resulting pancreatic enzymes or bile to move in a retrograde fashion into the pancreas. This may be responsible for pancreatic autolysis.

3. Acute pancreatitis can result from the initial injury to the zymogen-producing cells (granules in which Pancreatic enzymes are produced and stored as inactive proenzymes) [2].

Symptoms

1. Sudden upper abdominal pain is the most common symptom.

2. Pain may radiate to the back, and ecchymosis may be present in the flank and periumbilical areas.

3. Nausea and vomiting are other common symptoms.

4. Tachycardia, hypotension, fever, and abdominal distention may be present [2].

Diagnosis

1. Diagnosis is based on patient history, signs and symptoms, and laboratory values. The history can identify
risk factors for acute pancreatitis, including alcohol abuse and medications.

2. A serum lipase greater than three times the normal limit supports the diagnosis.

3. Abdominal ultrasound but has limited sensitivity.

4. Computed tomography (CT) may be more useful in staging pancreatitis or identifying complications.

5. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are more costly options that can be used to evaluate severity and pancreatic abnormalities [2].

Treatment

Non Pharmacologic Therapy

Therapy of acute pancreatitis is primarily supportive unless a specific etiology is identified. Supportive therapy involves fluid repletion, nutrition support, and analgesia. Patients with acute pancreatitis are administered IV fluids to maintain hydration and blood pressure. The total amount of fluids administered should be based on vital signs and urine output. Enteral nutrition is preferred, but if a patient is not meeting caloric goals, it may be supplemented with total parenteral nutrition. If pancreatic necrosis or abscesses are present, surgical or interventional procedures may be necessary.

Pharmacologic Therapy

1. Analgesics: Meperidine, Hydromorphone, morphine, and fentanyl**.**

2. Antibiotic [2].

References:

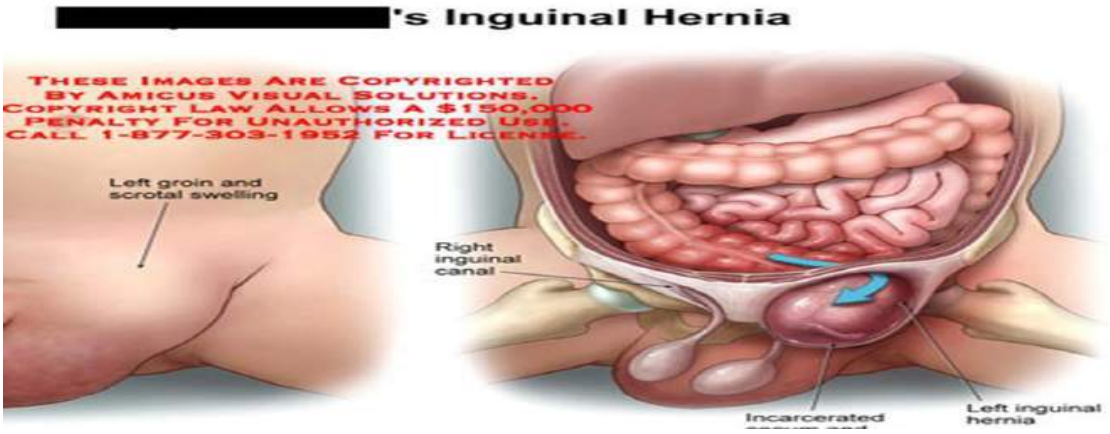
1- "Pancreatitis". A.D.A.M., Inc. Retrieved 2013-01-05.

2- Alldredge, Brian K.; Corelli, Robin L.; Ernst, Michael E.; Guglielmo, B. Joseph; Jacobson, Pamala A.; Kradjan, Wayne A.; Williams, Bradley R., Applied Therapeutics: The Clinical Use of Drugs, 10th Edition. 2013.

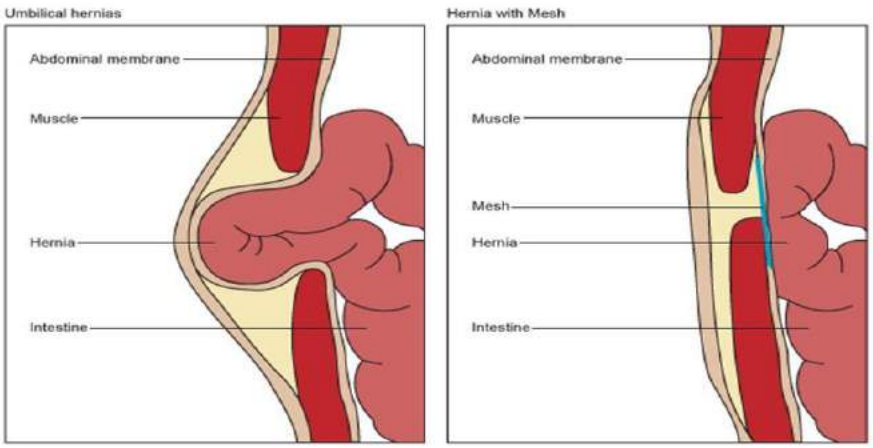
Hernia

A hernia occurs when an organ or fatty tissue squeezes through a weak spot in a surrounding muscle or connective tissue called fascia. The most common types of hernia are inguinal (inner groin), incisional (resulting from an incision), femoral (outer groin), umbilical (belly button), and hiatal (upper stomach).

In an **inguinal hernia**, the intestine or the bladder protrudes through the abdominal wall or into the inguinal canal in the groin. About 96% of all groin hernias are inguinal, and most occur in men because of a natural weakness in this area.



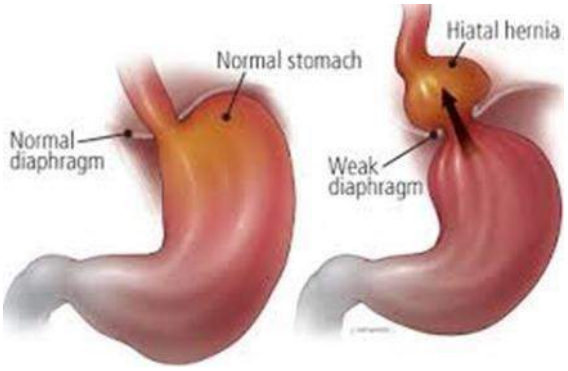
In an **incisional hernia**, the intestine pushes through the abdominal wall at the site of previous abdominal surgery. This type is most common in elderly or overweight people who are inactive after abdominal surgery.



A **femoral hernia** occurs when the intestine enters the canal carrying the femoral artery into the upper thigh. Femoral hernias are most common in women, especially those who are pregnant or obese.

In an **umbilical hernia**, part of the small intestine passes through the abdominal wall near the navel. Common in newborns, it also commonly afflicts obese women or those who have had many children.

A **hiatal hernia** happens when the upper stomach squeezes through the hiatus, an opening in the diaphragm through which the esophagus passes.



Causes of Hernias:

Ultimately, all hernias are caused by a combination of pressure and an opening or weakness of muscle or fascia; the pressure pushes an organ or tissue through the opening or weak spot. Sometimes the muscle weakness is present at birth; more often, it occurs later in life.

Anything that causes an increase in pressure in the abdomen can cause a hernia, including:

Lifting heavy objects without stabilizing the abdominal muscles
Diarrhea or constipation
Persistent coughing or sneezing

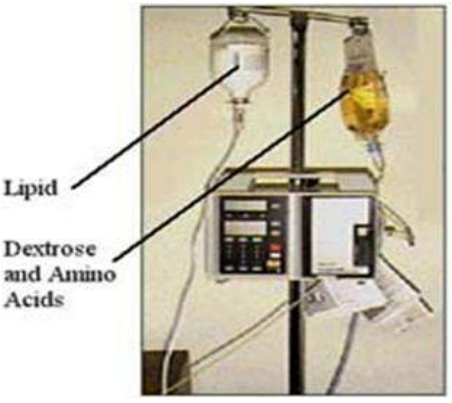
In addition, obesity, poor nutrition, and smoking, can all weaken muscles and make hernias more likely.

3-11: Guidelines on Parenteral Nutrition in Surgery [1]

Parenteral nutrition is a way of delivering, in the form of intravenous infusion, the nourishments necessary for the maintenance of life, such as amino acids—a source of proteins, glucose, and lipids—a supply of energy; and water, electrolytes, microelements, and vitamins .

***Central Parenteral Nutrition: often called Total Parenteral Nutrition (TPN); delivered into a central vein**
***Peripheral Parenteral Nutrition (PPN): delivered into a smaller or peripheral vein**

***Inadequate oral intake for more than 14 days is associated with a higher mortality.**



***Compounding Methods**

A- Total nutrient admixture (TNA) or 3-in-1

Dextrose, amino acids, lipid, additives are mixed together in one container. Lipid is provided as part of the PN mixture on a daily basis and becomes an important energy substrate.

B- 2-in-1 solution of dextrose, amino acids, additives

Typically compounded in 1-liter bags
Lipid is delivered as piggyback daily or intermittently as a source of EFA

Table 9 - Parenteral nutrition solutions.

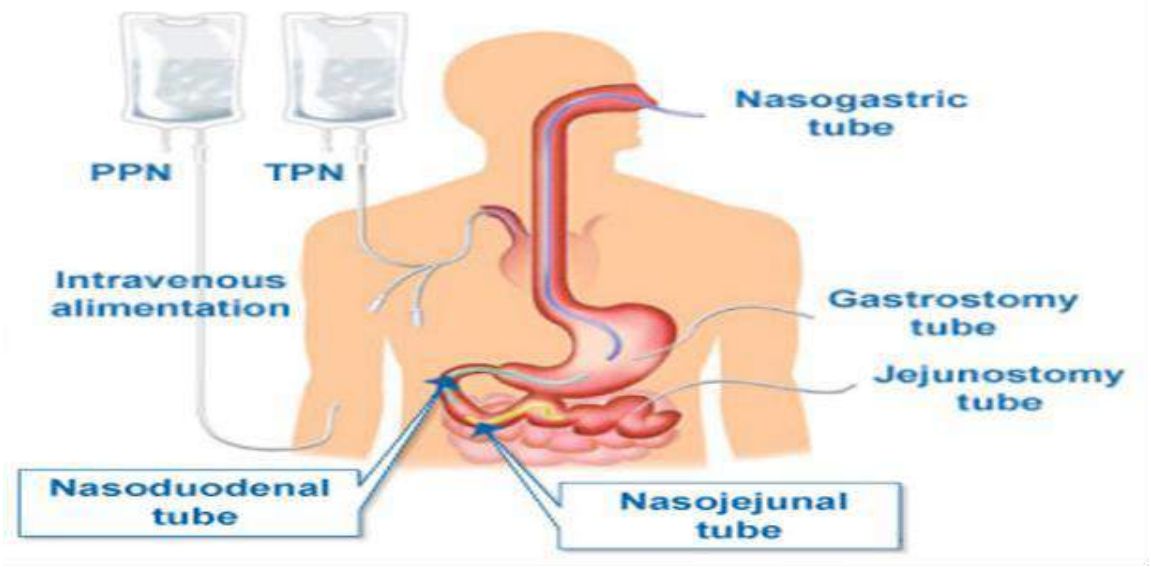
Constituent	Central vein	Peripheral vein
Glucose 50%	400 mL	100-150 mL
Amino acids 10%	200 mL	150 mL
Sodium acetate (10%)	40 mL	40 mL
Magnesium sulphate (20%)	5 mL	5 mL
Potassium chloride (19.1%)	8 mL	8 mL
Potassium acid phosphate (25%)	10 mL	10 mL
Calcium gluconate (10%)	20 mL	20 mL
Folic acid (0.1%)	5 mL	5 mL
Vitamin K	0.2 mg	0.2 mg
Vitamin B	1 amp	1 amp
Vitamin C	250 mg	250 mg
Distilled water to	1000 mL	1000 mL
Osmolarity (mOm/L)	1800 mOm/L	650-700 mOm/L
N/cal ratio	1/250	1/100 to 1/150

Uses Parenteral nutrition is used primarily in therapies of gastrointestinal patients after stomach resection, with short bowel syndrome, intestinal fistula, bowel obstruction, and absorption disorders (Crohn's disease, acute pancreatitis) and as perioperative treatment in malnourished or depleted patients with extensive burns, and those in shock and during chemo- and radiotherapy

The role of the pharmacist should ensure the therapeutic safety of parenteral nutrition in all its aspects including parenteral nutrition mixture preparation, choice of an appropriate administration route and drug form for the ongoing medication, implementation of alternative treatment methods, monitoring therapeutic and toxic effects, and instructing the medical and nursing staff about possible interactions of drugs with parenteral nutrition.

Type of formula

The commonly used formula of 25 kcal/kg ideal body weight furnishes an approximate estimate of daily energy expenditure and requirements. Under conditions of severe stress requirements may approach 30 kcal/kg ideal body weight.
*The Protein: Fat: Glucose caloric ratio should approximate to 20:30:50.



Complications

1-infections

TPN requires a chronic IV access for the solution to run through, and the most common complication is infection of this catheter. Infection is a common cause of death in these patients, with a mortality rate of approximately 15% per infection, and death usually results from septic shock.

2-Blood clots

Chronic IV access leaves a foreign body in the vascular system, and blood clots on this IV line are common. Death can result from pulmonary embolism wherein a clot that starts on the IV line but breaks off and goes into the lungs.
Patients under long-term TPN will typically receive periodic heparin flush to dissolve such clots before they become dangerous.

3-Fatty liver and liver failure

Fatty liver is usually a more long term complication of TPN. The pathogenesis is due to using linoleic acid (an omega-6 fatty acid component of soybean oil) as a major source of calories

Reference:

1-M. Stawny,1 R. Olijarczyk,1 E. Jaroszkiewicz,2 and A. Jelińska. Pharmaceutical Point of View on Parenteral Nutrition. The Scientific World Journal Volume 2013 (2013).

(Review of Antibacterial Agents)

Antibiotic Overview

Questions to ask before selecting an antibiotic:
Host factors:
1. Normal or abnormal immune status?
2. Underlying disease that will affect selection &/or dosing? (e.g. renal failure)
3. Seriousness of the infection?

Pathogen factors

4. What are the most likely bugs based on the infection site?
5. Where was the infection acquired? (community or hospital setting?)
6. Local susceptibility patterns?

Drug factors

7. Bioavailability at infected site? (e.g. blood-brain barrier)
8. Broad or narrow spectrum?
9. Bactericidal or bacteriostatic?
10. Side effect profile?

General Principles

1. Be elegant. Use the antibiotic with the narrowest spectrum that covers the pathogen.
2. Be smart. If a patient is very sick or immunocompromised, it's OK to cover broadly for the first 1-3 days while you identify the pathogen as long as you narrow your choice as soon as possible.
3. Follow the 3 day rule: Broad spectrum antibiotics markedly alter the normal host flora about 3 days into therapy AND cultures should be back in 3 days so always reassess your antibiotic choices and narrow it when possible.
4. New isn't always better. When several antibiotics have similar coverage, select the least expensive.

Antibiotic Classes by Coverage

Gram positive coverage

1. Penicillins (ampicillin, amoxicillin) penicillinase resistant (Dicloxacillin, Oxacillin)
2. Cephalosporins (1st and 2nd generation)
3. Macrolides (Erythromycin, Clarithromycin, Azithromycin)
4. Quinolones (gatifloxacin, moxifloxacin, and less so levofloxacin)
5. Vancomycin (MRSA)
6. Sulfonamide/trimethoprim*(Increasing resistance limits use, very inexpensive)
7. Clindamycin
8. Tetracyclines
9. Chloramphenicol (§causes aplastic anemia so rarely used)
10. Other: Linezolid, Synercid (VRE)

Pseudomonas coverage

Ciprofloxacin
Aminoglycosides
Some 3rd generation cephalosporins
4th generation cephalosporins
Broad spectrum penicillins

Gram negative coverage

1. Broad spectrum penicillins (Ticarcillin-clavulanate, piperacillin-tazobactam)*
2. Cephalosporins (2nd, 3rd, and 4th generation)*
3. Aminoglycosides* (renal and ototoxicity)
4. Macrolides (Azithromycin)*
5. Quinolones (Ciprofloxacin)*
6. Monobactams (Azetreonam)*
7. Sulfonamide/trimethoprim*
8. Carbapenems (Imipenem)
9. Chloramphenicol

Anaerobic coverage

1. Metronidazole
2. Clindamycin
3. Broad spectrum penicillins
4. Quinolones (Gatifloxacin, Moxifloxacin)
5. Carbapenems
6. Chloramphenicol

Atypical coverage

1. Macrolides (Legionella, Mycoplasma, chlamydiae)
2. Tetracyclines (rickettsiae, chlamydiae)
3. Quinolones (Legionella, Mycoplasma, Chlamydia)
4. Chloramphenicol§ (rickettsiae, chlamydiae, mycoplasma)
5. Ampicillin (Listeria)

Drugs most commonly used in surgical operations (1)

Tramadol hydrochloride

An opioid analgesic indicated for Moderate to severe pain, Moderate to severe acute pain, Moderate to severe chronic pain and postoperative pain.

It produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

SIDE-EFFECTS

- Common or very common : Malaise.

Acetaminophen (Paracetamol

A Non-opioid analgesic indicated for Mild to moderate pain or Pyrexia.

Ranitidine

A H_2-receptor antagonist heal gastric and duodenal ulcers by reducing gastric acid output as a result of histamine H_2-receptor blockade; also used to relieve symptoms of gastro-esophageal reflux disease.

Omeprazole

A proton pump inhibitor inhibits gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell.

It is effective short-term treatment for gastric and duodenal ulcers; also used in combination with antibacterials for the eradication of Helicobacter pylori. Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery. It can be used for the treatment of dyspepsia and gastro-oesophageal reflux disease, also used for the prevention and treatment of NSAID-associated ulcers, also be used to control excessive secretion of gastric acid in Zollinger–Ellison syndrome; high doses are often required.

Ceftriaxone and Cefotaxime

Are third generation' cephalosporins with greater activity than the 'second generation' cephalosporins against certain Gram negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably Staphylococcus aureus.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis.

Ceftriaxone SIDE-EFFECTS

- Common or very common Calcium ceftriaxone precipitates in gall bladder—consider discontinuation if symptomatic. calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised)—consider discontinuation if symptomatic.
- Antibiotic-associated colitis Antibiotic-associated colitis may occur.

Meropenem

A carbapenem (beta-lactam antibacterial) have good activity against Pseudomonas aeruginosa, not active against meticillin-resistant Staphylococcus aureus and Enterococcus faecium. used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary tract infections.

SIDE-EFFECTS

▸ Common or very common Abdominal pain. diarrhoea. disturbances in liver function tests . headache. nausea. pruritus. rash. thrombocythaemia. vomiting.

Vancomycin

The glycopeptide antibiotic vancomycin has bactericidal activity against aerobic and anaerobic Gram positive bacteria including multi-resistant staphylococci. However, there are reports of Staphylococcus aureus with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci. Penetration into cerebrospinal fluid is poor. With intravenous use Vancomycin has a long duration of action and can therefore be given every 12 hours.

SIDE-EFFECTS

▸ Common or very common: With intravenous use Blood disorders, including neutropenia . interstitial nephritis. nephrotoxicity. ototoxicity (discontinue if tinnitus occurs). renal failure.

Metronidazole

Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa..

Metoclopramide

A dopamine receptor antagonist indicated for Symptomatic treatment of nausea and vomiting, Nausea and vomiting in palliative care, and hiccup in palliative care.

SIDE-EFFECTS

▸Common or very common: Extrapyramidal effects (especially in children and young adults (15–19 years old). galactorrhoea. gynaecomastia. hyperprolactinaemia. menstrual changes.

▸Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

Ciprofloxacin

A quinolone active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as Streptococcus pneumoniae and Enterococcus faecalis; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.
Although ciprofloxacin licensed for skin and soft-tissue infections, many staphylococci are resistant to and use should be avoided in MRSA infections.

SIDE-EFFECTS

▸ Common or very common: Flatulence. diarrhoea .dizziness. headache. nausea. vomiting.

▸ With intravenous use Pain at injection site. phlebitis at injection site.

References:

1. BNF 73. 2017.

College of Pharmacy/University of Baghdad

Clinical Pharmacy Dept.

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إعداد

فرع الصيدلة السريرية/كلية الصيدلة/جامعة بغداد

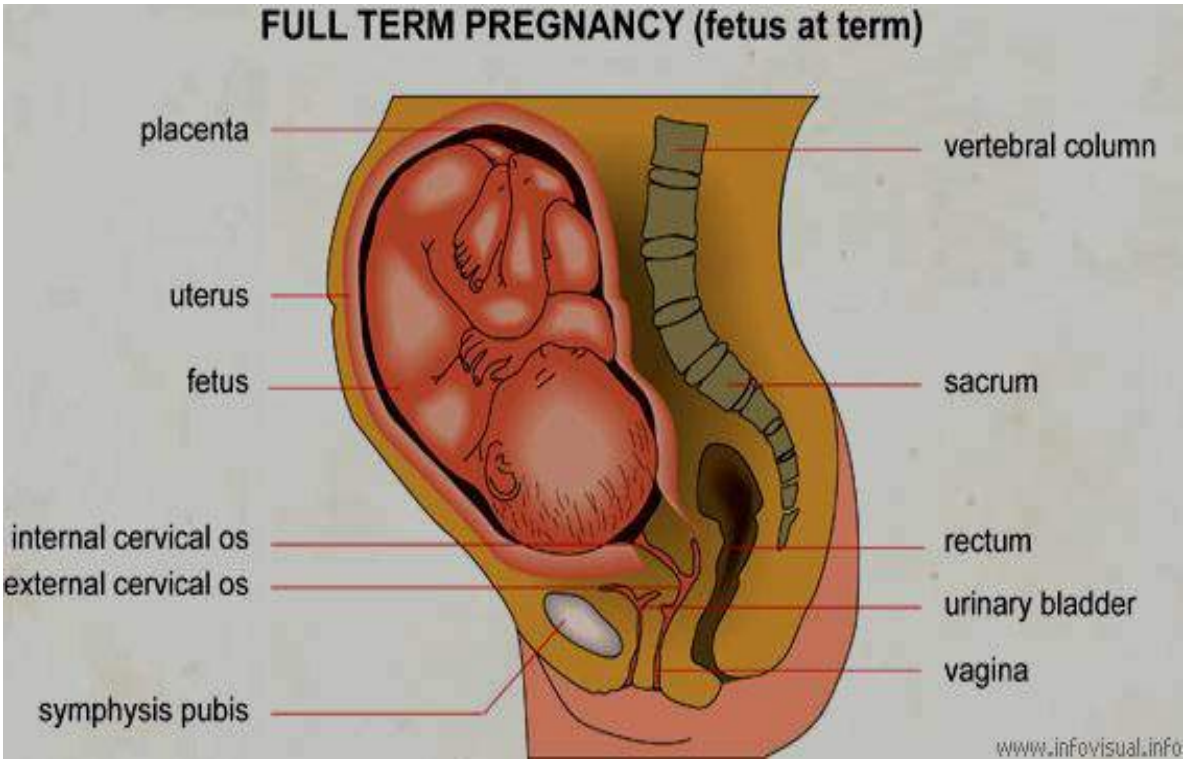


Table of Contents

History of the Patient

A- Patient demography: (age, weight and height).

B- Obstetric history: this required definition of some terms:

1- Parity: is the number of live birth at any age or stillbirth after 24 weeks of gestation[1].

2- Nullipara: describes a woman who has never delivered a fetus or fetuses beyond 20 weeks of gestation[2].

3- Multipara: describes a woman who has had two or more deliveries past 20 weeks of pregnancy[2].

4- Gravida: is the total number of pregnancies regardless of how they ended[1] (abortion, ectopic, normal pregnancy, hydatiform mole)[2].

5- Nullgravida: a woman who has never been pregnant[2].

6- Primigravidra: a woman who has been pregnant once[2].

e.g. a woman who has had two spontaneous abortions and three normal intrauterine pregnancies may be described as G_5 P_3 A_2.

C-Usual menstrual cycle history[2]

1- Age when period began (menarchae).

2- Regularity of cycle.

3- Duration of each period, length of cycle and first day of last period.

e.g. 13 5/28 regular: meaning that the period began at age of 13 years, last for 5 days and occur every 28 days.

An Overview of Pregnancy[3]

A- Signs and symptoms associated with pregnancy:

The signs of pregnancy can vary. Early signs can include nausea, breast tenderness, frequent urination, fatigue and headaches. Later signs can include heartburn, backache, constipation and fatigue.

1- **Nausea and vomiting:** Nausea predominantly affects women during the first three months of pregnancy. Hormonal changes are an attributing factor. **Hyperemesis gravidarum** is an extreme form of vomiting in pregnancy which can result in admission to hospital.

2- **Increased need to urinate**

3- **Headache**

4- **Feeling hot and sweaty**

5- **Dizziness and fainting.**

6- **Fatigue.**

7- **Varicose veins and hemorrhoids.**

8- **Epistaxis**

9- **Hypertension and pre-eclampsia** (see page 15).

10- **Thromboembolism**

11- **Oedema**

12- **Breathlessness.**

13- **Heartburn**

14- **Appetite and weight gain**

16- **Backache.**

17- **Leg cramp**

18- **Hyperpigmentation**

B- Prenatal period

1- Pregnancy is usually divided into **three trimesters** each one approximately 13 weeks [2].

2- Prenatal period is the development of the baby in the uterus and it is approximately 40 weeks. This is divided into[2]:

A- **Embryonic period:** is the first 8 weeks.

B- **Fetal period:** during 9-26 weeks.

C- **Perinatal period:** from 27 week till delivery.

C- EDD

The EDD is calculated by adding nine calendar months and seven days (around 280 days in total) to the date of the first day of the last menstrual period (LMP)[3]. (the period from fertilization of the ovum to birth is given as 40 weeks from LMP (gestation being regarded as 38 weeks) [4].

Some Commonly Used Abbreviations in Obstetrics

Abbreviations	Meanings	Abbreviations	Meanings
EDD	Expected Date of Delivery	FL	Fetal Life
FMP	First Missed Period	PT	Pregnancy Test
LMP	Last Menstrual Period	C/S	Caesarean Section
FM	Fetal Movement	NVD	Normal Vaginal Delivery
PCOS	Poly Cystic Ovary Syndrome	PUC	Premature Uterine Contractions
NTD	Neural Tube Defect	RDS	Respiratory Distress Syndrome

References:
1- Geoffrey Chamberlain. Obstetric by Ten Teachers. 8th edition. 2006.
2- Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.
3- Melanie Every, and Claire Hallam . Overview of Pregnancy. The Pharmaceutical Journal (Vol. 270) 8 February 2003. Pages: 194-196.
4-Pregnancy care. Chemist & Druggist 14 June 2003 . pages: 19-22.

Screening Tests and Investigations

1- Pregnancy Tests

The urine test rely on the detection of human chorionic gonadotropin (HCG) produced by the placenta. hCG levels increase shortly after implantation(1) (expected to become positive 3 days after implantation(2)), approximately double every 48 hours, reach a peak at 50-75 days, and fall to lower levels in the second and third trimesters. Laboratory and home pregnancy tests use antibodies specific for hCG.
These tests are performed on urine (1), (first morning specimen is recommended (2)) and are accurate at the time of the missed period or shortly after it(1).

2- Ultrasound

A- **Transvaginal ultrasound**
B- Transabdominal ultrasound
C- Doppler sonography

3- **Alpha-feto-protein test**

4- **Amniocentesis**

5- **Chorionic villus sampling (CVS)**

6- **Laparoscopy**

References:
1-Lawrence M. Tierney. Current Medical Diagnosis & Treatment, 45th edition (2006)
2-Frances Fischbach. A manual of laboratory and diagnostic tests. 6th edition. 2000

Abortion (Miscarriage)

Abortion: Is the termination (spontaneous or induced) of established pregnancy before 20 weeks of gestational age(1).

More than 60% of spontaneous abortions result from chromosomal defects due to maternal or paternal factors; about 15% appear to be associated with maternal trauma, infections, dietary deficiencies, diabetes mellitus, hypothyroidism, or anatomic malformations. There is no reliable evidence that abortion may be induced by psychic stimuli such as severe fright, anger, or anxiety. In about one-fourth of cases, the cause of abortion cannot be determined (2).

Note: By the ultrasonograsphic examination, the gestational sac can be identified at 5-6 weeks from the LMP, a fetal pole at 6 weeks, and fetal cardiac activity at 6-7 weeks. Serial observations are often required to evaluate changes in size of the embryo. A small, irregular sac without a fetal pole with accurate dating is diagnostic of an abnormal pregnancy(2).

Types of abortion:

1- **Threatened (مهدد) abortion:**

A- It refers to intrauterine bleeding before the 20th week of gestation, with or without uterine contraction, without cervical dilatation (i.e. closed cervix), and without expulsion of the products of conception (POC)(3). The pregnancy continues(2), but about 25-50% of threatened abortions eventually result in loss of pregnancy (1). B- Management

1- Ultrasonic examination to determine whether the fetus is present if so, whether it is alive (1).

2- Place the patient at bed rest for 24-48 hours(2) (or until 2 day after red loss has ceased (1)) followed by gradual resumption of usual activities, with abstinence from coitus and douching. Hormonal treatment with progesterone is contraindicated(2) (controversial)(3). Other therapy (e.g., tocolytics) is even more questionable(3).

3- If the patient is anxious and restless, diazepam 2 mg TID is recommended(1).

2- **Inevitable (حتمي) abortion:**

A- It is the intrauterine bleeding before the 20th gestational week, with continued cervical dilatation but without expulsion of the POC(3).

The passage of the products of conception is considered inevitable(2).

1- The uterus usually expels its content unaided(1).

3- If bleeding is heavy Ergometrine 500 mcg can be given(1).

3- Incomplete abortion:

A- It is the expulsion of some but not all of the POC before the 20th gestational week[3].

Some portion of the POC (usually placental) remains in the uterus. Only mild cramps are reported, but bleeding is persistent and often excessive[2].

B- Management

1- Insert IV line for fluid therapy or blood transfusion to prevent complication[1].

2- Prompt removal (under appropriates pain control) of any products of conception remaining within the uterus is required to stop bleeding and prevent infection[2].

4- Complete abortion

It is the expulsion of all the POC before the 20th gestational week. Pain ceases, but spotting may persist for a few days[3].

5- Missed abortion

A- Missed abortion occurs when the embryo dies but the POC are is retained in the uterus for several weeks or months[1].

Symptoms of pregnancy disappear. There is a brownish vaginal discharge but no free bleeding. Pain does not develop[2].

B- Management

1- Evacuate the conception surgically by aspiration is the method of choice for a missed abortion[2].

2- Prostaglandin E2 vaginal suppositories are an effective alternative[2].

6- Recurrent (Habitual:) abortion

It is the spontaneous, consecutive (م) loss of 3 or more nonviable pregnancies[3].

Recurrent abortion occurs in about 0.4-0.8% of all pregnancies. Abnormalities related to recurrent abortion can be identified in approximately half of the couples. If a woman has lost three previous pregnancies without identifiable cause, she still has a 70-80% chance of carrying a fetus to viability. If she has aborted four or five times, the likelihood of a successful pregnancy is 65-70%. Recurrent abortion is a clinical rather than pathologic diagnosis. The clinical findings are similar to those observed in other types of abortion (see above)[2].

Treatment

A. Preconception therapy[2]:

Preconception therapy is aimed at detection of maternal or paternal defects that may contribute to abortion. A thorough general and gynecologic examination is essential.

1- Polycystic ovaries should be ruled out.

2- A random blood glucose test and thyroid function studies (including thyroid antibodies) should be done.

3- Detection of lupus anticoagulant and other hemostatic abnormalities (proteins S and C and antithrombin III deficiency) and an antinuclear antibody test may be indicated.

4- Endometrial tissue should be examined to determine the adequacy of the response of the endometrium to hormones.
5- The hysteroscopy or hysterography used to exclude congenital anomalies.
6- Chromosomal analysis of both partners rules out balanced translocations (found in 5% of infertile couples).

B. Postconception Therapy

Provide early prenatal care and schedule frequent office visits. Complete bed rest is justified only for bleeding or pain. Empiric sex steroid hormone therapy is contraindicated[(2)].

Prognosis:

The prognosis is excellent if the cause of abortion can be corrected[(2)].

References:
1- Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.
2- Lawrence M. Tierney. Current Medical Diagnosis & Treatment, 45th edition (2006).
3- Martin L. Pernoll, M.D. Benson & Pernoll's. Handbook of Obstetric and Gynecology. 10th edition 2001.

Teratogenicity of Drugs

Congenital malformations can be defined as: non-reversible functional or morphological defects present at birth.

The Risk of Teratogenicity

Several factors determine the effects teratogenic drugs may have on the fetus during pregnancy, (Table 1).

Table 1[1].
Factors That Determine the Effects of Teratogens
1-Dose reaching fetus 2-Point in development when drug exposure occurs 3-Duration of exposure 4-Environmental factors 5-Susceptibility of the fetus

The duration of exposure and gestational age at exposure are very critical in the determination of teratogenic potential. During the period from conception to 2 weeks, there is a relative resistance to drug effects. Usually exposure during this time produces an "all or none" effect; that is, the zygote dies from exposure to the teratogen, or it is unaffected. The remainder of the first trimester is the most critical time for organ malformation[1]. Weeks 4 through 10, the period referred to as embryogenesis or organogenesis, is the most likely time for major congenital malformations to occur. Unfortunately, this is also a time when many women are unaware of their pregnancy. Drugs that reach the embryo at this point may produce abortion, no effect at all, an anatomic defect (teratogenesis), or a subtle metabolic or functional defect that may not be detected until later in life. During the second and third trimester, known as fetogenesis, drugs are less likely to be associated with major malformations, but they may influence neurologic development, growth, physiologic and biochemical functioning, mental development, and reproduction. Little is known about the exact time of the greatest risk for teratogenesis[1].

Teratogenic Effects

The most common teratogenic effects attributed to drugs are shown in table 2.

Some drugs, such as warfarin, phenytoin, and alcohol, cause a group of effects specific for exposure to that agent (Fetal warfarin syndrome, fetal alcohol syndrome, and fetal hydantoin syndrome).

Table 2[1] Effects of Teratogens on the Fetus
1-Spontaneous abortion
2-Defects in development
3-Malformations (major or minor)
4-Intrauterine growth retardation
5-Mental retardation
6-Carcinogenesis
7-Mutagenesis (causing genetic mutation

FDA Classifications of Drug Risk The Food and Drug Administration (FDA) instituted a rating system for drugs marketed after 1980 based upon their safety for use in pregnancy[1]. These categories are listed in Table 3.

Known Teratogens and Their Effects

The most recognized teratogens and the most dangerous time for exposure during pregnancy are shown in table 4. For more specific information on teratogenic potential or safe use during pregnancy, the reader is referred to reference no. 2.

Social Drugs:

Social or recreational drugs such as alcohol, caffeine, and nicotine may also be part of fetal exposure.

1- The heavy use of alcohol during pregnancy has been shown to lead to fetal alcohol syndrome, a pattern of defects including craniofacial defects, mild to moderate retardation, growth retardation, cardiac defects, and skeletal abnormalities. Since there are no known safe levels of alcohol during pregnancy, pregnant women should stop drinking alcohol completely during this period[1].

2- Caffeine has not proven to have a direct teratogenic effect in humans. Studies of caffeine use have suggested that heavy use (more than 7 or 8 cups of coffee daily) may be associated with perinatal complications, such as stillbirth, preterm birth, spontaneous abortion or low birth weight infants. The patients may be advised to limit their caffeine intake to perhaps one cup of coffee or its equivalent daily.

3- Smoking cigarettes has been linked to lower birth weight infants, and there may be an increased incidence of spontaneous abortion, stillbirth, preterm birth, and sudden infant death syndrome (SIDS) in the children of mothers who smoke during pregnancy.

Table 3 [1].

FDA Classification of Teratogenic Drug Risk	
Category	Description of Risk
A	No fetal risk shown in controlled human studies
B	No human data available and animal studies show no fetal risk or Animal studies show a risk but human studies do not show fetal risk
C	No controlled studies on fetal risk available for humans or animals or fetal risk shown in controlled animal studies but no human data available (Benefit of drug use must clearly justify potential fetal risk in this category)
D	Studies show fetal risk in humans (Use of drug may be acceptable even with risks, such as in life-threatening illness or where safer drugs are ineffective)
X	Risk to fetus clearly outweighs any benefits from these drugs

Table 4 [3]

Known Teratogens and Their Effects

No	Drug class	Trimester of Risk	Comment
1	ACE-I and Angiotensin-II receptor antagonists	1,2,3	Potential teratogen: cause renal tubular dysplasia, skull hypoplasia & oligohydramnios.
2	Alcohol	1, 2	Regular use is teratogen (cause fetal alcohol syndrome)
3	Aminoglycoside	2,3	Potential damage of VIII cranial nerve (auditory) might cause hearing loss.
4	Amiodarone	2, 3	Complication reported: hypothyroidism & neonatal goitre.

5	Androgens	1,2,3	Masculinisation of female fetus
6	Benzodiazepine	1,2, 3	Avoid regular use might cause neonatal withdrawal syndrome, hypothermia & hypotonia.
7	Beta-blockers	2, 3	May cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia.
8	Carbamazepine	1, 3	Teratogen risk of neural tube defect (NTD) & risk of neonatal hemorrhage due to vitamin K deficiency.
9	Carbimazole	2, 3	Neonatal goitre and hypothyroidism, might cause fetal malformation
10	Chloroamphenicol	3	Neonatal gray syndrome
11	Iron (parenteral)	1	Avoid in first trimester.
12	Lithium	1,2,3	Congenital defect (tricuspid valve malformation).
13	NSAID	3	With regular use closure of fetal ductus arteriosus, pulmonary hypertension of newborn & delay duration of labor.
14	Methotrexate	1,2,3	Teratogenic.
15	Phenytoin	1,3	Congenital malformation (fetal hydantoin syndrome), vitamin K deficiency causing neonatal bleeding.
17	Quinolones	1,2,3	Avoid, erosion of cartilage and arthropathy
18	Statins	1,2,3	Avoid, congenital anomalies reported.
19	Sulfonylurea	3	Neonatal hypoglycemia.
20	Tetracycline	1,2,3	Affect skeletal development, result in permanent yellow-brown staining of teeth.
21	Valproic acid	1, 3	Risk of NTD, craniofacial anomalies.
22	VIT A High dose	1	Excessive doses (>25000U/day) may be Teratogen.
23	Warfarin	1,2,3	Teratogen, fetal and neonatal hemorrhage.

References

1-Mary C. Gurnee, Mario F. Sylvestri, Teratogenicity of Drugs. US pharmacist.

2-Drugs in Pregnacy and Lactation. 6th ed. 2001. Briggs GG, et al. (CD ويتوفر على شكل)

3-BNF : 67.

Common Complications of Pregnancy

A- Liver and Gastrointestinal Diseases in Pregnancy 1-Nausea and Vomiting

General Considerations: Nausea and vomiting begin soon after the first missed period and cease by the fifth month of gestation. Up to three-fourths of women complain from nausea and vomiting during early pregnancy, with the vast majority noting nausea throughout the day. This problem exerts no adverse effects on the pregnancy and does not presage other complications[(1)].

Persistent, severe vomiting during pregnancy -hyperemesis Gravidarum- can be disabling and require hospitalization (can lead to metabolic acidosis, ketosis, hypovolemia, electrolyte disturbance & weight loss) [(2)]. Thyroid dysfunction can be associated with hyperemesis Gravidarum, so it is advisable to determine thyroid-stimulating hormone (TSH) and free T_4 values in these patients [(1)].

Treatment

A-Mild Nausea and vomiting: Reassurance and dietary advice (eating small but frequent meals, avoid greasy or spicy food, …...). Antiemetics, antihistamines, and antispasmodics are generally unnecessary to treat nausea of pregnancy. Vitamin B_6 (pyridoxine), 50-100 mg/d orally, is non-toxic and may be helpful in some patients[(1)].

B- Hyperemesis dravidarum: Hospitalize the patient with complete bed rest[(1)].

Protocol for the management of hyperemesis gravidarum includes: A- Fluid therapy: Normal saline 1 L + 20-40 mmol KCl 8 hourly.

B- Anti-emetic therapy: possible regimens include[(3)] :

1- Cyclizine 50 mg orally, im, iv, tid.

Note: Novidoxine ® tablet contains 25 mg Cyclizine and 50 mg B6.

2- Prochlorperazine (stemetil®) 5 mg orally tid , or 12.5 mg im, iv, tid.

3- Metoclopramide (plasil ®) 10 mg orally, im, iv, tid.

4- Chlopromazine (Largactil ®) 10-25 mg orally tid, or 25 mg im, tid.

5- Ondansetron 4-8 mg orally or iv q8h can be used for further refractory cases.

2- Gastro-esophageal Reflux Disease (GERD):

About two-third of women experience GERD or heart burn during and commonly in third trimester. Reflux of gastric contents lead to heart burn (aggregated by meal and recumbent position), water brash and dyspepsia[(3)].

Treatment

Non-pharmacological approach [(2)].

1- Eating small but frequent meals

2- Avoid recumbent position especially after meal & to use extra pillow to elevate head when sleeping.

Pharmacological approach:

1- Antacid therapy (taken 1-3 hr after meal & at bed time) [(2)].

2- Histamine 2-Recepter antagonists: like Ranitidine (Zantac) 150 mg BID in refractory case[(2)].

3- Metoclopramide maybe helpful also[(3)].

4-Proton Pump Inhibitors (PPI): like Omeprazole 20-40mg can be use and appear safe from limited data[(3)].

3- Acid Aspiration Syndrome (Mendelson's Syndrome)[(2)]

The pregnant patient in labor is at an increase risk of acid aspiration because of 1- Delay gastric emptying.

2- Increase gastric acidity.

3- Increase intra-abdominal & intragastric pressure.

These factors make regurgitation more likely.

Therefore women in the labor should be advised to eat light meal before coming to hospital.

Liquid antacid such as Maalox suspension is given every 3-4 hr during labor.

4- Obstetric Cholestasis (Intrahepatic cholestasis of pregnancy):

This is a liver disease specific to pregnancy. Characterized by pruritus affecting the whole body but particularly the palms and soles, and abnormal liver function tests. It most commonly occurs in the third trimester of pregnancy and any woman with pruritus without rash should have liver function tests[3]

Management:

1- Current guideline suggest that in the absence of premature labour, delivery should be induced at 37-38 weeks[3].

2- Vitamin K should be given to the mother (10 mg orally) from there time of diagnosis to reduce the postpartum hemorrhage[3].

3- Control of symptoms may be achieved by a combination of antihistamines and emollient. And these are insufficient, Ursodeoxycholic acid (UDCA) (300 mg 2-3 times per day)[2,3].

Following delivery, liver function tests return to normal. Recurrent of obstetric cholestasis is in subsequent pregnancies exceeds 90%[3].

References:

1- Lawrence M. Tierney. Current Medical Diagnosis & Treatment, 45th edition (2006) .

2- Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.

3- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence – based text for MRCOG.2004.

B- Diabetes mellitus in pregnancy

The pregnancy may be complicated by maternal diabetes mellitus where: A- Women with pre-existing diabetes (and are classified as either IDDM or NIDDM) B- Those developing carbohydrate intolerance during pregnancy (usually during third trimester) and are classified as Gestational Diabetes Mellitus (GDM) [1].

Diagnosis[2]:

The American Diabetes Association suggests the following targets for women who develop gestational diabetes during pregnancy. More or less stringent glycemic goals may be appropriate for each patient.

Before meal (preprandial): 95mg/dl or less.

1 h after meal (postprandial): 140mg/dl or less.

2 h after meal (postprandial): 120mg/dl or less.

Complications of GDM

1- Fetal: Medical problems encountered in infants born to diabetic mothers (whether GDM or pre-existing g DM) are shown in the following table 1 [3]:

Table 1: Medical Problems Encountered in Infants Born to Diabetic Mothers
1- Macrosomia (large babies: greater than 4 kg)
2- Hypoglycemia
3- Intrauterine growth retardation

4- Late fetal death
5- Cardiomyopathy (asymmetric septal hypertrophy)
6- Pulmonary hypertension
7- Idiopathic respiratory distress syndrome (RDS)
8- Hyperbilirubinemia
9- Hypocalcemia and hypomagnesemia
10-Thrombosis and abnormal clotting

2-Maternal:

A- Complications of GDM to pregnant women include[4]:

1- Pre-eclampsia and gestational hypertension.
2- Preterm labor.
3- Recurrent vulvo-vaginal infection (thrush, UTI …..).
4- Long-term development of diabetes mellitus.
5- Increased incidence of operative delivery (like Caesarean section).

B- Complications of preexisting diabetes to pregnant women include[4]:

1- Pre-eclampsia and gestational hypertension.
2- Preterm labor.
3- Recurrent vulvo-vaginal infection (thrush, UTI …..).
4- Increased incidence of operative delivery (like Caesarean section).
5- Exacerbation of pre-existing disease (retinopathy, nephropathy, and cardiac disease).

Management:

A- Pregnant woman with preexisting diabetes:

1- The aim is to maintain glucose level within these ranges and to avoid hypoglycemia and hyperglycemia[4].
2- Most patents with pre-pregnancy diabetes are taking insulin, and this therapy must be maintained during pregnancy[4].
3- For those on oral antidiabetic agents, it is advisable to convert them on insulin , because of the possible teratogenic effects and insulin facilitates a more effective manipulation of requirements as pregnancy progress[4].
4- In addition to insulin therapy, dietary advice is essential as it make glycemic control with insulin easier[4].

B-Pregnant woman with GDM:

1- The aim is to maintain fasting glucose level below 100 mg/dL (about 5.5 mmol/dL) , below 125 mg/dL (about 7 mmol/dL) for 2 hours post-prandial glucose level, and to avoid hypoglycemia and hyperglycemia[4].
2- Glucose control can be achieved through[4]:
1- Dietary control.
2- Insulin Therapy[5]: If dietary control does not reduce hyperglycemia sufficiently to reach the recommended glucose levels, insulin therapy is needed[5].

(Note: many practitioners will try to control glucose using dietary method for 2 weeks prior to switching to insulin)[4].
The initial starting insulin dose should be based on existing weight. And a total daily insulin dose of 0.5 to 0.7 units/kg is given. Two thirds of this dose is usually given in the morning and one third in the evening. Also, one third of each dose is given as rapid-acting insulin and the remaining dose as intermediate. The second dose may be divided so that rapid-acting insulin is given at suppertime and intermediate at bedtime[5].

C-Delivery:
The most common risk with GDM is macrosomia (large babies), which can lead to birth injuries. Clinical judgment often becomes the determinant on whether a Cesarean delivery is appropriate [5].

References:

1- Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.

3- Lincy S , Charlene Offiong . Pregnancy in a Diabetic Patient .US pharmacist
4-David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence – based text for MRCOG.2004.
5- M. Saljoughian. Gestational Diabetes . U.S. Pharm. 2004;9:HS-3-HS-HS.

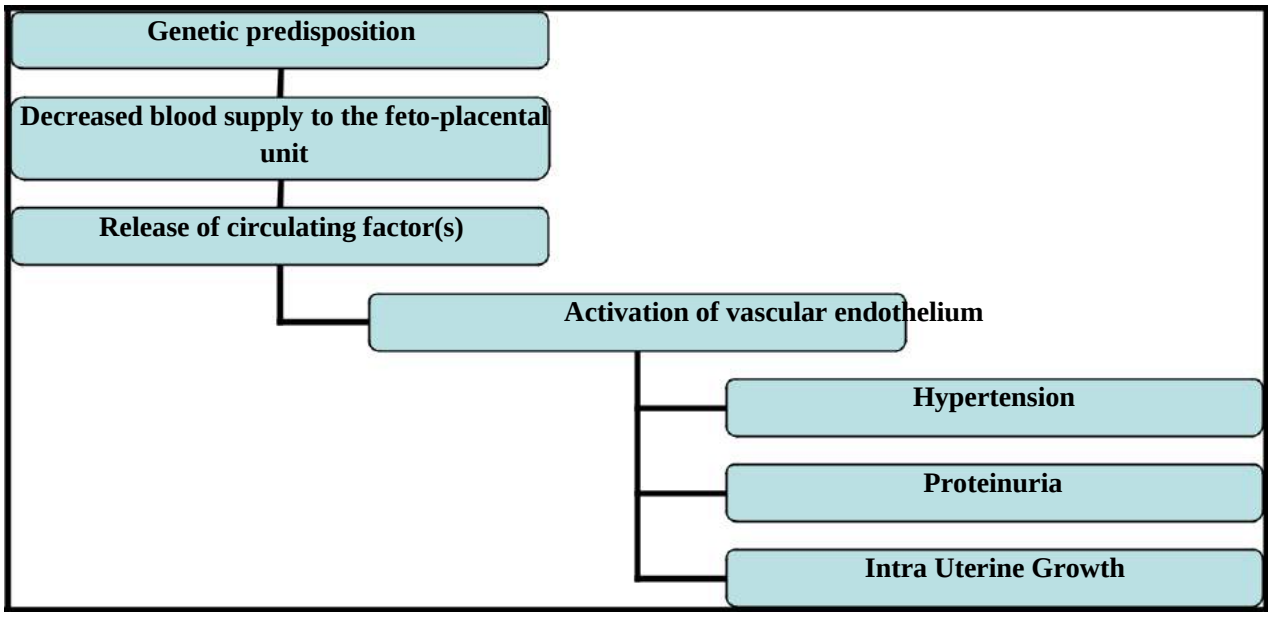
C- Pre-eclampsia

Definitions:

1-Pre-eclampsia is a disorder of pregnancy characterized by hypertension (blood pressure (BP) >140/90 mmHg) and clinically significant proteinuria (protein in urine >300 mg/24 h) developing after 20 weeks of gestation[1].
2-Eclampsia: is a convulsion occurring in women with established Pre-eclampsia, in the absence of other neurological or metabolic causes[2].
3-Chronic hypertension is defined as BP elevation (BP >140/90 mmHg) that has persisted since before conception or 20 weeks of gestation[1].
4-Gestational hypertension refers to hypertension that develops in previously normotensive women after 20 weeks of gestation without other symptoms of pre-eclampsia[1].

Pre-eclampsia

Etiology: Although the primary events leading to pre-eclampsia are still unclear, there are cascade of events leads to the clinical syndrome:



Sign and Symptoms of Pre-eclampsia[2]:

Symptoms: may be asymptomatic, headache, visual disturbance, and epigastric pain.
Signs: Elevation of BP, edema.

Investigations for Pre-eclampsia:

The diagnosis and severity of pre-eclampsia-eclampsia can be measured with reference to the six major sites in which it exerts its effects: the central nervous system, the kidneys, the liver, the hematologic and vascular systems, and the fetal-placental unit. By evaluating each of these areas for the presence of mild to moderate versus severe pre-eclampsia, the degree of involvement can be assessed, and an appropriate management plan can be formulated, (Table 1)[5].

Management

The only cure for pre-eclampsia is delivery of the fetus &while it is the best treatment for the mother, it is not always the best option for the fetus because prematurity is the leading cause of neonatal mortality & morbidity. Therefore, if the patient were > 34 week of gestation she would delivered of her fetus. While women with severe pre-eclampsia or eclampsia should be delivered after a period of stabilization, regardless of the gestation age of the fetus[4].

A-Mild to moderate pre-eclampsia

1-For mild to moderate pre-eclampsia-eclampsia, bed rest is the cornerstone of therapy. This increases central blood flow to the kidneys, heart, brain, liver, and placenta and may stabilize or even improve the degree of pre-eclampsia-eclampsia for a period of time. Bed rest may be attempted at home or in the hospital. Prior to making this decision, the provider should evaluate the following six sites to make an assessment about the severity of disease, (Table 1)[5]:

Table 1: Indicators of mild to moderate versus severe pre-eclampsia-eclampsia.

Site	Indicator	Mild to Moderate	Severe
Central nervous system	Symptoms and signs	Hyperreflexia Headache	Seizures Blurred vision Scotomas Headache Irritability
Kidney	Proteinuria	0.3–5 g/24 h	>5 g/24 h or catheterized urine with 4+ protein
	Uric acid	↑ > 4.5 mg/dL	↑↑ > 4.5 mg/dL
	Urinary output	> 20–30 mL/h	< 20–30 mL/h
Liver	AST, ALT, LDH	Normal	Elevated LFTs Epigastric pain Ruptured liver
Hematologic	Platelets Hemoglobin	> 100,000/mcL Normal range	< 100,000/mcL Elevated
Vascular	Blood pressure	< 160/110 mm Hg	> 160/110 mm Hg
	Retina	Arteriolar spasm	Retinal hemorrhages
Fetal-placental unit	Growth restriction Oligohydramnios Fetal distress	Absent May be present Absent	Present Present Present

AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; LFTs = liver function tests.

2-Antihypertensive therapy should be use especially if diastolic BP reaches 100 mmHg

a- Methyldopa (aldomet ®) is centrally acting α2 agonist. It is the most commonly used antihypertensive for hypertension during pregnancy. Usual dose is 750mg /day i.e. (250mg q 8 h) increase to 2-3gm/day[4].

Adverse effect: Lethargy, somnolence, drowsiness & potential depression[4].

Labetalol (Trandate ®) which is α and β blocker. This agent has good safety record in pregnancy [2]. Daily dose is 400-800mg [4].

c- Calcium channel blocker(CCB).

Administration of CCB nifedipine appears to be safe and is used commonly to treat hypertension during pregnancy particularly severe hypertension unresponsive to standard treatment but some adverse effect reported (flushing, headache & reflex tachycardia & ankle edema) [4].

B-Severe Pre-eclampsia

Symptoms are more dramatic and persistent. The blood pressure is often quite high, with readings over 160/110 mm Hg. Thrombocytopenia (platelet counts < 100,000/mcL) may be present and progress to disseminated intravascular coagulation. Severe epigastric pain may be present from. The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is a form of severe Pre-eclampsia [5].

Mean arterial pressure (MAP): calculated as diastolic blood pressure + [(systolic diastolic)/ 3] is used to guide management and most protocols recommend the use of IV antihypertensive therapy if the MAP is > 125 mmHg [3].

IV labetalol or hydralazine are most common drugs used[2]. If one agent is ineffective, or if the side effect occur (e.g. tachycardia with hydralazine), the other agent can be used [3].

1- Hydralazine: Hydralazine (given IV) is the most commonly used treatment of severe hypertension in pre-eclamptic women. Since it is a potent vasodilator, hydralazine may increase a patient's risk of decreased intervillous blood flow and thus may impair uteroplacental perfusion. Consequently, some clinicians pretreat patients with plasma volume expansion (colloids) in an effort to prevent hypotension and fetal distress [1].

Dosing regimen (many regional protocols) for example:

Bolus dose of 5 mg IV if the mean arterial pressure (MAP) remains > 125 mmHg, followed by a further boluses of 5 mg (every 20-30 minutes) up to a cumulative dose of 15 mg. Once the MAP is < 125 mmHg, an infusion of 10 mg /hour is commenced, doubling (if necessary) at 30 minutes intervals, until a satisfactory response or a dose of a 40 mg/hour is attained[3].

2-Labetalol (given IV) is currently recognized as a second-line antihypertensive agent for treatment of severe hypertension in pre-eclamptic women and is reserved for use when target blood pressure is not achieved with hydralazine. It should not be administered to patients with asthma or congestive heart failure, as it is a nonselective beta-receptor antagonist [1].

Dosing regimen (many regional protocols) for example :

Bolus dose of 20 mg IV if the mean arterial pressure (MAP) remains > 125 mmHg, followed at 10-minutes intervals by 40, 80, 80 mg boluses up to a cumulative dose of 220 mg. Once the MAP is < 125 mmHg, an infusion of 40 mg /hour is commenced, doubling (if necessary) at 30 minutes intervals, until a satisfactory response or a dose of a 160 mg /hour is attained[3].

3-Nifedipine (Adalat ®): is also common choice to treat severe hypertension during pregnancy. Nifedipine 10 mg cap is given orally every 30-60min until the diastolic BP decrease < 110mmHg[4].

C-Eclampsia:

The occurrence of seizures defines eclampsia. The other abnormal findings of severe pre-eclampsia are also observed with eclampsia[5]. It is associated with high mortality rate[4].

1- Magnesium sulphate is the drug of choice for the prevention of recurrent seizures in eclampsia. Regimens may vary between hospitals. Calcium gluconate injection is used for the management of magnesium toxicity [6].

Prevention of seizure recurrence in eclampsia, initially by intravenous injection over 5-15 minutes, 4 g, followed by intravenous infusion, 1 g/hour for at least 24 hours after last seizure; if seizure recurs, additional dose by intravenous injection, 2 g (4 g if body-weight over 70 kg) [6].

Urinary output is checked hourly and the patient assessed for signs of possible magnesium toxicity such as loss of deep tendon reflexes or decrease in respiratory rate and depth, which can be reversed with calcium gluconate [5]. 1g (10ml of 10% calcium gluconate) should given iv over 3 minutes[4].
2-Diazepam (valium®) 10 mg is suitable alternative[4].
3-Phenobarbital (luminal®) also can be use [4].
If seizure does not resolved by medical intervention, termination of pregnancy is recommended [4].

Additional Points in management

Premature delivery of the fetus is often required in severe pre-eclampsia. Therefore, corticosteroid should be given to enhance fetal lung maturity[3].
If immaturity is present, corticosteroids dexamethasone 12 mg, two doses intramuscularly 12 hours apart) can be administered to the mother. Fetuses between 26 and 30 weeks of gestation can be presumed to be immature, and corticosteroids should be given [5].

The Role of Prophylaxis

A-low dose of aspirin (e.g. 75mg/day) : use to reduce the incidence of pre-eclampsia but it increase the incidence of abruptio-placenta, therefore low dose of aspirin use only in high risk group (e.g. those with previous pre-eclampsia , multiple gestation or those with chronic hypertension, DM)[2,3,4].
2-Vitamin C and E (act as anti-oxidants) and calcium:
Clinical trials published in recent years have investigated various treatments for pre-eclampsia.
Many studies had shown that the use of vitamin C and E (act as anti-oxidants) or calcium reduce the likelihood of pre-eclampsia but the subject is of an ongoing trials[3].

References:

1- Christina Song. Preeclampsia-Eclampsia, Pathogenesis, Diagnosis and Treatment. US pharmacist
2- Geoffrey Chamberlain. Obstetric By ten teachers. 8th edition. 2006.
3- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence – based text for MRCOG.2004.
4- Neville F. Hacker Essentials of Obstetric and Gynecology. 4th edition. 2004.

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D-Preterm Labor

Definitions:

In pregnancy, **term** refers to the period from 37-41 weeks of gestation, with **preterm** occurring between the 24-36 weeks of gestation[1].

Etiology

1- Spontaneous preterm birth (idiopathic).
2- Infections (like bacterial vaginosis).
3- Over distension (like in multiple pregnancy).
4- Vascular (like antepartum hemorrhage and abruption).
5- Intercurrent illness (serious infections like pyelonephritis, pneumonia, …)

Risk factors (للاطلاع)

Non-modifiable (major) 1-previous preterm birth 2-Twin pregnancy 3-uterine abnormality	Non-modifiable (minor) 1-Parity = 0 or >5 2-Teeneger having second or subsequent Babies.
modifiable 1-Smoking 2-Body mass index < 20 (underweight)	Factors in current pregnancy: 1-recurrent antepartum hemorrhage 2-intercurrent (e.g. sepsis) 3-any surgery

Clinical Finding[1,2]:

The diagnosis of preterm labour is difficult in the absence of advanced dilatation.
1- Symptoms such as low back pain or cramping are often cyclical.
2- Vague compliance such as pelvic pressure or increased vaginal discharge are usually common.
3- The co-existence of vaginal bleeding is serious mark.

Management:

1-Management of asymptomatic high risk women: A- Bacterial vaginosis: Bacterial vaginosis has been associated with an increased risk of preterm birth. Oral 5-7 days course of metronidazole or clindamycin significantly
lower the risk of preterm birth, by 60% in high risk women positive for bacterial vaginosis[1,2].
B- Asymptomatic bacteriuria: Asymptomatic bacteriuria carry an increased risk for preterm birth. This risk is reduced significantly by appropriate antibiotic course[1,2].
C-Group B streptococcal genital colonization: Group B streptococcal genital colonization has been linked to prematurity. Therefore mother at risk of preterm delivery should be screened for Group B streptococcal genital colonization, if positive, then a appropriate antibiotics course should be offered[1,2].
D-Lifestyle modification: There is no evidence that lifestyle modification improve outcomes. And in some studies hospitalization for bed rest led to an increase in preterm birth[1,2].

2-Management of symptomatic women:

A- Steroid: Current evidence shows that a single course of maternal steroid (2 injections 12-24 hours apart) given between the 28 and 32 weeks' gestation and received within 7 days of delivery results in a marked neonatal outcome (mainly due to the reduction in the neonatal respiratory distress syndrome (RDS)), maximum benefit from the injection is seen after 48 hours.

However courses received less than 48 hours, or more than 7 days, as well as courses given below 28 weeks are still lead to benefits[1, 2].

B-Tocolytics (Drugs that inhibit uterine contraction): There little evidence about the benefit of tocolytics agents like (ritodrine, Beta-agonists, Oxytocin antagonist (atosiban), magnesium sulphate, nifedipine (10-20 mg orally every 6 hours), and glyceryl trinitrate (GTN)). Therefore the use of tocolytics is usually inappropriate if steroids have been given and intensive care cots are available[1,2].

References:

1- Geotffrey Chamberlain. Obstetric by Ten Teachers. 8th edition. 2006.

2- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence-based text for MRCOG.2004.

E-Prevention of Hemolytic Disease of the Newborn

The antibody anti-Rh_o (D) is responsible for most severe instances of hemolytic disease of the newborn. If an Rh_o(D)-negative woman carries an Rh_o(D)-positive fetus, she may develop antibodies against Rh_o(D) when fetal red cells enter her circulation during small fetomaternal bleeding episodes in the early third trimester or during delivery, abortion, ectopic pregnancy, abruptio placentae, or other antepartum bleeding problems[1].

This antibody, once produced, remains in the woman's circulation and poses the threat of hemolytic disease for subsequent Rh-positive fetuses. Passive immunization against hemolytic disease of the newborn is achieved with Rh_o(D) immune globulin, a purified concentrate of antibodies against Rh_o(D) antigen. The Rh_o(D) immune globulin (one vial of 300 mcg I.M) is given to the mother within 72 hours after delivery (or spontaneous or induced abortion or ectopic pregnancy)[1].

The antibodies in the immune globulin destroy fetal Rh positive cells so that the mother will not produce anti-Rh_o(D). During her next Rh-positive gestation, of hemolytic disease of the newborn will be prevented. An additional safety measure is the administration of the immune globulin (300 mcg of anti-D immunoglobulin) at the 28th week of pregnancy. The passive antibody titer that results is too low to significantly affect an Rh-positive fetus. The maternal clearance of the globulin is slow enough that protection will continue for 12 weeks[1].

References:

1-Lawrence M. Tierney. Current Medical Diagnosis & Treatment, 45th edition (2006) .

F-Toxoplasmosis

Toxoplasma gondii, the cause of toxoplasmosis, is an intracellular protozoan parasite[1].

Epidemiology and etiology:

The definitive host of this organism is the domestic cat. Transmission may occur transplacentally (from the mother to fetus), by ingestion of raw or undercooked meat containing protozoan cysts, or by exposure to oocysts in soil contaminated with cat faeces[1].

Congenital Toxoplasmosis:

Congenital toxoplasmosis arises almost exclusively when the mother develops a primary infection during gestation. Congenital infection almost never develops from latent toxoplasmosis acquired before pregnancy[2].

The risk of fetal infection depends on when maternal infection occurs where it is rises throughout gestation from about 10% during the first trimester to about 60% during the third trimester[2].

Presentation

Adults and adolescents with primary infection are generally asymptomatic. Therefore specific treatment for non-pregnant adults and adolescents is not required[1].

The consequences of fetal infection also depend on when infection occurs A-Early fetal infection can results in more severe sequelae: (Congenital chorioretinitis, cerebral calcification, hydrocephalus, ….), spontaneous abortion is common[1].

B- Late fetal infection can results in less severe sequelae: The majority of infants are born without any obvious problems[1].

Diagnosis: By serological tests [1].

Management:

A- The prevention of congenital toxoplasmosis is of major importance:

1- Pregnant women should minimize contact with cats[2].

2- They should wash their hands after contact with cats[2].

3- In addition, pregnant women should wash all fruits and vegetables before eating them and should not eat undercooked meat[2].

B- If maternal infection is confirmed, the macrolide antibiotic Spiramycin (in a 3 weeks course of 2-3 gm /day)[3] should be administered to reduce the likely of fetal infection (reduced by about 60%). Spiramycin should be started as soon as maternal infection has been confirmed, as the longer the delay the greater risk of fetal damage[1].

C-Termination of pregnancy is also an option if infection occurs early in gestation or if there is an ultrasound evidence of congenital infection[1].

References:

1- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence – based text for MRCOG.2004.
2- David C. Dale. Infectious Diseases: The Clinician's Guide to Diagnosis, Treatment, and Prevention. 2003)
3-Geoffrey Chamberlain. Obstetric By ten teachers. 8th edition . 2006.

Labor

False labor: during the last 4-8week of gestation, the uterus undergoes irregular contraction that are painless and they are not associated with progressive cervical dilation or effacement(1).

Stages of labor: there are three stages of labor:

A-First stage: consists of two phases:
1- Latent phase during which cervical effacement & early dilation occur(1).
2- Active phase more rapid cervical dilation occurs with strong regular uterine contraction(1).

B-Second stage: starts with complete cervical dilation & end with the delivery of the fetus(1).

C-Third stage of labor is the time between delivery of fetus & the delivery of placenta(1).

References:
1- Neville F. Hacker Essentials of Obstetric and Gynecology. 4th edition 2004.

Induction and Augmentation of labour

Induction: is the process whereby labour is initiated by artificial mean(1).

Common Indications for induction of labour:
1- Post dates (i.e. 12 days or more beyond EDD) (2) (pregnancy passing 41 weeks)(3).

3- Maternal request(3).
4- Maternal disease: like: diabetes mellitus, hypertensive /renal diseases(3).
5- Pregnancy-related conditions: like: Pre-eclampsia, placental abruption(3).
6- Fetal conditions: like: Intrauterine growth restriction(3).

Induction and Augmentation of labour are done either:
A- Mechanically by special procedures.

B- Pharmacologically (through administration of prostaglandin E2 like Dinoprostone & E1 Like misoprostol (cytotec ®)) or low dose oxytocin[1].

1-Dinoprostone is available as vaginal tablets, pessaries and vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.
2-Oxytocin (Petocin ®, Syntocinon ®) is administered by slow intravenous infusion to induce or augment labour. Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.
3-Misoprostol is given orally or vaginally for the induction of labour.

Guidance for induction of labour

1-Dinoprostone is preferable to oxytocin for induction of labour in women with intact membranes, regardless of parity or cervical favorability[4].
2-Dinoprostone or oxytocin are equally effective for the induction of labour in women with ruptured membranes, regardless of parity or cervical favorability[4].
3-Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins; when used to induce labour, the recommended dose of oxytocin by intravenous infusion is initially 1 mU (0.001 U) - 2 mU (0.002) units/minute increased at intervals of at least 30 minutes until a maximum of 3-4 contractions occur every 10 minutes (0.012 units/minute is often adequate); the maximum recommended rate is 32 mU/minute[4] .
Note: Oxytocin should be used in standard dilutions of 10 units/500 mL (infusing 3 mL/hour delivers 1 mU/minute) or, for higher doses, 30 units/500 mL (infusing 1 mL/hour delivers 1mU/minute) [4].

References

1- Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.
2- Geoffrey Chamberlain. Obstetric by Ten Teachers. 8th edition 2006.
3- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence-based text for MRCOG.2004.

Obstetric Hemorrhage

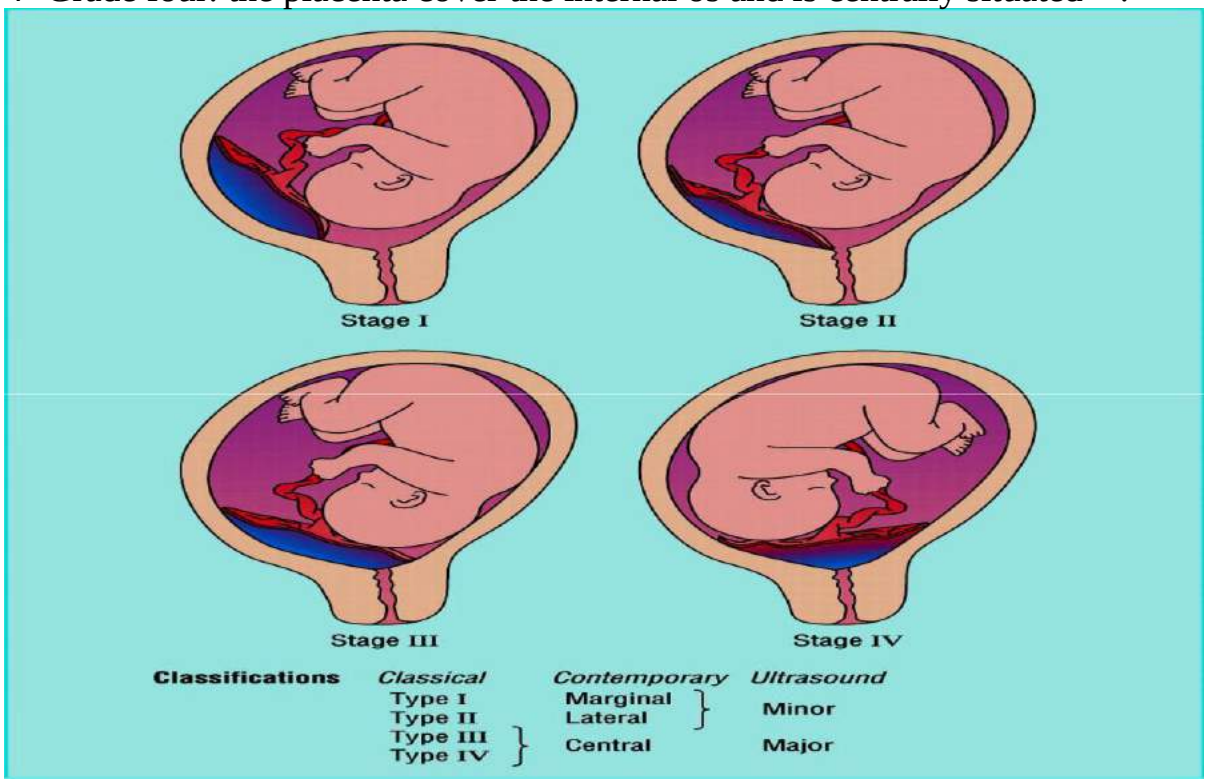
A-Antepartum hemorrhage

Vaginal bleeding in the third trimester complicates about 4% of all pregnancies. The main causes are:

1-Placenta Praevia

A-Definition: is defined as the presence of placental tissue over or near the internal cervical os[1]. It is graded in two ways as either grade 1- 4 or major/minor[2].
1- Grade one: The placental edge is in the lower uterine segment but does not reach the internal os[2].
2- Grade two: The placenta reach the edge of the lower uterine segment but does not cover the internal os[1].
3- Grade three: The placenta cover the internal os and is asymmetrically situated[1].

4- Grade four: the placenta cover the internal os and is centrally situated[2].



The grades 1 and 2 represent the minor placenta praevia while the grades 3 and 4 are the major[2].

B- Predisposing factor of placenta praevia:

Predisposing factor of placenta praevia are [3] :

2- Increasing maternal age.
3- Prior placenta praevia.
4- Multiple gestations.

C-Presentation:

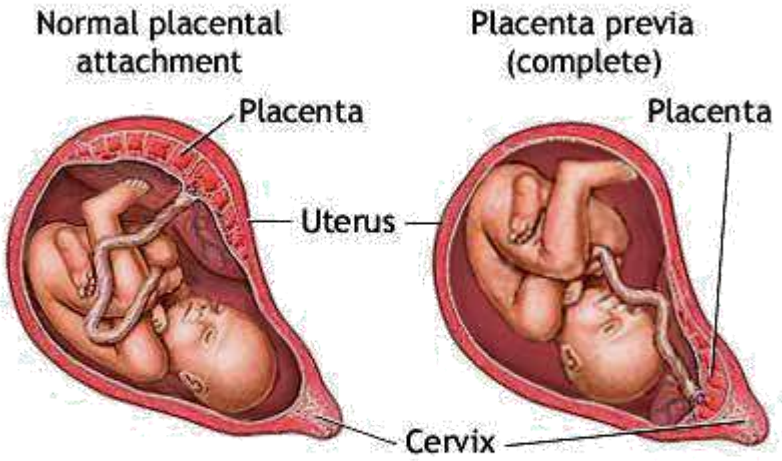
Placenta praevia usually presents with painless vaginal bleeding[2].

D-Diagnosis

Diagnosis is done by ultrasound [3].

E-Management

Management depends on the severity of bleeding and the gestational age of the fetus[3].
1-With preterm pregnancy, the goal is to attempt to obtain fetal maturation without compromising the mother health[3].
2-If the bleeding is excessive, the delivery must be accomplished by Cesarean section irrespective of gestation[3].



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2- David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence-based text for MRCOG.2004.
3-Neville F. Hacker Essentials of Obstetric and Gynecology. 4th edition 2004.

2-Apruptio Placenta (Placental abruption)

A-Definition: Abruption is defined as bleeding following premature separation of normally sited placenta(1).

B-Risk factors
1- Maternal hypertension(2).
2- Trauma(2).
3- Polyhydroaminos with rapid uterine decompression(2).
4- Premature rupture of the membrane(2).
5- Smoking(2).
6- Previous abruption(1).

C-Presentation:
The patient presents with painful vaginal bleeding in association with uterine tenderness, hyperactivity and increased tone(2).

D-Diagnosis:
The diagnosis of placenta abruption is primarily a clinical one(1). Ultrasound (U/S) detect only 2% of abruption (2).

E-Complications(3):

1-Effects on the mother: Hypovolemic shock, disseminated intravascular coagulation (DIC), acute renal failure and maternal mortality.
2-Effect on the fetus: Perinatal mortality and Intrauterine growth restriction.

F-Management

1-If the abruption is small, fetus is uncompromised and the mother is well, conservative management may be utilized(1).
2-Vaginal delivery is the preferred method of delivery for a fetus that has died secondary to placental abruption(4).
3-Cesarean section is indicated when fetal compromise is present and the fetus is likely to survive (1).

References:
1-David M. Luesley and Philip N. Baker. Obstetric and Gynecology. An evidence – based text for MRCOG.2004.
2-Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .2004.

4-e-medicine.Abruptio placenta.

3-Uterine Rupture

Classically rupture is characterized by intense abdominal bleeding & some vaginal bleeding(1).
Sometimes it is possible to repair the uterus, but frequently the only safe forward is hysterectomy (2).

References:
1-Neville F. Hacker Essentials of Obstetric and Gynecology .4th edition .20042-Ten teachers.

B-Postpartum Hemorrhage (PPH)

Definitions:

1-Primary postpartum hemorrhage: is defined as blood loss in excess of 500 ml from the genital tract following (but within 24 hours) of the delivery of the baby(1).
If the blood loss is greater than 1000 ml or 1500 ml, it considered massive postpartum hemorrhage(1).
2-Secondary postpartum hemorrhage: is the blood loss from the genital tract of volume greater than expected after the first 24 hours but within the first 6 weeks of delivery(1).

Etiology:

A-Primary postpartum hemorrhage caused by:

1-Uterine atony (when the uterus is not contracted) (anesthesia, marked uterine distention, prolonged or excessive oxytocin administration[2]. It is the major cause of postpartum hemorrhage and account for about 90% of cases[3].
2-Placental problems (abruptio placenta, placenta praevia, incomplete placental separation)[2].
3-laceration(s) of the birth canal, rupture of the uterus, or mismanagement of the third stage of labour[2].

B-Secondary postpartum hemorrhage is usually due to retained products of conception (like placental tissue) (which can be removed by curettage) [2, 4].

Complications:
The complications of postpartum hemorrhage include shock, anemia, infection and disseminated intravascular coagulation (DIC) (a life threatening complication of massive hemorrhage [2 ,4].

Treatment:
Significant PPH is an obstetric emergency.
1- Obtain a CBC, coagulation panel, blood type and cross match.
2- Ensure an open IV line.
3- Closely monitor further blood loss and vital signs.
4-Initiate appropriate blood component replacement (fresh frozen plasma, packed platelets , ….)
5- Manually deliver the partially separated placenta.
6-Explore the uterus, and carefully remove any retained products of conception (this may require uterine curettage).
7-To reverse uterine atony after placental recovery: by performing gentle uterine massage. And by giving uterotonic drugs (oxytocin). If that fails to slow bleeding, consider the addition of prostaglandins or ergometrine. (See Uterotonics below).
8-Hysterectomy or ligation of uterine arteries or hypogastric arteries may be lifesaving in certain extreme cases.

Uterotonics:
A-Suggested dosage of Uterotonics [1]:

Uterotonic	Route of administration	Dosage
Oxytocin	I.V	Bolus dose of 5 IU, followed by infusion of 40 IU in 40 mL of saline run at 10 mL/hour.
Syntometrine ®(ergometrine maleate 500 µg, oxytocin 5 u./mL)	I.M	1 mL
Ergometrine	I.V /I.M	250-500 mcg
Carboprost	I.M	250 mcg every 15 -90 min(total cumulative dose is 2 mg) (i.e. 8 doses)
Misoprostol	Rectally	800 mcg
Gemeprost	Intrauterine	1-2 mg.

Caesarean Section

Definition: Caesarean section refers to an operation that is performed to deliver the baby via a transabdominal route.

Some of the indications for Caesarean section:

1-Patient has a previous history of Caesarean section.
2-Baby is too big to pass safely through the vagina.
3-The baby's buttock or feet enter the birth canal first instead of the head, this is called breech position.
4-The baby's shoulder enter the birth canal first instead of the head this is called shoulder or transverse position.
5-Labour is too slow or stops (no dilation of cervix after time is finish).
6-There are problems with the placenta (placenta praevia or abruption) which may cause dangerous bleeding during vaginal delivery.
7-Mother has infection like genital herpes.
8-Twins, triplets or more.
9-Baby has problem during labor (such as a slow heart rate) this is called fetal distress.
10-Mother has DM or high BP.

Ectopic Pregnancy

Ectopic pregnancy is derived from the Greek word *ektopos*, meaning out of place, and it refers to the implantation of a fertilized egg in a location outside of the uterine cavity, including the fallopian tubes [1] (About 98% of ectopic pregnancies are tubal[2]), cervix, ovary, cornual region of the uterus, and the abdominal cavity.

This abnormally implanted gestation grows and draws its blood supply from the site of abnormal implantation. As the gestation enlarges, it creates the potential for organ rupture because only the uterine cavity is designed to expand and accommodate fetal development. Ectopic pregnancy can lead to massive hemorrhage, infertility, or death [1].

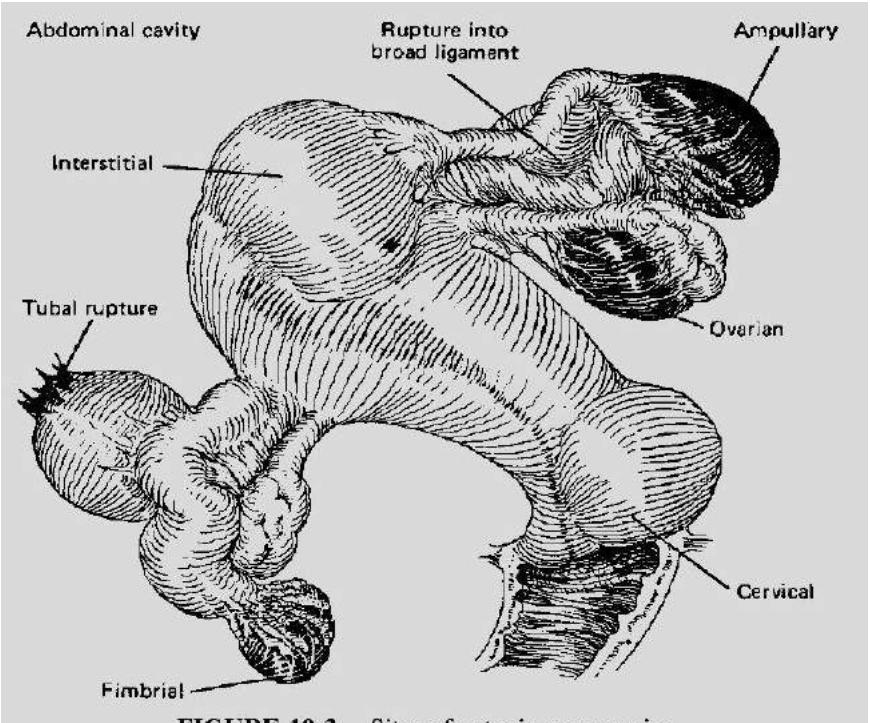

FIGURE 10-3. Sites of ectopic pregnancies.

Any condition that prevents or retards migration of the fertilized ovum to the uterus can predispose to an ectopic pregnancy, including a history of infertility, pelvic inflammatory disease, ruptured appendix, and prior tubal surgery. Combined intrauterine and extrauterine pregnancy (heterotopic) may occur rarely [2].

Etiology[1]:

The following risk factors have been linked with ectopic pregnancy: 1-Pelvic inflammatory disease (The most common cause is infection caused by *Chlamydia trachomatis).*

2-History of prior ectopic pregnancy.

3-History of tubal surgery and conception after tubal ligation.

4-Use of fertility drugs (clomiphene citrate or injectable gonadotropin) or assisted reproductive technology.

5-Use of an intrauterine device.

6-Increasing age, smoking, and others.

Diagnosis:

A-Clinical Findings

The classic clinical triad of ectopic pregnancy is pain (secondary to tubal distention or rupture), amenorrhea, and vaginal bleeding. Unfortunately, only 50% of patients present typically. Some patients may be collapsed and shocked from bleeding[1,3].

B-Laboratory Findings

Blood studies may show anemia. Quantitative serum pregnancy tests will show levels generally lower than expected for normal pregnancies of the same duration. If pregnancy tests are followed over a few days, there may be a slow rise or a plateau rather than the near doubling every 2 days associated with normal early intrauterine pregnancy or the falling levels that occur with spontaneous abortion[2].

C-Imaging

Ultrasonography can reliably demonstrate a gestational sac 6 weeks from the LMP and a fetal pole at 7 weeks if located in the uterus. An empty uterine cavity raises a strong suspicion of extrauterine pregnancy, which can occasionally be revealed by endovaginal ultrasound. Specified levels of serum hCG have been reliably correlated with ultrasound findings of an intrauterine pregnancy. For example, an hCG level of 6500 mU/mL with an empty uterine cavity by transabdominal ultrasound is virtually diagnostic of an ectopic pregnancy. Similarly, an hCG value of 2000 mU/mL or more can be indicative of an ectopic pregnancy if no products of conception are detected within the uterine cavity by transvaginal ultrasound[2].

D-Special Examinations

Laparoscopy is the surgical procedure of choice both to confirm an ectopic pregnancy and in most cases to permit pelviscopic removal of the ectopic pregnancy[2].

Treatment

When a patient with an ectopic pregnancy is unstable or when surgical therapy is planned, the patient is hospitalized. Blood is typed and cross-matched. Surgical treatment is definitive[2].

In a stable patient, a single dose methotrexate IM (50 mg/m^2 or approximately 1mg/kg)[4] is acceptable medical therapy for early ectopic pregnancy[2].

Iron therapy for anemia may be necessary during convalescence. Give Rh_o(D) immune globulin (300 mcg) to Rh-negative patients[2].

Prognosis

Repeat tubal pregnancy occurs in about 12% of cases. This should not be regarded as a contraindication to future pregnancy, but the patient requires careful observation and early ultrasound confirmation of an intrauterine pregnancy[2].

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Heavy and Irregular Menstruation

Definitions:

Menorrhagia: heavy (usually more than 80 ml/period) regular blood loss occurring over several consecutive cycles. Regular heavy bleeding without an identified local cause is also called Dysfunctional Uterine Bleeding (DUB) [1].

Treatment

A-Non-Hormonal therapy: For women with menorrhagia requiring non-hormonal therapy, antifibrinolytic drugs (e.g. tranexamic acid (cyklokapron®)) is used for the reduction of blood loss. While the NSAIDs (like mefenamic acid) for the associated menstrual pain[1].

B-Combined Oral Contraceptives (COCP): COCP is effective for menorrhagia (reduce both the pain and bleeding) provided that there are no contraindications[1]. C-Progestogens: Cyclical progestogens are effective for menorrhagia when given for 21 days out of 28 days (between the day 5 and 26 of cycle), (e.g. norethisterone(Primolut N®) 5 mg tid for 21 days[1]. (BNF give different time dosage 5 mg 3 times daily for 10 days to arrest bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26)[2].

Also, continuous high dose progestogens (e.g. depot preparations like medroxyprogesterone acetate (Depo-Provera®)) are also effective if they induce amenorrhea [1].

D-other second line agents includes: Danazol, Gestrinone, and gonadotropin-releasing hormone agonists (1).

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Polycystic Ovarian Syndrome

Definition (1): Any woman with at least two of the following three criteria are said to

1-Evidence of hyperandrogenism (biochemical or clinical). Most commonly hirsutism, acne and crown pattern baldness.
2-Ovulatory dysfunction: amenorrhea , oligomenorrhoea (menstruation occurring at an interval >35 days).
3-Morphological polycystic ovaries.

Etiology : 1-there have been many theories about the cause of PCOS. Around 40 per cent of sufferers have raised levels of LH and 30 per cent have raised levels of testosterone. LH stimulates the ovary to produce testosterone and consistently raised levels of LH(2)

2-Insulin resistance: Recent evidence has suggested that the principal underlying disorder may be insulin resistance with the resultant raised serum insulin concentrations stimulating excess ovarian androgen production. Excess circulating insulin also reduces the production of proteins that bind sex hormones, increasing the free testosterone levels.
3-Obesity: A high body mass index could also be a cause or effect. Increased weight can lead to increased serum insulin concentrations and, as described above, increased free testosterone levels.
4-There may be a genetic factor but this remains controversial.

Sign and symptoms:

The most common symptom is infertility, which occurs in 75% of patients. Other manifestations of PCO include hirsutism (70%), menstrual irregularities (amenorrhea 50%, functional bleeding 30%, and dysmenorrhea 25%), obesity (40%), insulin resistance, and virilization (20%)(3).

Treatment:

A-Lifestyle:

Weight loss in women with elevated BMI is an effective management strategy in women with PCOS[(1)].

B-Anovulation and Infertility (if pregnancy is desired):

1-Clomifene citrate and Tamoxifen is an effective treatment for anovulation in PCOS[(1)]. Current recommendation being not to exceed 6 months of continuous therapy[(1)].

2-Gonadotrophin therapy: Recombinant FSH and human menopausal gonadotrophin are both effective for ovulation induction in women with clomifene-resistant PCOS[(1)]. 3-As recent evidence has suggested that insulin resistance may be a cause and not an effect of PCOS, then treating insulin resistance has the potential to be the most appropriate action[(1)]. Metformin (Glucophage ®) has been the most commonly used drug in clinical trial[(1,2)]. (initially 500 mg with breakfast for 1 week, then 500 mg with breakfast and evening meal for 1 week, then 1.5–1.7 g daily in 2–3 divided doses[(4)]). However, this use still requires further evaluation and is still unlicensed[(1)]. C-Management of skin manifestations and hyperandrogenism[(1)]:

1-Acne:

Mild acne: Topical agents like benzyl peroxide, azalaic acid, clindamycin lotion, erythromycin gel.

Mild: it may require oral antibiotics such as tetracyclines or erythromycin.

Severe: Oral isotretinoin.

2-Hirsutism:

A-Combination of oral contraceptive pill and cyproterone acetate (anti-androgen)

B-Spironolactone: oral aldosterone antagonist with anti-androgenic properties.

C-Flutamide: Anti-androgenic agent

D-Finasteride: (5-α reductase inhibitor).

Long-Term Health Implications of PCOS[(1)]: 1-Incrteased incidence of multiple pregnancy with subsequent increase in Perinatal mortality and morbidity.

2-Increased incidence of gestational DM and pregnancy-induced hypertension.

3-Increased incidence of endometrial and ovarian cancer.

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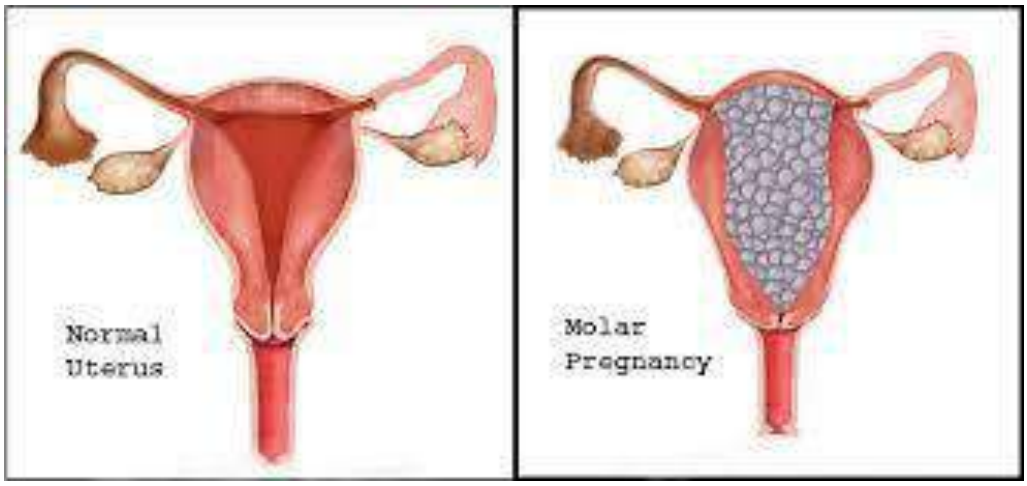
Molar Pregnancy

Molar pregnancy is an abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus and will fail to come to term. A molar pregnancy is a non-cancerous (benign) tumor that develops in the uterus that has swollen chorionic villi. These villi grow in clusters that resemble grapes. A molar pregnancy can develop when fertilized egg had not contained an original maternal nucleus. The products of conception may or may not contain fetal tissue. Molar pregnancies are also called gestational trophoblastic disease (GTD), hydatidiform mole or simply referred to as a "mole".



Molar pregnancy can either complete or partial, Complete molar pregnancies have only placental parts (there is no baby), and form when the sperm fertilizes an empty egg. Because the egg is empty, no baby is formed. The placenta grows and produces the pregnancy hormone, hCG.

Partial Mole occurs when the mass contains both the abnormal cells and an embryo that has severe birth defects. In this case the fetus will be overcome by the growing abnormal mass rather quickly.

Risk factors for a molar pregnancy:

Women over the age of 40
Women who have had a prior molar pregnancy
Women with a history of miscarriage

Symptoms:

Vaginal spotting or bleeding
Nausea and vomiting
Develop rare complications like thyroid disease
Early preeclampsia (high blood pressure)
Increased hCG levels
No fetal movement or heart tone detected

Diagnosis: by pelvic examination that may reveal a larger or smaller uterus, enlarged ovaries, and abnormally high amounts of hCG and ultrasound (will often show a "cluster of grapes" appearance).

Treatment: A molar pregnancy can't continue as a normal viable pregnancy. To prevent complications (in order to avoid the risks of choriocarcinoma), the molar tissue must be removed either by:

1- Dilation and curettage (D&C).
2- Hysterectomy.

Patients are followed up until their serum human chorionic gonadotrophin (hCG) level has fallen to an undetectable level. Invasive or metastatic moles (cancer) may require chemotherapy and often respond well to methotrexate (MTX) or EMA/CO therapy.

The majority of women with persistent trophoblast disease after a molar pregnancy will fall into the low-risk treatment group and start chemotherapy with intramuscular methotrexate combined with oral folinic acid rescue as shown in the box below. The first cycle of treatment is given as an inpatient, with the following cycles administered closer to home. Women with an initial pretreatment hCG of >1000 IU/l may stay as inpatients for longer as they have a higher risk of bleeding: the larger tumors shrink rapidly with the initiation of chemotherapy.

a) Methotrexate/folinic acid treatment schedule

Day 1	methotrexate 50 mg IM at noon
Day 2	folinic acid 15 mg orally at 6 p.m.
Day 3	methotrexate 50 mg IM at noon
Day 4	folinic acid 15 mg orally at 6 p.m.
Day 5	methotrexate 50 mg IM at noon
Day 6	folinic acid 15 mg orally at 6 p.m.
Day 7	methotrexate 50 mg IM at noon
Day 8	folinic acid 15 mg orally at 6 p.m.

b) EMA/CO chemotherapy

Week 1

Day 1 dactinomycin 0.5 mg IV
etoposide 100 mg/m^2 IV
methotrexate 300 mg/m^2 IV

Day 2 dactinomycin 0.5 mg IV
etoposide 100 mg/m^2 IV
folinic acid 15 mg orally 12 hourly × 4 doses, starting 24 hours after commencing methotrexate

Week 2

Day 8 vincristine 1.4 mg/m^2 (maximum 2 mg)
cyclophosphamide 600 mg/m^2

IM = intramuscularly; IV = intravenously

The use of folinic acid as a supplement is because MTX is classified as an antimetabolite due to its antagonistic effect on folic acid metabolism (folate antagonist). Many patients treated with MTX experience mucosal, gastrointestinal, hepatic or haematologic side effects. Supplementation with folic or folinic acid (a reduced folic acid) during treatment with MTX may ameliorate these side effects and minimize its toxicity.

Some Drugs that are Used in Obstetric and Gynecology(1)

1-**Clomifene** (clomiphene) citrate (Clomid® citrate 50 mg tablet) Anti-oestrogens used in female infertility caused by anovulation (oligomenorrhoea or secondary amenorrhoea). Dose : 50 mg daily for 5 days, starting within about 5 days of onset of menstruation (preferably on 2nd day) or at any time if cycles have ceased; second course of 100 mg daily for 5 days may be given in absence of ovulation; 3 courses should constitute adequate therapeutic trial .

2-**Dydrogesterone** (Duphaston ® 10mg tablet)

Progesterone analogue used in: Endometriosis, dysfunctional uterine bleeding, dysmenorrhoea, amenorrhoea, and premenstrual syndrome .

It may be used in the following but not recommended: Infertility, irregular cycles, and recurrent miscarriage (habitual abortion).

3-**Norethisterone** (Primolut N® 5 mg tablet): Progesterone analogue used in: Endometriosis, dysfunctional uterine bleeding, dysmenorrhoea, amenorrhoea, premenstrual syndrome and postponement of menstruation.

4-**Medroxyprogesterone Acetate** (Provera®: 2.5, 5 and 10 mg tablets, Depo-Provera® 150 mg injection) Progesterone analogue used orally in: dysfunctional uterine bleeding , secondary amenorrhoea, endometriosis, progestogenic opposition of oestrogen HRT.

Depo-Provera® 150 mg injection used as a contraceptive for about three months.

5-**Methyl ergometrine** (methergin ®) tablet 125mcg, injection: 200 mcg /mL (1 mL ampoule). Use in the prevention and treatment of post partum hemorrhage.

6-**Oxytocin** (Pitocin®) 10 IU / mL (1 mL ampoule) use to induce or augment labour and the prevention and treatment of post partum hemorrhage.

7-**Tamoxifen** (10 and 20 mg tablet) used in breast cancer, and anovulatory infertility.

8-**Human Chorionic Gonadotrophin; HCG** (Pregnyl ® Injection, 500-unit amp, 1500-unit amp 5000-unit amp) is used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene.

9-**Pergonal**® injection contain 75 units of FSH, and 75 units of human LH) is used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene. lutropin alfa (Recombinant human LH) Injection, 75-unit Luveris®.use like pergonal®.

10-**Conjugated oestrogens** (Premarin® 652 mcg, and 1.25 mg tablets) use as a Hormone replacement therapy (HRT) for a alleviating menopausal symptoms.

11-**Trisequens** ® tablets: 12 blue tablets of estradiol 2 mg; 10 white tablets of estradiol 2 mg, norethisterone acetate 1 mg and 6 red tablets of estradiol 1 mg. use as a hormone replacement therapy (HRT) for a alleviating menopausal symptoms.

12-**Danazol** (Danol®100 mg, 200 mg cap). It is licensed for the treatment of endometriosis and for the relief of severe pain and tenderness in benign fibrocystic breast disease where other measures have proved unsatisfactory.

13-**Bromocriptine** (Parlodel® 2.5 mg tablet): is used for the prevention of lactation in galactorrhoea.

14-**Cabergoline** (Dostinex ® 0.5 mg tablet) has actions and uses similar to those of bromocriptine, but its duration of action is longer.
15-**Goserelin** (Zoladex® 3.6 mg injection): Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility and breast cancer.
16-**Buserelin, Leuprorelin acetate, Nafarelin, Triptorelin**: Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility and breast cancer.
17-**Tranexamic acid** (Cyklokapron®, Exacyl® 500 mg tablet, and 500 mg /5 mL injection). It is used to stop vaginal bleeding.
18-**Isoxsuprine** (Duvadilan® 10 mg and 20 mg tablet): uterine relaxant.

Reference:
1-BNF 67

College of Pharmacy / University of Baghdad

Manual of Pediatrics

Second Edition.2019-2020

خاص بطلبة كليات الصيدلة /المرحلة الخامسة

(تدريب مستشفيات / ردهة الأطفال)

إعداد

فرع الصيدلـــــــة السريـــــــريـــــــة

Lists of Contents

Age Group Terminology

Premature	**Birth before 37 completed weeks gestation**
Neonate	**0-4 weeks**
Infant	**1month-1 year**
Child/children	**1-12 years**
Adolescent	**13-18 years**
Adult	**>18 years**

A-Neonatology

1-Hyperbilirubinemia in the Newbornb (Neonatal Jaundice)

Background

1-Bilirubin is derived primarily **from the breakdown of heme in the reticuloendothelial system**. Nonpolar and water-insoluble unconjugated bilirubin is conjugated inside liver cells to form Water-soluble conjugated bilirubin [(1)].

2-Most conjugated bilirubin is excreted through the bile into the small intestine and eliminated in the stool. Some bilirubin may undergo hydrolysis back to the unconjugated fraction by intestinal glucuronidase, and may be reabsorbed (**enterohepatic recirculation**) [(2)].
3- Nearly all newborns develop transient hyperbilirubinemia (serum bilirubin >2 mg/dL) and nearly 65% (two third) are clinically jaundiced (serum bilirubin>5 mg/dL) [(1)].
4-Onset of jaundice in the **first 24 hours of life is always pathological** [(3)].

5-Kernicterus **(Bilirubin Encephalopathy)** results when indirect **(unconjugated)** bilirubin is deposited in brain cells and disrupts neuronal function [(2)]. Kernicterus usually does not develop in term infants when bilirubin levels are less than 20 to 25 mg/dL. **The incidence of kernicterus increases as serum bilirubin levels increase to greater than 25 mg/dL** [(2)].
6-Kernicterus may be noted at bilirubin levels less than 20 mg/dL in the presence of some conditions like **sepsis**, **meningitis**, and prematurity [(2)].

Unconjugated hyperbilirubinemia

1-Nonpathologic unconjugated hyperbilirubinemia

A-Physiologic Jaundice

1-Physiologic jaundice is **an unconjugated hyperbilirubinemia that occurs after the first postnatal day and can last up to 1 week**. Total serum bilirubin (TSB) concentrations peak in the first 3 to 5 postnatal days and decline to adult values over the next several weeks [(4)].
2-The underlying mechanisms for physiologic jaundice in newborn are related to:

(a) **Increased bilirubin production** because of elevated red blood cell volume per body weight and a shorter and shorter life span [2, 4].
(b) **Infants have immature hepatic glucuronosyl transferase**, a key enzyme involved in the conjugation of bilirubin [4].
(c) **Increased enterohepatic circulation** in newborn [2].

B-Breast milk jaundice

1-It occurs in some breast-fed infants because **breast milk may contain an inhibitor of bilirubin conjugation or may increase the enterohepatic recirculation of bilirubin because of breast milk glucuronidase** [2].

2-Jaundice appears in the **seventh** day and it **gradually increased in severity** till it reaches its peak during third week [5]. It may persists for several weeks [5].
3-**Interruption of breast feeding and use of formula feeding for 1–3 days causes a prompt decline in bilirubin**[1] (which do not increase significantly after breastfeeding resumes) [2] but is only recommended for infants with serum bilirubin concentrations that put them at risk for kernicterus [1].

C-Breast feeding jaundice

1-Breastfeeding jaundice occur when a breastfeeding baby **is not getting enough breast milk** , which leads to infrequent bowel movements and increased enterohepatic circulation of bilirubin. It occurs during the first week of life) [6, 7].

2-**Water and dextrose solutions should not be used** to supplement breastfeeding because they do not prevent hyperbilirubinemia and may lead to hyponatremia [4].

D-Prematurity.

1-Although preterm infants develop hyperbilirubinemia by the same mechanisms as term infants, **it is more common and more severe in preterm infants and lasts longer** (due to the relative immaturity of the red blood cells, hepatic cells, and gastrointestinal tract) [4].

2-Kernicterus is extremely uncommon. However, kernicterus in preterm infants can occur at lower TSB concentrations [4]. (see Kernicterus).

2-Pathologic Unconjugated Hyperbilirubinemia.

A-Acute Hemolysis:

In this condition, jaundice appears at birth or during the ***first day*** and it is commonly severe. Serum bilirubin level may rise rapidly to reach serious levels where kernicterus may occur.
Kernicterus is a real risk and it may occur when serum bilirubin exceeds the critical level, which depends on the birth weight and the condition of the baby. The critical level is lower in those with low birth weight and in sick neonates [5].

The cause of haemolysis can be identified by clinical and laboratory evaluation.

1-Rh incompatibility:

- It is the ***commonest*** cause of hemolysis. **It occurs in some Rh positive babies born to Rh negative mothers**. Hemolysis occurs due to placental passage of maternal antibodies active against the fetal red cells. The ***first baby*** is usually not affected as maternal sensitization usually occurs during delivery of the first baby [(5)].

- Rh incompatibility can be prevented by injection of ***Rh immune globulin to the mother within 72 hours after delivery*** which prevents her from forming antibodies which might affect subsequent babies [(5)].

2-ABO incompatibility:

ABO incompatibility may occur if the **mother's blood type is O** and **the infant's blood type is A or B** [(4)]. The ***first baby*** may be affected. ***Jaundice*** is not severe. ***kernicterus*** is rare. [(5)].

B-Neonatal septicemia:

1-Jaundice in septicemia, if present, usually appears between the ***fourth and seventh day*** or later and is usually moderate in severity [(5)].

2-The most important clinical signs are the markedly affected ***general condition(***The baby is not doing well with lethargy, poor suckling, fever or hypothermia, ...). Immediate hospitalization and combined parenteral antibiotic therapy are important [(5)].

C-Other *rare* causes :

1-Hemolysis Present :(e.g. -Red *blood cell enzyme defects*: glucose-6-phosphate dehydrogenase) [(2)].

2- Hemolysis Absent : Mutations of glucuronyl transferase enzyme (Crigler-Najjar syndrome, Gilbert disease), hypothyroidism [(2)].

Conjugated Hyperbilirubinemia

1-Conjugated (Direct-reacting) hyperbilirubinemia **is never physiologic** and should always be evaluated thoroughly [(2)].

2-Direct-reacting bilirubin (composed mostly of conjugated bilirubin) **is not neurotoxic** to the infant, but **signifies a serious underlying disorder** involving cholestasis , hepatocellular injury [(2)] or biliary atresia [(4)]. (atresia is an unusual closing or absence of a tube in the body).

Biliary Atresia:1- is an obstruction of the biliary tree that causes severe cholestasis [(10)] and is characterized by elevation of the conjugated, or direct, bilirubin fraction [(2)] , which leading to cirrhosis and death if left untreated in a timely manner [(10).]

2- The jaundice of biliary atresia usually is not evident immediately at birth, but develops in the first week or two of life. The reason is that extrahepatic bile ducts are usually present at birth, but are then destroyed by an idiopathic inflammatory process [(2)] .

3- Treatment of extrahepatic biliary atresia is the surgical **Kasai procedure**, in which the fibrotic extrahepatic bile duct remnant is removed and replaced with a roux-en-Y loop of jejunum. This operation must be performed before 3 months of age to have the best chance of success [(2)] .

4- many children require liver transplantation [(2)].

Therapy of Indirect (unconjugated) Hyperbilirubinemia

The main concern is to prevent Kernicterus [(3)]. Charts exist indicating levels at which treatment should be initiated.

Treatment options are: **A-Phototherapy.** **B-Exchange transfusion** [(3)].

Table 2 show the bilirubin level at which these treatment options indicated [(8)].

Table 2:bilirubin level at which phototherapy and exchange are indicated

	Phototherapy				**Exchange transfusion**			
	Healthy term baby		**Preterm or any risk factors***		**Healthy term baby**		**Preterm or any risk factors**	
	Mg/dl	**µmol/l**	**Mg/dl**	**µmol/l**	**Mg/dl**	**µmol/l**	**Mg/dl**	**µmol/l**
Day 1	Any visible jaundice**				15	260	13	220
Day 2	15	260	13	220	25	425	15	260
Day 3	18	310	16	270	30	510	20	340
Day 4 and after	20	340	17	290	30	510	20	340

* Risk factors include small size (less than 2.5 kg or born before 37 weeks gestation), haemolysis, and sepsis. ** Visible jaundice anywhere on body on day 1.

A-Phototherapy

1-Blue light (not ultraviolet) of wavelength 450 nm **converts the bilirubin in the skin and superficial capillaries into harmless water-soluble metabolites, which are excreted in urine and through the bowel** [(3)].

2-The **eyes are covered to prevent discomfort** and additional fluids are given to counteract increased losses from skin [(3)].

B-Exchange transfusion

1-This is required if the bilirubin rises to levels considered dangerous despite phototherapy [(3)].

2- Twice the infant's blood volume (i.e. 2 x 80 mL/kg) is exchanged over about 2 hours [(3)] (or 2 x 85 mL/kg) [(2)].

3-The procedure is carried out **through umbilical vein catheter** [(9)].

C-Pharmacological agents

1-High dose intravenous immunoglobulin is the only pharmacological treatment used in clinical practice for infants presenting with high jaundice levels secondary to rhesus or ABO incompatibility [(11)] .

Management of conjugated hyperbilirubinemia

Management depend on the treatment of the causative diseases (if treatable e.g. surgical correction of biliary atresia) [(5)].

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2-Neonatal Sepsis and Meningitis

Background

1-Neonates, especially preterm newborns, are at increased risk for infections and **should be considered immunocompromised** [(1)].

2-Risk factors **of neonatal sepsis** include **prematurity**, **low birth weight**, **and predisposing maternal conditions** (e.g., urinary tract infection) [(1)].

3-**Early-onset neonatal sepsis** (sepsis that presents during the first 7 days of life) usually is **caused by organisms acquired from the maternal genital tract** [(1)]. (see table 1) [(3)].

4- Late-onset sepsis (8 to 28 days) usually occurs in a healthy full-term infant who was discharged in good health [(2)]. (see table 1) [(3)].

5-**Meningitis occurs as a complication of bacterial sepsis** [(1)]. The major pathogens causing neonatal sepsis are also the primary pathogens that cause neonatal meningitis [(1)].

Table 1 [3]

Organisms associated with early-onset and late-onset neonatal sepsis	
Early-Onset Sepsis	**Late-Onset Sepsis**
Group B *Streptococcus*	Coagulase-negative *Staphylococcus*
Escherichia coli	*Staphylococcus aureus*
Listeria monocytogenes	Enterococci
Other streptococci: *Streptococcus pyogenes*, viridans group streptococci, *Streptococcus pneumoniae*	Multidrug-resistant gram-negative rods (*E coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Citrobacter*, *Serratia*)
Enterococci	*Candida*
Nontypable *Haemophilus influenzae*	

Clinical Manifestations of Neonatal Sepsis

1- The most common signs are **poor feeding**, **temperature instability** (**Hypothermia** is more common than fever in neonatal sepsis, especially in preterm newborns), **lethargy**, or **apnea** [1].

2-Other signs of neonatal sepsis include **tachycardia**, dyspnea or cyanosis, **tachypnea**, disseminated intravascular coagulation (**DIC**)and **abdominal distension** [1, 6].

3-The clinical manifestations of sepsis are difficult to separate from the manifestations of meningitis in the neonate [2].

Laboratory Diagnosis of Neonatal Sepsis

A- Positive cultures of body fluids confirm the diagnosis, including the following:

1. **Blood**: Must be obtained as a part of every evaluation for sepsis.
2. **CSF:** CSF analysis is indicated for all infants with a positive blood culture.
3. **Urine**: urine cultures are indicated, as urinary tract infections are a frequent source of infection [4].

B- Hematologic studies:

1. An extremely elevated total WBC or very depressed count is more suggestive of infection.
2. Thrombocytopenia is also associated with sepsis [4].

C- A chest radiograph is indicated in all infants with respiratory symptoms [4].

D-C-reactive protein(CRP): CRP levels are often elevated in neonatal patients with bacterial sepsis [2].

E-Coagulation studies : prolonged values may indicate DIC [4].

Treatment of Sepsis and Meningitis

1-The initial empiric antibiotic treatment of choice for early-onset neonatal sepsis and meningitis is **ampicillin plus an aminoglycoside** (Tables 2 and 3) [1].
[In some nurseries, **a third-generation cephalosporin** (e.g., cefotaxime), instead of an aminoglycoside is added to ampicillin] [1].

Table 2
Gentamicin Dosing Guidelines for Neonates and Infants

Traditional Dosing		
Age	Weight	Dosing Regimen
GA <38 weeks	<1,000 g	3.5 mg/kg/dose every 24 hours
PNA 0–4 weeks	<1,200 g	2.5 mg/kg/dose every 18–24 hours
PNA ≤7 days	≥1,200 g	2.5 mg/kg/dose every 12 hours
PNA >7 days	1,200–2,000 g	2.5 mg/kg/dose every 8–12 hours
PNA >7 days	>2,000 g	2.5 mg/kg/dose every 8 hours

GA, gestational age; PNA, postnatal age.

2-If meningitis is highly suspected**, gentamicin may be replaced by a third generation cephalosporin** (cefotaxime) owing to greater CSF penetration [1].

3-For late-onset sepsis or meningitis , a combination of **vancomycin with an aminoglycoside** (gentamicin or tobramycin) is appropriate [2].

4-Amphotericin remains the treatment of choice for invasive candidiasis when meningitis is a consideration; liposomal amphotericin or an echinocandin (caspofungin or micafungin) are options for hepatic or splenic candidiasis. Fluconazole might be an effective therapy for susceptible organisms [7] .

Duration of therapy

1-Therapy for most bloodstream infections should be continued for **a total of 7-10 days or for at least 5-7 days after a clinical response has occurred** [4].

2-**Meningitis** should be treated for **14-21 days** [4].

Table 3

Antimicrobial Dosage Regimens for Neonates: Dosages and Intervals of Administration

	Weight < 1,200 g	Weight 1,200–2,000 g		Weight > 2,000 g	
Drug	0–4 Weeks (mg/kg)[a]	0–7 Days (mg/kg)[a]	8–28 Days (mg/kg)[a]	0–7 Days (mg/kg)[a]	8–28 Days[a] (mg/kg)[a]
Amphotericin B					
Deoxycholate	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours
Lipid complex/ Liposomal	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours
Ampicillin					
Meningitis	100 every 12 hours	100 every 8 hours	75 every 6 hours	50 every 8 hours	75 every 6 hours
Other diseases	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	25 every 6 hours
Cefazolin	25 every 12 hours	25 every 12 hours	25 every 12 hours	25 every 12 hours	25 every 8 hours
Cefepime	30 every 12 hours	50 every 12 hours	30 every 12 hours[b]	50 every 12 hours	30 every 12 hours[b]
Cefotaxime[c]	50 every 12 hours	50 every 12 hours	50 every 8 hours	50 every 12 hours	50 every 8 hours
Ceftazidime[c]	50 every 12 hours	50 every 12 hours	50 every 8 hours	50 every 12 hours	50 every 8 hours
Ceftriaxone[c]	25 every 24 hours	50 every 24 hours	50 every 24 hours	50 every 24 hours	75 every 24 hours
Clindamycin	5 every 12 hours	5 every 12 hours	5 every 8 hours	5 every 8 hours	5 every 6 hours
Erythromycin	10 every 12 hours	10 every 12 hours	10 every 8 hours	10 every 12 hours	13.3 every 8 hours
Fluconazole	6 every 72 hours	12 every 48 hours	12 every 24 hours	12 every 48 hours	12 every 24 hours
Linezolid	10 every 12 hours	10 every 12 hours	10 every 8 hours	10 every 8 hours	10 every 8 hours
Meropenem[c]	20 every 12 hours	20 every 12 hours	20 every 8 hours	20 every 8 hours	30 every 8 hours
Metronidazole	7.5 every 48 hours	7.5 every 24 hours	7.5 every 12 hours	7.5 every 12 hours	15 every 12 hours
Oxacillin	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	37.5 every 6 hours
Nafcillin	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	37.5 every 6 hours
Penicillin G					
Meningitis	50,000 U every 12 hours	50,000 U every 12 hours	50,000 U every 8 hours	50,000 U every 12 hours	50,000 U every 8 hours
Other diseases	25,000 U every 12 hours	25,000 U every 12 hours	25,000 U every 8 hours	25,000 U every 12 hours	25,000 U every 8 hours
Piperacillin/tazobactam	50 every 12 hours	75 every 12 hours	75 every 8 hours	75 every 12 hours	75 every 8 hours
Ticarcillin or Ticarcillin/ clavulanate	75 every 12 hours	75 every 12 hours	75 every 8 hours	75 every 12 hours	75 every 8 hours
Vancomycin	15 every 24 hours[d]	15[e]	15[e]	15[e]	15[e]

Supportive care

1-**Fluids, electrolytes, and glucose levels** should be monitored carefully with correction when needed [(5)].

2-Seizures should be treated with anticonvulsants [(5)].

3-DIC may complicate neonatal septicemia. DIC may require fresh frozen plasma, platelet transfusions, or whole blood [(5)].

4-The use of **intravenous immunoglobulin** (IVIG) has been shown to decrease mortality in patients with sepsis [(5)].

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B-Nephrology

1-Nephrotic syndrome

1-**Nephrotic syndrome** (NS) is characterized by persistent heavy **proteinuria** (mainly albuminuria) ; **hypoproteinemia** (serum albumin <3.0 g/dL); **hypercholesterolemia** (>250 mg/dL); and **edema** [1].

2- Nephrotic syndrome is **primarily a pediatric disorder** and is 15 times more common in children than adults [2] with a peak age of onset in children aged <6yrs [3].

3-The underlying abnormality in nephrotic syndrome is an increase in permeability of the glomerular capillary wall, which leads to massive **proteinuria and hypoalbuminemia** [2].

4-Hypoalbuminemia causes a decrease in the plasma oncotic pressure and shift of fluid from the intravascular compartment to the interstitial space. Reduced plasma volume stimulates antidiuretic hormone (ADH) secretion and the renin–angiotensin system, producing sodium and water retention, exacerbating the edema [2, 4].

Classification:

Approximately 90% of children with NS **have idiopathic** NS. Idiopathic NS includes three histologic types [2]:

A-**Minimal change nephrotic syndrome** (MCNS) is the most common form of NS in children (accounts for about 85%) [1, 2].

2-Other less common types are [**Focal segmental glomerulosclerosis** (FSGS), **and Membranoproliferative glomerulonephritis** (MPGN)] [1].

Clinical features

1-Children usually present with mild **edema**, which is initially noted around **the eyes** (Periorbital) and in the lower extremities [2]. Periorbital oedema is often most noticeable in **morning on rising** [3].

2-With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema [2].

Treatment

1-NS edema is treated by **restricting salt intake**. Severe edema may require the use of **loop diuretics**. When these therapies do not alleviate severe edema, parenteral administration **of 25% albumin** (0.5 to 1.0 g/kg intravenously over 1 to 2 hours) with an intravenous loop diuretic usually results in diuresis [1].

2-Children with onset of nephrotic syndrome between **1 and 8 yr of age are likely to have steroid-responsive minimal change disease**, therefore, steroid

therapy (prednisolone 2 mg/kg/day)(60 mg/m^2/day) may be initiated without renal biopsy [2].

3-After the initial 4-6 wk course, the prednisone dose should be tapered to 40 mg/m^2/day given every other day as a single morning dose. The alternate-day dose is then slowly tapered and discontinued over the next 2-3 mo [2].
4-**Steroid-dependent patients** (relapse while on alternate-day steroid therapy or within 28 days of stopping prednisone therapy), **frequent relapsers**, and steroid- resistant patients may be candidates for **alternative agents** (e.g. Cyclophosphamide) [2].
5-Rituximab has been effective in the treatment of refractory NS in children, and it could reduce the use of steroid and immunosuppressants [5] .
6-Acute hypertension (HTN) is treated with β -blockers or calcium channel blockers. Persistent HTN usually responds to ACE inhibitors [1].

7-**ACE inhibitors and angiotensin II blockers** may be helpful as an adjunct therapy to **reduce proteinuria** in steroid-resistant patients [2].

Complications

1-**Infection is the major complication of nephrotic syndrome**. Children in relapse have increased susceptibility to bacterial infections owing to urinary losses of immunoglobulins and use of immunosuppressive therapy. Spontaneous bacterial peritonitis is the most frequent type of infection [2].

2-The role of **prophylactic antibiotic** therapy during relapse remains **controversial** [2].
3-Children with nephrotic syndrome are also at **increased risk for Thromboembolism (TE).** (related to increased prothrombotic factors (e.g. fibrinogen,) and decreased fibrinolytic factors) . **Prophylactic anticoagulation is not recommended in children unless they have had a previous TE**. Warfarin, low-dose aspirin, or dipyridamole may minimize the risk of clots in NS patients with a history of TE or high risk for TE [1, 2].

Prognosis

1-The majority of children with steroid-responsive NS have repeated relapses, which generally decrease in frequency as the child grows older [2].

2-**Steroid-responsive patients have little risk of chronic renal failure** [1].
3-Children with **steroid-resistant NS**, most often caused by focal segmental glomerulosclerosis, generally have a much **poorer prognosis**. These children develop progressive renal insufficiency, ultimately leading to end-stage renal failure requiring dialysis or renal transplantation [2].

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2-Hemolytic-Uremic Syndrome

1-The hemolytic-uremic syndrome (HUS) is the most **common cause of acute renal failure in young children** and is characterized by **hemolytic anemia, thrombocytopenia, and uremia** (1).
2- HUS typically occurs in children **less than 5 years of age** but can occur in older children (2).
3-Two forms of HUS are recognized.
A-HUS following infection with Shiga toxin-producing Escherichia coli **(STEC-HUS or typical HUS, formally D+HUS)** is the most common cause of HUS, responsible for up to 90% of cases in children.
B- Atypical HUS **(aHUS, formally D−HUS)** describes HUS in the absence of evidence of STEC infection(3).
Note: D+ HUS diarrhea associated, D-HUS not diarrhea associated.

Clinical Manifestations.

1-Classic D+HUS begins with **gastroenteritis** characterized by fever, vomiting, and diarrhea that is often bloody. **Followed in 7 to 10 days** by weakness, lethargy, and oliguria/anuria. Physical examination reveals irritability,pallor, and petechiae (1, 2).

Treatment and Prognosis

1-Therapy for HUS is **supportive** and includes **volume repletion**, and managing complications of renal insufficiency, **including dialysis when indicated** (2).

2-**Red blood cell transfusions** are provided as needed (2).

3-**Antibiotics and antidiarrheal agents may increase the risk of developing HUS** (2). [Antibiotics should be avoided in patients with acute enteritis presumed secondary to *E. coli* 0157:H7 as they may increase the risk of developing HUS.

4-Most children (>95%) with D+HUS survive the acute phase and recover normal renal function, although some may have evidence of long-term morbidity (2).

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1-Nelson Textbook of pediatrics. 29th edition.
2-Robert M. Kliegman. Nelson essentials of pediatrics. 7th edition. 2015.
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C-Infections

1-Bronchiolitis

1-**Bronchiolitis,** a lower respiratory tract infection (LRTI) that primarily affects the small airways (bronchioles), is a common cause of illness and hospitalization in infants and young children [(1)].
2-Bronchiolitis is seasonal, with **peak activity during winter and early spring** [(2)].
3-Bronchiolitis occurs almost **exclusively during the first 2 years of life**, with a peak age at 2 to 6 months [(3)].

4- Acute bronchiolitis is characterized by bronchiolar **obstruction with edema, mucus, and cellular debris** [(2)].

Etiology

1-Acute bronchiolitis is predominantly a viral disease. **Respiratory syncytial virus (RSV)** is responsible for more than 50% of cases [(2)].

2-Other agents include parainfluenza, adenovirus, *Mycoplasma,* and occasionally other viruses [(2)].

Clinical Manifestations.

1-The infant first develops a mild upper respiratory tract infection with **sneezing and clear rhinorrhea**. This may be accompanied by diminished appetite and fever [(2)].
2-Gradually, respiratory distress ensues, with paroxysmal **wheezy cough**, **dyspnea**, and **irritability**. The infant is often **tachypneic**, which interferes with feeding [(2)].

3-As a result of limited oral intake due to coughing combined with fever, infants are frequently **dehydrated** [(6)].

Diagnosis

The diagnosis of bronchiolitis is based primarily on **history and clinical findings** [(6)].

Treatment

1-The mainstay of treatment is **supportive**. Therapy of bronchiolitis primarily consists of administration of supplemental **oxygen** and replacement of fluid deficits (**hydration**) as needed [(2, 4)].

2-The risk of aspiration of oral feedings may be high in infants with bronchiolitis owing to tachypnea and the increased work of breathing. **The infant may be fed through a nasogastric tube** [(2)].

3-A number of agents have been proposed as adjunctive therapies for bronchiolitis:

A-Bronchodilators produce modest short-term improvement in clinical features. **Nebulized epinephrine may be more effective than β-agonists** [2].

B-Corticosteroids, whether parenteral, oral, or inhaled, are widely used despite **conflicting studies** [2].

C-Ribavirin, is a compound with antiviral activity against RSV administered by **aerosol**, has been used for infants with congenital heart disease (CHD)or chronic lung disease (CLD) [2, 4]although **its benefit is uncertain** [5].

D-Antibiotics have no value unless there is secondary bacterial pneumonia [2].

Prophylaxis

1-Palivizumab is a monoclonal antibody to RSV and can be used as prophylaxis [5] initiated just before the onset of the RSV season (monthly IM injection for 5months starting in October) confers some protection from severe RSV disease [3, 5]

2-Palivizumab is indicated for some infants under 2 years old with CLD, severe CHD or prematurity [2, 3] .

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2-Pneumonia

1-Pneumonia is defined as **infection of the lung parenchyma** (that is of the alveoli rather than the bronchi or bronchioles) and **characterized by consolidation** [1].

(**Consolidation** is a pathological process in which the alveoli are filled with a mixture of inflammatory exudate, bacteria and WBCs that on chest X-ray appear as an opaque shadow in the normally clear lungs) [1].

Etiology

Viruses alone account for 14–35% of all community acquired pneumonia in childhood [2].

M. pneumoniae and *Chlamydophila pneumoniae* are principal causes of **atypical pneumonia** [3]. Common infecting bacterial agents by age are [ليست للحفظ] [2] :

1-**Neonates**: group B streptococcus, *Escherichia coli*, *Klebsiella*, *Staphylococcus aureus*.

2-**Infants**: *Streptoccus pneumoniae*, *Chlamydia*.

3-**School age**: *Streptococcus pneumoniae*, *Staphylococcus aureus*, group A

streptococcus, *Bordetella pertussis*, *Mycoplasma pneumoniae*.

Clinical Manifestations

In many cases these symptoms are preceded by minor upper respiratory tract infection symptoms. The patient may also be complaining of pleuritic chest pain or abdominal pain. The typical history will have:

- **Temperature** ≥ 38.5 ^{0}C;
- **Tachypnea and Shortness of breath**;
- **Cough**; [with sputum production in older children (>7yrs)] [2, 4].

Diagnosis

- Diagnosis of pneumonia in many cases is made based on the **presence of clinical signs and symptoms.**
- **Chest x-ray** are often used to confirm the diagnosis [4].

Treatment [2].

1-Oral antibiotics are safe and effective in the treatment of community acquired pneumonia. IV antibiotics are used in children who cannot absorb oral antibiotics or in those with severe symptoms.

Antibiotic therapy for pneumonia

Under 5yrs

Streptococcus pneumoniae is the most likely pathogen. The causes of atypical pneumonia are *Mycoplasma pneumoniae* and *Chlamydia trachomatis*

- *First-line treatment:* amoxicillin
- *Alternatives:* co-amoxiclav or cefaclor for typical pneumonia; erythromycin, clarithromycin, or azithromycin for atypical pneumonia

Over 5yrs

Mycoplasma pneumoniae is more common in this age group

- *First-line treatment:* amoxicillin is effective against the majority of pathogens, but consider macrolide antibiotics if mycoplasma or chlamydia is suspected
- *Alternatives:* if *Staphylococcus aureus* is suspected consider using a macrolide, or a combination of flucloxacillin with amoxicillin

Severe pneumonia

Co-amoxiclav, cefotaxime, or cefuroxime IV

2-Supportive therapies Consider whether any of the following are needed:

- **Antipyretics** for fever.
- **IV fluids**: consider if dehydrated or not drinking.

• Supplemental **oxygen**.

Complications

1-Bacterial pneumonias frequently cause inflammatory fluid to collect in the adjacent pleural space, causing an **empyema** [empyema is collection of pus in a cavity, especially in the pleural cavity] . Small empyema may not require any special therapy. **Large empyema may restrict breathing and require drainage** [3].

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3-Meningitis

1-Meningitis is an inflammation of the membranes (the meninges), whereas **encephalitis** is an inflammation of the brain tissue [1]. **75% of cases of meningitis are believed to occur in those <15yrs of age** [2].

2-**Three organisms** (***Streptococcus*** *pneumoniae*, ***Neisseria*** *meningitides* and ***Haemophilus*** *influenzae* type b) account for 80% of the cases [2]. [In newborns, *Group B streptococcus* , *E. coli*, and *Listeria monocytogenes* are the most common pathogens] [3].

Clinical Manifestations [2, 4].

1- In **young infants symptoms may be non-specific** including fever, poor feeding, lethargy.

2-In older children clinical features include:

- ***General****:* fever, with headache.
- ***Central****:* irritability, disorientation, altered mental state.
- ***Seizures****:* occur in 30%.
- ***Neck stiffness****:* more common in older children.
- **Kernig** and **Brudzinski** signs of meningeal irritation are often positive in children older than 12 months.

Diagnosis

1-If bacterial meningitis is suspected, a **lumbar puncture** should be performed . Routine CSF examination includes a white blood cell count, differential, protein and glucose levels, and Gram stain [4].

Treatment

1-Treatment of bacterial meningitis focuses on **sterilization of the CSF by antibiotics** (Table 1) [4].

2-Duration of treatment is 5 to 7 days for *N. meningitidis,* 7 to 10 days for *H. influenzae,* and 10 to 14 days for *S. pneumoniae* [4].

3-Steroids In bacterial meningitis:

• Do not use corticosteroids in children younger than 3mths [2].

• There is benefit from the use of dexamethasone and the dosing schedule is 0.15mg/kg qds for 4 days **to reduce the severity of neurological sequelae**, **particularly deafness**, after bacterial meningitis) [2].

• If dexamethasone was not given before the first dose of antibiotics, but was indicated, try to give the first dose within 4hr of starting antibiotics, but do not start dexamethasone more than 12 hours after starting antibiotics [2].

Table 1: Initial Antimicrobial Therapy by Age for Presumed Bacterial Meningitis

AGE	RECOMMENDED TREATMENT	ALTERNAT TREATME
Newborns (0–28 days)	Cefotaxime or ceftriaxone plus ampicillin with or without gentamicin	Ampicillin plus gentamicin Ceftazidime p ampicillin
Infants and toddlers (1 mo–4 yr)	Ceftriaxone or cefotaxime plus vancomycin	Cefotaxime or ceftriaxone pl rifampin
Children and adolescents (5–13 yr) and adults	Ceftriaxone or cefotaxime plus vancomycin	Cefepime or ceftazidime pl vancomycin

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4-Encephalitis

1-Encephalitis is an inflammation **of the brain tissue** . **Viruses are the principal causes** of acute infectious encephalitis [1].

Clinical Manifestations

1-Acute infectious encephalitis usually is preceded by a prodrome of several days of nonspecific symptoms such as sore throat, fever, and headache followed by the **characteristic symptoms** of progressive **lethargy**, **behavioral changes**, and **neurologic deficits**. **Seizures are common** at presentation [(1)].

Diagnosis

The diagnosis of viral encephalitis is supported by **examination of the CSF** [(1)].

Treatment

1-With the exception of HSV, varicella-zoster virus, cytomegalovirus, and HIV, there is no specific therapy for viral encephalitis. **Management is supportive** [(1)].

2-Intravenous **acyclovir is the treatment of choice for HSV** and **varicella-zoster virus** infections. **Cytomegalovirus** infection is treated with **ganciclovir**. HIV infections may be treated with a combination of antiretroviral agents [(1)].

References

1-Robert M. Kliegman. Nelson essentials of pediatrics. 7th edition. 2015.

5-Visceral Leishmaniasis (Kala-azar) (Black fever)[(1, 2)]

1-Visceral Leishmaniasis (VL) is caused by the protozoon **Leishmania donovani**.

2- Infection are introduced by the feeding female **sand fly**.

3- The great majority of people infected remain asymptomatic. In visceral diseases the spleen, liver, bone marrow and lymph nodes are primarily involved.

Clinical features

1-VL is predominantly a disease of small children and infants.

2-The **first sign of infection is high fever**, usually accompanied by rigor and chills.
3-**Splenomegaly** develops quickly in the first few weeks and becomes massive as the disease progresses. Moderate hepatomegaly occurs later. Lymphadenopathy may also seen .

4-Blackish discoloration of the skin, from which the disease derived its name, kala-azar (the Hindi word for 'black fever'), is a feature of advanced illness and is now rarely seen.

5-**Pancytopenia** is a common feature.
6-Without adequate treatment most patients with clinical VL die.

Diagnosis

1-Demonstration of amastigotes in **splenic smears** is the most efficient means of diagnosis, with 98% sensitivity ; however, it carries a risk of serious haemorrhage in inexperienced hands.

2-Serodiagnosis, by ELISA or indirect immunofluorescence antibody test (**IFAT**). A significant proportion of the healthy population in an endemic region will be positive for these tests due to past exposure.

Treatment

1- The pentavalent antimony compound [**sodium stibogluconate** (Pentostam®)]. The daily dose is 20 mg/kg body weight, given either intravenously or intramuscularly **for 28 days.**
2-Side-effects are common and include arthralgias, myalgias, raised hepatic transaminases, pancreatitis and ECG changes.

3-**Amphotericin B** is very useful in the treatment of antimony-unresponsive VL

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6-Cytomegalovirus [1-3].

1- **Cytomegalovirus** (CMV) **is the most common congenital infection** and the leading cause of hearing loss, mental retardation, retinal disease, and cerebral palsy.
2-Transmission occurs **transplacentally or perinatally** through contact with cervical secretions or through breast milk. Perinatal exposure is not usually associated with disease in term infants, but preterm infants may be infected.

3-When primary infection occurs in mothers during a pregnancy, the virus is transmitted to the fetus in approximately 35% of cases.

4-The earlier in gestation that the primary maternal infection occurs, the more symptomatic the infant will be at birth.

Presentation

1-More than 90% of infants who have congenital CMV infection **exhibit no clinical evidence of disease at birth.**

2-Approximately 10% of infected infants are small for gestational age and have symptoms at birth. The characteristic signs and symptoms include:

Intrauterine growth retardation, **prematurity**, **hepatosplenomegaly** and **jaundice**, **thrombocytopenia and purpura, microcephaly (small head)and intracranial calcifications**. Other neurologic problems include **retinitis**, and **hearing abnormalities**.

3-Mortality is 10% to 15% in symptomatic newborns.
4-In case of perinatal CMV infection acquired during birth or from mother's milk, the majority of infants remain asymptomatic and do not exhibit sequelae.

Diagnosis.

1-Congenital CMV infection is diagnosed by detection of virus in the urine or saliva.

2- Positive CMV immunoglobulin M (IgM) serology is highly suggestive, but NOT diagnostic.

Treatment

1-There are limited options for treatment of CMV infection. Treatment is not indicated for immunocompetent persons, but is recommended for immunocompromised persons, and remains controversial for infants with symptomatic congenital infection.
2-first, **ganciclovir** and, then, **valganciclovir** have been evaluated for the treatment of babies with symptomatic disease [(4)] .
3-only those children with symptomatic and congenital CMV infection should be treated as no data exist on the potential efficacy of valganciclovir in the treatment of **asymptomatic disease** [(4)] .
4-Treatment of Congenital Infection: Trial studies in severely symptomatic newborns of the antiviral agent **ganciclovir** have shown a lack of progression of **hearing loss**.
Dose: 6 mg/kg I.V every 12 hours for 6 weeks.
5-Ganciclovir is related to aciclovir but it is more active against cytomegalovirus; it is also much more toxic (**Myelosuppression**) than aciclovir.

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D-Neurology

1-Guillain–Barré syndrome [1-3].

1-Guillain-Barré syndrome (GBS): is a postinfectious autoimmune **peripheral neuropathy** that can occur about **10 days after a respiratory or gastrointestinal infection** (bacterial or viral).

2-It occurs in people of all ages and is the most common cause of acute flaccid paralysis in children.

Clinical Manifestations

1-The characteristic symptoms are **flaccidity**, and symmetrical **ascending weakness**.

2-**Ascending weakness**: Weakness begins usually in the lower extremities and progressively involves the trunk, the upper limbs, and finally the bulbar muscles ((tongue, pharynx, larynx).

3-**Respiratory insufficiency** may result.

4-**Recovery**: should begin within 2–4wks, in a descending manner, though full recovery sometimes takes a number of months.

Diagnosis

The **main diagnostic features of GBS is clinical**(muscle weakness, with loss of reflexes in an ascending fashion).

Prognosis

1-**The clinical course is usually benign**, and spontaneous recovery begins within 2-3 wk. Most patients regain full muscular strength, although some are left with residual weakness.

2-Bulbar and respiratory muscle involvement may lead to death if the syndrome is not recognized and treated.

Treatment

1-Intravenous **immunoglobulin** (IVIG)(400mg/kg/day **for 5 days**) is normally used initially.

2-**Plasmapheresis** and immunosuppressive drugs are alternatives when IVIG treatment is unsuccessful[4] .

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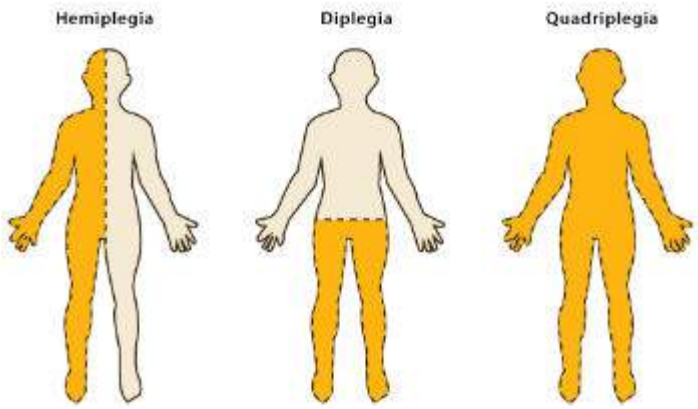
2-Cerebral palsy (CP) [1-4].

Definition: a chronic disorder of movement and/or posture that presents early (i.e. before the age of 2yrs) and continues throughout life.
Causation: CP is caused by nonprogressive (static) injury to the developing brain [1].

Causes of CP

The cause is unknown in many patients but identified risk factors can be categorized into antenatal, intrapartum, and postnatal:

A-Antenatal: congenital infections(rubella, cytomegalovirus, toxoplasmosis).
B-Intrapartum: birth asphyxia.
C-Postnatal: (hyperbilirubinemia, hypoglycemia, meningitis, encephalitis,….).



Clinical features

CP can present with:
1-**Delayed motor milestones** : Most children with CP, except in its mildest forms, are diagnosed in the first 18 months of life when they fail to attain motor milestones.

2-**Feeding difficulties** due to lack of oromotor coordination.
3-**Speech and language** delay.

Classification

1-CP classified into 4 types (Spastic CP, Ataxic CP, Dyskinetic CP, and Mixed CP).
2-**Spastic CP the most common form of CP**, it accounts for 70%–80% of cases. It can be hemiplegic (affects one side of the body), diplegic (affects legs or arms), or quadriplegic (affects all the four limbs).

Problems associated with CP

1-Mental retardation and learning difficulty.
2-seziures
3-gastro-esophageal reflux
4-feeding problems and failure to thrive (FTT).
5-Recurrent pneumonia.
6-hearing and vision abnormalities.

Diagnosis

The diagnosis is made on **clinical examination**. An MRI scan of the brain is generally indicated to determine the location and extent of lesions .

Treatment.

1-Treatment of CP required multidisciplinary approach including (Speech, physiotherapy, and occupational therapy).The primary therapists are the child's carers.

2-Several drugs have been used to **treat spasticity**, including dantrolene sodium, the benzodiazepines, and **baclofen**. These medications should be considered if severe spasticity is not controlled by other measures.

3-Patients with rigidity, and **spastic quadriparesis** sometimes respond to **levodopa**.

References

1- Robert M. Kliegman. Nelson essentials of pediatrics. 7th edition. 2015.
2- Nelson Textbook of pediatrics. 29th edition.
3- Robert C. Tasker. Oxford Handbook of Paediatrics. 2nd edition.2013
4- Shyam Bhakthavasala. Crash course pediatrics.3rd edition 2008.

3-Febrile convulsion

1-A febrile convulsion is a fit occurring in a child (**generally between the ages of 6mths and 6yrs**), **precipitated by fever** (temp > 38 C) arising from infection outside the nervous system in a child who is otherwise neurologically normal [1-3] and in case of absence of acute electrolyte imbalance [4].

2-They occur in up to 4% of all children . The vast majority of febrile seizures are **harmless** [3].

3-Children prone to febrile seizures **are not considered to have epilepsy** (95–98% of children who have experienced febrile seizures do not go on to develop epilepsy) [3].

Etiology

1-The **etiology is unknown**. Genetic predisposition appear to be a risk factor [1,2]

2-Typically febrile seizure **occurs within the 1st 24 hour of a febrile episodes** [1] and most commonly due to acute viral respiratory infections [5].

Types of febrile seizure

1-**Simple febrile seizures** last **less than 15 minutes**, and occur **only once in a 24-hour** period [6]. The risk of subsequent epilepsy is not substantially greater than that for the general population [6].

2-If the seizure lasts **longer than 15 minutes** or **recurs within 24 hours** the seizure is referred to as a **complex or atypical febrile seizure** [6]. It signify a greater risk of later epilepsy [1,4].

Diagnosis:

Diagnosis is made by **exclusion of other causes** of symptomatic seizures like meningitis or metabolic abnormalities [4].

Treatment

1-Intervention to stop the seizure usually is unnecessary as the seizure has typically resolved by the time the child is evaluated by a physician. On the other hand, treatment should be initiated if the seizure is still ongoing by the time the child arrives at a medical facility. If that is the case, the child can be treated with **intravenous lorazepam (0.05–0.1 mg/kg) or diazepam (0.1–0.2 mg/kg)** which is very efficient in terminating the seizure [9] .

2-**Control fever** : Measures to reduce elevated temperature should be initiated. Acetaminophen (or ibuprofen) and tepid sponge baths usually are helpful [1]. However, **administration of antipyretics during febrile illnesses does not prevent febrile seizures** [6].

3-Febrile seizures always are **outgrown** [7], so typically, **Long-term treatment or prophylaxis with antiepileptic drug (AED) for simple febrile seizures is not recommended** [1].

4-Oral diazepam (Valium) prophylaxis, **started at the onset of fever**, **prevents febrile seizure** [7] (oral diazepam, 0.3 mg/kg q8h , is administered for the duration of the illness (usually 2-3 days). This strategy may be useful when parental anxiety associated with febrile seizures is severe [8].

5-Patients who have **prolonged febrile seizures** can benefit from **rectal diazepam gel** given soon after the onset of a febrile seizure to prevent additional prolonged seizures [7].

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E-Rheumatic Diseases of Childhood

1- Kawasaki disease (KD)[1-4]

1-Kawasaki disease (KD) is a **systemic vasculitis** of unknown etiology . KD most commonly occurs in children younger than 5 years of age, with a peak between 2 to 3 years.

2-The etiology is unknown but the disease process is a vasculitis affecting small to medium-sized arteries including the **most importantly the coronary arteries leading to coronary artery aneurysms.**

3-Subsequent scar formation causes vessel narrowing , myocardial ischemia or even infarction and sometimes sudden death.

Clinical Manifestations and diagnosis

1-The diagnosis can be made in children with fever present for at least 5 days, without other explanation, in the presence of 4 of the 5 following criteria

A- Bilateral **conjunctival** injection.
B- Changes in the **mucosa of the oropharynx** including dry fissured lips, and strawberry tongue.
C- Changes of the peripheral extremities, such as **edema and/or erythema of the hands or feet.**
D- **Skin rash**.
E-**Cervical adenopathy**.

Treatment

1-Intravenous i**mmunoglobulin** (IVIG) is the mainstay of therapy for KD, although the mechanism of action is unknown. A single dose of IVIG (2 g/kg over 12 hours) results in rapid resolution of clinical illness in most patients and, more important, reduces the incidence of coronary artery aneurysms.

2-Aspirin is initially given in **anti-inflammatory doses** (80 to 100 mg/kg/day divided every 6 hours) . Once the fever resolves, aspirin is reduced to **antithrombotic doses** (3 to 5 mg/kg/day as a single dose) (there is an increased coagulability) and usually given for 6 to 8 weeks, until follow-up echocardiography documents the absence or resolution of coronary artery aneurysms.

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F-Cardiovascular Disorders

1-Acute rheumatic fever

1-Acute rheumatic fever remains an important preventable cause of cardiac disease [(1)]. Acute rheumatic fever **usually affects children** (most commonly between 5 and 15 years) or young adults [(2)].

2-The condition is triggered by **an immune-mediated response to infection with specific strains of group A streptococci**, which have antigens that may cross-react with cardiac myosin and membrane protein. Antibodies produced against the streptococcal antigens cause inflammation in **the heart as well as the joints and skin** [2].

Clinical features

1-Acute rheumatic fever is a multisystem disorder that usually presents with **fever**, and **joint pain**, **2–6 weeks after an episode of streptococcal pharyngitis** [1, 2].

Table 1: criteria for the diagnosis of rheumatic fever [2].

Major manifestations	
• Carditis	• Erythema marginatum
• Polyarthritis	• Subcutaneous nodules
• Chorea	
Minor manifestations	
• Fever	• Raised ESR or CRP
• Arthralgia	• Leucocytosis
• Previous rheumatic fever	• First-degree AV block
Plus	
• Supporting evidence of preceding streptococcal infection: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, positive throat culture	

2-The presence of either two **major criteria** or one major and two **minor criteria**, along with evidence of preceding **streptococcal infection**, confirm a diagnosis of acute rheumatic fever [1].
[Streptococcal antibody tests, such as the antistreptolysin O (**ASO**) titer, are the most reliable laboratory evidence of prior infection] [1].

Management of the acute attack

1-A single dose of benzyl penicillin 1.2 million U i.m. or oral phenoxymethyl penicillin for 10 days should be given on diagnosis to eliminate any residual streptococcal infection. If the patient is penicillin-allergic, erythromycin or a cephalosporin can be used [2].
2-**Bed rest is important**, as it lessens joint pain and reduces cardiac workload [2].
3-**Aspirin:** This will usually relieve the symptoms of arthritis rapidly [2]. The usual dose of aspirin is 100 mg/kg/24 hr divided qid PO for 3-5 days, followed by 75 mg/kg/24 hr divided qid PO for 4 wk [3].

4-Patients with carditis and cardiomegaly or congestive heart failure should receive **corticosteroids**.
The usual dose of prednisone is 2 mg/kg/24 hr in 4 divided doses for 2-3 wk followed by a tapering of the dose that reduces the dose by 5 mg/24 hr every 2-3 days [3].

5-Supportive therapies for patients with moderate-to-severe carditis include **digoxin**, **fluid** and **salt restriction**, **diuretics**, and **oxygen** [3].

6-Sedatives may be helpful early in the course of chorea; Phenobarbital is the drug of choice. If phenobarbital is ineffective, then haloperidol or chlorpromazine should be initiated [3].

Secondary prevention

1-Patients are susceptible to further attacks of rheumatic fever if another streptococcal infection occurs, and long-term prophylaxis with penicillin should be given as **i.m benzathine penicillin monthly** [2].

2-Further attacks of rheumatic fever are unusual after **the age of 21**, when treatment may be stopped [2].

Chronic rheumatic heart disease

Chronic valvular heart disease develops in at least half of those affected by rheumatic fever **with carditis** [2]. This result in scarring and fibrosis of the heart valves (most commonly **mitral** valve) and may result in incompetent valves **requiring replacement** [4].

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1- Robert M. Kliegman. **Nelson essentials of pediatrics**. 7th edition. 2015.
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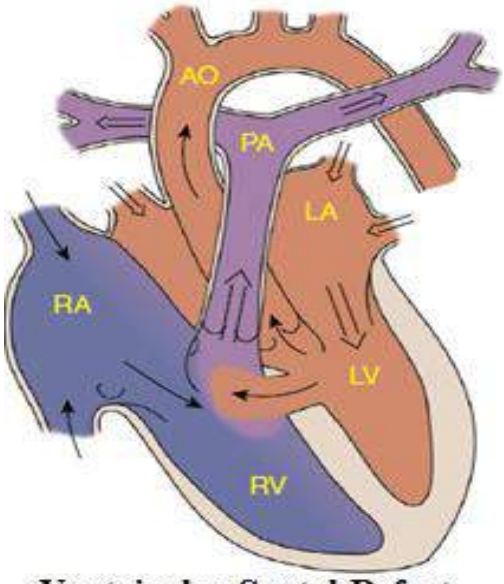
2-Congenital Heart Disease

A-Ventricular Septal Defect (VSD)

VSD is the most common congenital heart defect accounts for 25% of all congenital heart disease [1].



Ventricular Septal Defect

Clinical Manifestations

Small VSDs with little are often asymptomatic. Moderate to large VSDs result in excessive pulmonary blood flow , pulmonary hypertension and heart failure [1, 2].

Small VSD

1-The child is **asymptomatic** [3].
2-**Antibiotic prophylaxis against bacterial endocarditis** should be provided for dental visits (including cleanings) [2, 3].
3-Spontaneous closure might occur [3].

Medium VSD

1-These usually present with symptoms during infancy including **slow weight gain**, **feeding difficulties**, and **recurrent chest infections** [3].

2-Heart failure, if present, should be treated by **diuretics (± digoxin) and ACE inhibitors** [1, 3] .

3-Spontaneous improvement occurs in many childhood cases and surgical correction can be avoided. However, if there significant VSD at 4 years, closure should be considered before the child starts school [3].

Large VSD

Heart failure develops early on. Initial treatment of heart failure is required and **surgical closure is usually necessary** [3].

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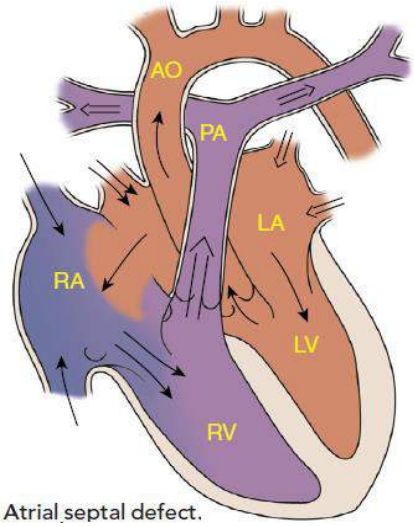
3-Shyam Bhakthavasala. ***Crash course pediatrics***.3rd edition 2008.

B-Atrial Septal Defect (ASD)

1-Atrial septal defects are common, representing 5–10% of all congenital heart defects [1].



Atrial septal defect.

2-Children with an atrial septal defect *are asymptomatic* [1].

3-While patients with ASD are asymptomatic in childhood, problems with **congestive heart failure**, and **pulmonary hypertension** can **develop in the third decade of life** and beyond [1].

4-**Treatment**: **ASD closure is required and advised for all patients, even if asymptomatic**. Intervention should be performed in early childhood, before school entry [2].

References

1-Thomas P. Green. ***Pediatrics Just the Facts***. Copyright © 2005 by The McGraw-Hill Companies.
2-Robert C. Tasker. Oxford Handbook of Paediatrics. 2nd edition.2013

G-Gastroenterology

1-Acute Gastroenteritis (GE)

It is an infection of the small intestine, which present with a combination of **diarrhea** and vomiting [1] , but sometimes present without vomiting [2].

Etiology

1-**Rota virus** is the most common pathogen in children **under 2 years** [3], other causes include:

A-Acute **bacterial infections** (shigellae, Salmonellae, E coli and Vibirio cholera which secrete enterotoxins) [3].
B-**Parasites** like E. histolytica, and Giardia lambilia [2].

Clinical Features

1-**Rotaviruse cause watery diarrhea** . **Respiratory illness** occur in about half of patients followed by vomiting and diarrhea [1, 2].

2-Acute **bacterial** infection cause invasion of GIT, so there is **fever**, and small volume **bloody stool** [3].

Complication of Gastroenteritis

Dehydration, **metabolic disturbances** and even **death** [4].

Treatment

1-Uncomplicated viral GE requires no specific treatment except attention to fluid and electrolyte replacement [3] Most of these episodes are self-limited [4].

2-There is **no role for antiemetic or antidiarrheal** in GE [1].

3-**Antibiotics are rarely indicated** except for specific infections such as invasive salmonellosis, cholera , amebiasis or giardiasis [1, 3].

4-The **key management of GE is rehydration** with correction of fluid and electrolyte imbalance [1].

A-Unless the child has persistent vomiting,oral fluid is the best means for rehydration, smaller more frequent sips may be better tolerated and should be encouraged [1].

B-**Mild Dehydration**: ORS are used [1].

C-**Moderate dehydration:** Oral rehydration is still indicated if tolerated.
D-**I.V fluid** should be reserved for those **with vomiting or severe dehydration** [1].

5-**Zinc supplementation** (10–20 mg for 10–14 days) has been recommended by the WHO for the treatment and prevention of diarrheal disease in children in developing countries [4].

6-**Continuation of oral feeding**, despite diarrheal episodes, decreases the duration of illness; and improves nutritional status [4].

Reference

1- Shyam Bhakthavasala. ***Crash course pediatrics***.3rd edition 2008.
2- Bernard Valman. ABC of first year, 5th edition, 2002.

3- **Judith M. Sondheimer, MD**. Current Essentials Pediatrics. Copyright © 2008 by The McGraw-Hill Companies, Inc.
4- Koda-Kimble and Young's. ***Applied Therapeutics***: ***The clinical use of drugs***, 10th ed., 2013 by Lippincott Williams & Wilkins.

2-Viral Hepatitis

Etiology

1-There are six primary hepatitis viruses: Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis D virus (HDV), Hepatitis E virus (HEV) and Hepatitis G virus (HGV) [(1)].

2-They differ in their transmission, severity, likelihood of persistence, and subsequent risk of hepatocellular carcinoma [(1)].

	HAV	**HBV**	**HCV**	**HDV**	**HEV**	**HGV**
Transmission	Fecal -oral	Transfusion , sexual, perinatal	Parenteral, transfusion, perinatal	Similar to HBV	Fecal -oral	Parenteral, transfusion

Note - The most important risk factor for acquisition of **HBV in children is perinatal exposure to infected mother**. In most cases, transmission **occurred at the time of delivery**; virus contained in amniotic fluid or in maternal blood may be the source. However less commonly intrauterine infection occurred [(2)].

3-**HBV and HCV cause chronic infection**, which may lead to **cirrhosis** and is a significant risk factor for **hepatocellular carcinoma** [(1)].

Clinical Manifestations

1-**Asymptomatic or mild**, nonspecific illness without icterus (jaundice) **is common** with HAV, HBV, and HCV, **especially in young children**[(1)].

2-The **preicteric phase**, which lasts approximately 1 week, is characterized by headache, anorexia, malaise, abdominal discomfort, nausea, and vomiting and usually precedes the onset of clinically detectable disease [(1)].

3-**Jaundice** and tender **hepatomegaly** are the most common physical findings and are characteristic of the **icteric phase**. Hepatic enzymes may increase 15- to 20-fold [(1)].

4-Resolution of the hyperbilirubinemia and normalization of the transaminases may take 6 to 8 weeks [(1)].

Complications

1-Most cases of acute viral hepatitis resolve without specific therapy, with less than 0.1% of cases progressing to **fulminant hepatic necrosis** which is associated with a high mortality rate [(1)].

2-**HAV and HEV cause acute infection only**. HBV, HCV, and HDV may persist as **chronic infection** with chronic inflammation, fibrosis, and **cirrhosis and the associated risk of hepatocellular carcinoma** [(1)].

Diagnosis

The diagnosis of viral hepatitis is confirmed by **serologic testing** [(1)].

Treatment

1-The treatment of acute hepatitis [(1)] (**except HCV** [(3)]) is largely supportive and involves rest, hydration, and adequate nutrition. Hospitalization is indicated for severe cases [(1)].

2-**Chronic HBV** infection may be treated with **interferon alfa-2b or lamivudine**, and HCV may be treated with interferon alfa usually in combination with Ribavirin [(1)].

References

1-Robert M. Kliegman. Nelson essentials of pediatrics. 7th edition.2015.
2-Nelson Textbook of pediatrics. 29th edition.
3-Edward T. Bope, et al, eds. ***Conn's Current Therapy*****.** Copyright 2014.

3-Wilson's disease [(1, 2,3)]

1- Wilson's disease is a rare autosomal recessive disorder leading to **toxic accumulation of copper in the liver** and, subsequently, other tissues especially the brain and eye..

Presentation

• Kayser–Fleischer rings (**copper deposition in the eye**)
• **Hepatic problems** usually present in childhood (hepatitis, cirrhosis, fulminant hepatic failure).
• Adolescents/young adults usually present with **neurological disease**.

Diagnosis

The diagnosis is made by identifying **depressed serum levels of ceruloplasmin**, **elevated** 24-hour **urine copper excretion**, and the presence of **Kayser-Fleischer rings in the iris**.

Treatment

1-Treatment consists of administration of copper-chelating drugs (**penicillimine**) (reverses pre-cirrhotic liver disease, but not neurological damage).

2-**Zinc salts** often replace chelating agents after chelation therapy has successfully reduced excessive body copper stores.

3-Adequate therapy must be **continued for life** to prevent liver and CNS deterioration.
4-Liver transplantation is a highly effective treatment of WD as it reverses the systemic copper metabolism disturbances, changing hepatocyte copper metabolism (3).

References

1- Robert M. Kliegman. Nelson essentials of pediatrics. 7th edition. 2015.
2- Robert C. Tasker. Oxford Handbook of Paediatrics. 2nd edition.2013.
3-Litwin T, Dusek P, Skowrońska et al. Treatment of Wilson's disease–an update. Expert Opinion on Orphan Drugs. 2019 Jun 3;7(6):287-94.

H-Respiratory Disorders

1-Cystic Fibrosis

Background

1-Cystic fibrosis (CF) is an autosomal recessive multisystem disorder caused by mutations in the *cystic fibrosis transmembrane regulator* (**CFTR**) gene [(1)].

2- CFTR is important for the proper movement of salt and water across epithelial cell membranes especially in the airways, liver, and pancreas [(2)]. The term *cystic fibrosis* arises from the fibrotic scar tissue that replaces the destroyed pancreas [(3)].

Pathophysiology

A-Pulmonary System

1-In CF, there are reduced chloride secretion with excessive sodium resorption which lead to dehydration of the airway lining [(4)] leading to airway obstruction. This, in turn, leads to colonization with bacteria especially *Staphylococcus aureus* and *Pseudomonas aeruginosa* [(2)].
2-Chronic lung disease is a hallmark of CF, leading to death in 90% of patients [(5)]. CF patients will usually experience **chronic respiratory infections** [(6)].

B-Gastrointestinal Involvement

1- Approximately 10% of patients with CF are born with intestinal obstruction caused by inspissated meconium (**meconium ileus**). In older patients, intestinal obstruction may result from thick inspissated mucus in the intestinal lumen [(2)].

C-Hepatic Involvement

1-In patients with CF, there is reduction in water and sodium movement into the bile. **The resulting decrease in the volume and flow of bile leads to stasis and obstruction of the biliary tree**. With chronic obstruction, this leads to **biliary cirrhosis** [(3)].

D-Pancreatic Involvement

1-The obstruction of the pancreatic ducts result in the inability to excrete pancreatic enzymes into the intestine. This leads to malabsorption of proteins, sugars (to a lesser extent), and **especially fat**. Fat malabsorption manifests clinically as **steatorrhea** (large foul-smelling stools), **deficiencies of fat-soluble vitamins** (A, D, E, and K), and **failure to thrive** [2].

E-Sweat Gland

In the sweat duct, CFTR reabsorbs chloride from sweat. Dysfunctional CFTR results in a **nearly fivefold elevation in sweat chloride concentrations**. This is the principal laboratory criterion for diagnosis of CF (**sweat chloride test**) [7].

Diagnosis

CF is most commonly diagnosed on the basis of typical **signs and symptoms** and an abnormal sweat chloride concentration (>60 mEq/L) (**sweat chloride test**) [3, 7].

Treatment

The treatment of CF is multifactorial, but it is primarily directed toward the gastrointestinal and pulmonary complications [2].

A-Gastrointestinal System

1-**Pancreatic enzyme replacement** (lipase, protease, and amylase) is the mainstay of gastrointestinal therapy [5].

2-**Fat-soluble vitamins (A, D, E, and K) supplementation** is usually required in pancreatic insufficiency [5].

3-The use **of ursodeoxycholic acid (UDCA)** may improves bile flow, prevent obstruction and slow progression of liver disease [5, 7].

B-Treatment of Cystic Fibrosis Airway Disease

Treatment of CF airway disease involves the use of medications and techniques to mobilize pulmonary secretions, and antibiotics to manage infection [3].

1-Mucociliary Clearance

A-Physical Therapy: Airway clearance can be performed using various techniques. These techniques are recommended **on a daily basis to help mobilize secretions** [8].

B-Mucolytic Therapy: Sputum viscosity is increased by the large quantities of extracellular DNA that result from chronic airway inflammation and degradation of neutrophils [9]. **Inhaled recombinant human deoxyribonuclease** (rhDNase, dornase alpha) cleaves extracellular DNA in sputum [9].

C-Airway Hydration Therapies : Inhalation of hypertonic saline rehydrates the airways through osmotic flow of water [(3)].

D-Bronchodilators: β-Agonists keep airways open and facilitate airway clearance [(8)].

2-Antibiotics

1-Antibiotics are used to treat lung infection. *Typical regimens for severe infections include an antipseudomonal β-lactam plus an aminoglycoside for added synergy and delay of resistance development* [(5)].

2-**Fluoroquinolone** use is common among CF patients infected with ***P. aeruginosa*****,** even in children [(5)].

3-**Chronic maintenance antibiotic therapy may be used in patients with *Pseudomonas* colonization** in an attempt to prevent bacterial overgrowth [(5)]. **Inhaled tobramycin** has been studied the most extensively [(5)].

Pharmacokinetic Considerations

CF patients have **larger volumes of distribution of many antibiotics** and also have an enhanced total body clearance [(5)]. As a result of these pharmacokinetic changes, **higher doses of antibiotics** (e.g. aminoglycosides, and β-lactam antibiotics) are needed [(5)].

Lung transplantation

Lung transplantation is currently the only definitive treatment for advanced cystic fibrosis [(9)].

Prognosis

The longevity of patients with cystic fibrosis is increasing, and the median survival age is over 35 years. Death occurs mostly from pulmonary complications [(9)].

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1-Thomas P. Green. ***Pediatrics Just the Facts***. Copyright © 2005 by The McGraw-Hill Companies, Inc.

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I-Endocrinology

1-Diabetic ketoacidosis (DKA)

1-**Definition**: Arterial pH <7.30, bicarbonate <15 meq/L, glucose >250 mg/dL, and Urinary ketones [1, 2].

2-DKA is a major **medical emergency** and remains a serious cause of morbidity, principally in people **with type 1 diabetes** [3] (**More common in type 1 DM** but can occur in type 2 DM) [4].

3-A significant number of **newly diagnosed diabetic children** present with DKA. In children with known diabetes, DKA occurs in patient who omit insulin doses or who do not successfully manage an intercurrent illness [3, 5].

Risk Factors

1-**Omission of insulin** is the most common precipitant of DKA [6].

2-**Infections**, acute medical illnesses, and stress of recent surgical procedures can contribute to the development of DKA [6].

Pathophysiology

1-The **hyperglycaemia** causes a profound **osmotic diuresis** leading to **dehydration**, hyperosmolarity, and **electrolyte loss**, particularly of sodium and potassium [3, 6].

2-Owing to increased lipolysis and decreased lipogenesis, free fatty acids are converted to ketone bodies and lead to **metabolic acidosis** [6, 7].

3- **Electrolyte abnormalities** occur through a loss of electrolytes in the urine [7]. In addition, The resulting metabolic acidosis causes efflux of potassium from cells, results in intracellular potassium depletion [3, 6].

Clinical Presentation

1-Patients with DKA present initially with **polyuria**, **polydipsia**, **nausea**, and **vomiting**. **Abdominal pain** occurs frequently [7].

2-Respiratory compensation for acidosis results in **tachypnea with deep (Küssmaul) respirations**. The **fruity odor of acetone** frequently can be detected on the patient's breath [7].
3-An altered mental status can occur, ranging from disorientation to coma [7].

Management

1-DKA is a **medical emergency** which should be treated in hospital [3]. The principal components of treatment are :
• The administration of **short-acting** (soluble) insulin [3].

• **Fluid** replacement [3].
• **Potassium** replacement [3].
• The administration of **antibiotics** if infection is present [3].
Note: for more detailed about for the management of ketoacidosis , there is **a Diabetic Ketoacidosis Treatment Protocol** [5].

Complications

The most concerning complication of DKA is **cerebral oedema** (Treatment by Mannitol 1 g/kg IV) [2].

References

1-Thomas P. Green. ***Pediatrics Just the Facts***. Copyright © 2005 by..
2-Robert C. Tasker. Oxford Handbook of Paediatrics. 2nd edition.2013
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4-ACCP Updates in Therapeutics® 2012: ***The Pharmacotherapy Preparatory Review and Recertification Course*.**
5-Nelson Textbook of pediatrics. 29th edition,
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Most commonly used ANTIBIOTICS IN PEDIATRICS (the last 2 columns to be filled by the student)

No.	Antibiotics	indication	Doses	Sever interactions	Fluid-compatibilities
1	Amoxicillin	Susceptible infections (including UTIs,otitis media, sinusitis, uncomplicated community acquired pneumonia, salmonellosis	***IV injection and IV infusion*** a.Neonate up to 7 days: **30 mg/kg every 12 hours**, increased if necessary to 60 mg/kg every 12 hours, increased dose used in severe infection, community-acquired pneumonia or salmonellosis. b.Neonate 7 days to 28 days: **30 mg/kg every 8 hours,**increased if necessary to 60 mg/kg every 8 hours,increased dose used in severe infection, community acquired pneumonia or salmonellosis. c.Child: **20-30 mg/kg** every 8 hours (max. per dose 500 mg), ↑ if necessary to 40-60 mg/kg every 8 hours (max. per dose 1 g every 8 hours), ↑dose used in severe infection		
2	Cefotaxime	Infections due to sensitive Gm+ve and Gm –ve bacteria | Surgical prophylaxis |Haemophilus epiglottitis Severe susceptible infections due to sensitive	▸ BY I.M INJECTION, or by I.V INJECTION, OR BY IV INFUSION ▸a.Neonate up to 7 days: 25 mg/kg every 12 hours. b.Neonate 7 days to 20 days: 25 mg/kg every 8 hours. c.Neonate 21 days to 28 days: 25 mg/kg every 6-8 hours. d. Child: 50 mg/kg every 8-12 hours. ▸ BY I.M Inj, OR BY I.V inj.or by I.V infus. ▸a. Neonate up to 7		

		Gm +ve and Gm -ve bacteria | Meningitis	days: 50 mg/kg every 12 hours. ▸ b.Neonate 7 days to 20 days: 50 mg/kg every 8 hours. ▸ c.Neonate 21 days to 28 days: 50 mg/kg every 6-8 hours. ▸ d.Child: 50 mg/kg every 6 hours;		
3	Ceftriaxone	Community-acquired pneumonia | Hospital-acquired pneumonia | Intra-abdominal infections | Complicated UTIs.	▸ BY INTRAVENOUS INFUSION ▸ a.Neonate up to 15 days: 20-50 mg/kg once daily, doses at the higher end of the recommended range used in severe cases. ▸b. Neonate 15 days to 28 days: 50-80 mg/kg once daily, doses at the higher end of the recommended range used in severe cases. ▸c. Child 1 month–11 years (body-weight up to 50 kg): 50-80 mg/kg once daily, doses at the higher end of the recommended range used in severe cases; maximum 4 g per day ▸ d.Child 9–11 years (body-weight 50 kg and above): 1-2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸e. Child 12–17 years: 1-2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸ BY INTRAVENOUS INJECTION ▸ a.Child 9–11 years (body-weight 50 kg and		

			above): 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸ b.Child 12–17 years: 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸ BY DEEP INTRAMUSCULAR INJECTION ▸ a.Child 1 month–11 years (body-weight up to 50 kg): 50–80 mg/kg daily, doses at the higher end of the recommended range used in severe cases;maximum 4 g per day ▸ b.Child 9–11 years (body-weight 50 kg and above): 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸ c.Child 12–17 years: 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases ▸ BY INTRAVENOUS INFUSION ▸a. Neonate up to 15 days: 50 mg/kg once daily. ▸b. Neonate 15 days to 28 days: 80–100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis. ▸ c.Child 1 month–11		
		Bacterial meningitis | Bacterial endocarditis			

			years (body-weight up to 50 kg): 80‑100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis; maximum 4 g per day ▸ d.Child 9–11 years (body-weight 50 kg and above): 2‑4 g once daily, doses at the higher end of the recommended range used in severe cases ▸ e.Child 12–17 years: 2‑4 g once daily, doses at the higher end of the recommended range used in severe cases ▸ BY INTRAVENOUS INJECTION ▸ Child 9–11 years (body-weight 50 kg and above): 2‑4 gonce daily, doses at the higher end of the recommended range used in severe cases; doses of 50 mg/kg or more should be given by infusion ▸ Child 12–17 years: 2‑4 g once daily, doses at the higher end of the recommended range used in severe cases		
4	Meropenim	Aerobic and anaerobic Gram-positive and Gram-negative infections | Hospital-acquired septicaemia	BY I.V INFUSION, or by I.V INJECTION ▸ a.Neonate up to 7 days: 20 mg/kg every 12 hours. ▸ b.Neonate 7 days to 28 days: 20 mg/kg every 8 hours. ▸ c.Child 1 month–11 years (body-weight up to 50 kg): 10‑20 mg/kg every 8 hours		

		Severe aerobic and anaerobic Gram-positive and Gm -ve infections Meningitis	▸ d.Child 1 month–11 years (body-weight 50 kg and above): 0.5‑1 g every 8 hours ▸ e.Child 12–17 years: 0.5‑1 g every 8 hours ▸ BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION ▸ Neonate up to 7 days: 40 mg/kg every 12 hours. ▸ Neonate 7 days to 28 days: 40 mg/kg every 8 hours. ▸ BY INTRAVENOUS INFUSION ▸ a.Neonate up to 7 days: 40 mg/kg every 12 hours. ▸b. Neonate 7 days to 28 days: 40 mg/kg every 8 hours. ▸ c.Child 1 month–11 years (body-weight up to 50 kg): 40 mg/kg every 8 hours ▸d. Child 1 month–11 years (body-weight 50 kg and above): 2 g every 8 hours ▸ e.Child 12–17 years: 2 g every 8 hours		
5	Metronidazole	Anaerobic infections	BY INTRAVENOUS INFUSION ▸a.Neonate up to 26 weeks corrected gestational age: Loading dose 15 mg/kg, followed by 7.5 mg/kg after 24 hours, then 7.5 mg/kg daily usually treated for a total duration of 7 days (for 10‑14 days in Clostridium difficile infection). ▸ b.Neonate 26 weeks to 34 weeks corrected		

			gestational age: Loading dose 15 mg/kg, followed by 7.5 mg/kg after 12 hours, then 7.5 mg/kg every 12 hours usually treated for a total duration of 7 days (for 10‑14 days in Clostridium difficile infection). C,Child 1 month: Loading dose 15 mg/kg, followed by 7.5 mg/kg after 8 hours, then 7.5 mg/kg every 8 hours usually treated for a total duration of 7 days (for 10‑14 days in Clostridium difficile infection) ▸ d.Child 2 months–17 years: 7.5 mg/kg every 8 hours (max. per dose 500 mg) usually treated for 7 days (for 10‑14 days in Clostridium difficile infection)		
6	Ciprofloxacin	Severe respiratory-tract infections,gastrointestinal infection Pseudomonal lower respiratory-tract infection	▸ BY MOUTH ▸ Neonate: 15 mg/kg twice daily. ▸ Child: 20 mg/kg twice daily (max. per dose 750 mg) ▸ BY INTRAVENOUS INFUSION ▸ Neonate: 10 mg/kg every 12 hours, to be given over 60 minutes. ▸ Child: 10 mg/kg every 8 hours (max. per dose 400 mg),to be given over 60 minutes ▸ BY MOUTH ▸ Child: 20 mg/kg twice daily (max. per dose 750 mg)		

		in cystic fibrosis	▸ BY IV INFUSION ▸ Child: 10 mg/kg every 8 hours (max. per dose 400 mg),to be given over 60 minutes		
7	Co-amoxiclav	Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites	▸ BY MOUTH USING TABLETS ▸ Child 12–17 years: 250/125 mg every 8 hours; increased to 500/125 mg every 8 hours, increased dose used for severe infection ▸ BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION ▸ Neonate: 30 mg/kg every 12 hours. ▸ Child 1–2 months: 30 mg/kg every 12 hours ▸ Child 3 months–17 years: 30 mg/kg every 8 hours (max. per dose 1.2 g every 8 hours)		
8	Piperacillin with tazobactam	Hospital-acquired pneumonia | Septicaemia | Complicated infections involving the urinary-tract | Complicated infections involving the skin | Complicated infections involving the soft-tissues	▸ BY INTRAVENOUS INFUSION ▸a. Neonate: 90 mg/kg every 8 hours. ▸b. Child 1 month–11 years: 90 mg/kg every 6‑8 hours (max. per dose 4.5 g every 6 hours) ▸ c.Child 12–17 years: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections Complicated intra-abdominal infections ▸ BY INTRAVENOUS INFUSION ▸ a.Child 2–11 years: 112.5 mg/kg every 8 hours (max. per		

		Infections in neutropenic patients	dose 4.5 g) ▸ b.Child 12–17 years: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections ▸ BY INTRAVENOUS INFUSION ▸ Child: 90 mg/kg every 6 hours (max. per dose 4.5 g)		
9	vancomycin	Complicated skin and soft tissue infections | Bone infections | Joint infections | Community-acquired pneumonia | Hospital-acquired pneumonia [including ventilator-associated pneumonia] | Infective endocarditis | Acute bacterial meningitis | Bacteraemia [occurring in association with or suspected to be associated with the licensed indications]	a.Child 1 month–11 years: 10‑15 mg/kg every 6 hours adjusted according to plasma-concentration monitoring, duration should be tailored to type and severity of infection and the individual clinical response−consult product literature for further information, doses higher than 60 mg/kg/day cannot be generally recommended as the safety of increased dosing has not been fully assessed ▸ b.Child 12–17 years: 15‑20 mg/kg every 8‑12 hours (max. per dose 2 g) adjusted according to plasma concentration monitoring, duration should be tailored to type and severity of infection and the individual clinical response− consult product literature for further information, in		

			seriously ill patients, a loading dose of 25‑30 mg/kg (usual max. 2 g) can be used to facilitate rapid attainment of the target trough serum vancomycin concentration		

Some Pediatric Doses (to be filled by the student)

	Drug	Pediatric Dose
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		