A-Cardiovascular Disorders

1-Hypertension (HTN)

Definitions :

1-**Hypertension** : is a condition where the BP is **consistently** above **140/90 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 [2].

4-**Hypertensive crises**: are situations in which measured BP values are markedly elevated[2] (BP >180/120 mm Hg) [3].

Clinical Presentation and complications:

1-Patients with uncomplicated primary hypertension are usually **asymptomatic** [3].

2- The most common and important cardiovascular complications associated with hypertension are **stroke** and **myocardial infarction** [4].

Diagnosis

1-The diagnosis of hypertension is made only after the average of two or more measurements, taken on separate occasions [5](Repeated after weeks) [4].

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** [3].

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 ,<140 mmHg. 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. Patients with diabetes should be treated to a diastolic blood pressure (DBP) ,<80 mmHg [7].

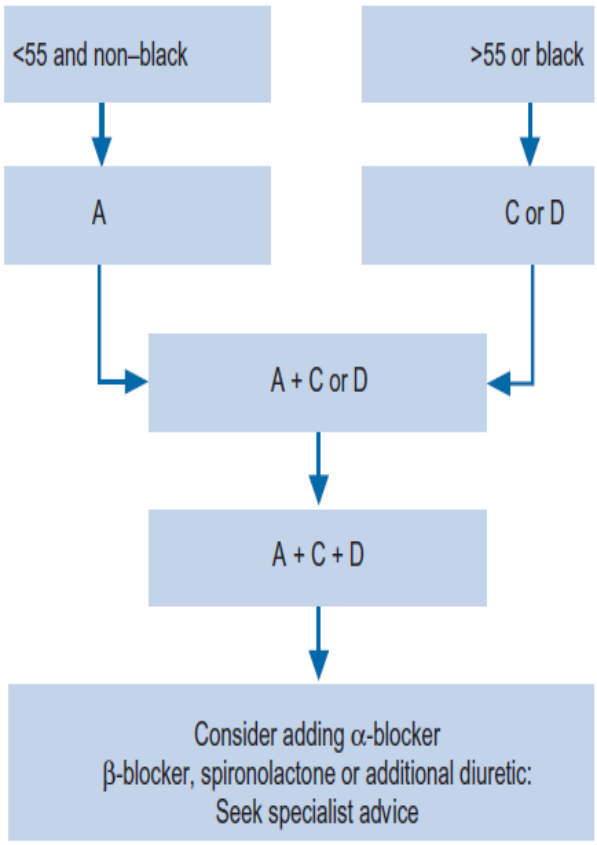
A-Nonpharmacologic Therapy [2]

- Weight reduction - BMI should be < 25 kg/m^2
- Low-fat and saturated fat diet, Low-sodium diet - < 3.8g 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** [3].

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)** [3]. (figure 1) [4].



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 [6].

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 [3].

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. They are also a suitable choice if heart failure is present [4].

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 [4].

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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) [10]. 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] [1], **aldosterone antagonists** (in select patients) [1, 5] [1, 2] and most recently the combination of angiotensin-receptor/neprilysin inhibitor (ARNI) [(sacubitril/valsartan (Entresto®)] [14].

A-Neprilysin inhibitors [14-17].

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 [14].

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** [14].

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 [14].

2-ACE inhibitors should be initiated at low doses, followed by increments in dose if lower doses have been well tolerated [10].

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)**[12] 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 [10].

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 III-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, 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, 11]. 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 [9].

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) [9] to slow ventricular rate regardless of HF symptoms [2].

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** [13](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** [13].

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].

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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** [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 (**PCI**) should be considered [4].
In PCI, 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).

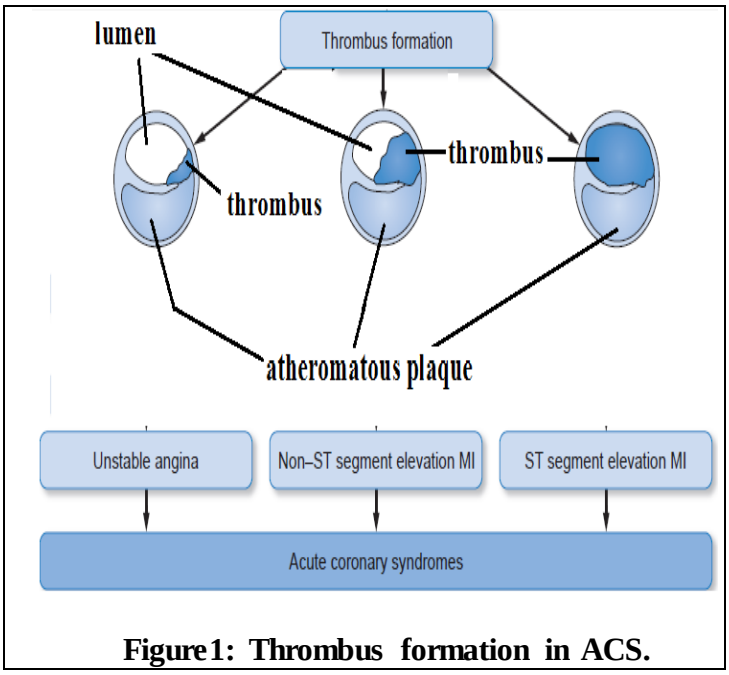

Figure1: Thrombus formation in ACS.

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].

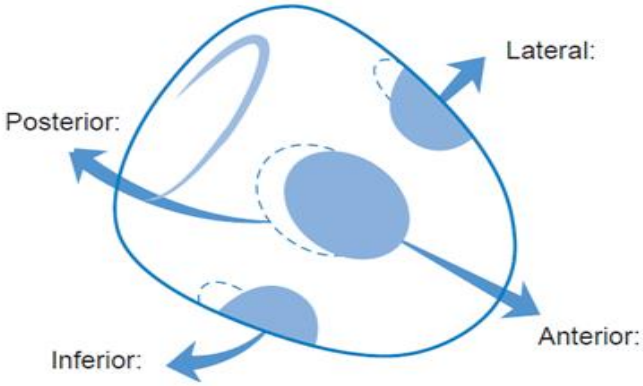

Figure 3: Location of an anterior, lateral, inferior, or posterior infarction

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

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].

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 [3].

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].

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:

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 (1).

Diagnosis

1- Historically, venography was considered the gold standard test in diagnosing DVT; however, its use has decreased (3). **Duplex ultrasound imaging** has become the gold standard for the diagnosis of DVT (2).

2-The diagnosis of PE historically has involved pulmonary angiography. However, the most current techniques include **spiral CT scanning and MRI** (2).

Treatment

1-For the **initial** treatment of DVT and PE a **low molecular weight heparin** (LMWH) is used; alternatively, **unfractionated heparin** (UFH)is given (4). LMWH is now preferred over UFH for the initial treatment of VTE (2).

2-An oral anticoagulant (usually **warfarin**) is started at the same time as UFH or LMWH (2). 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 (2).

3- 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** [5].

4-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** [6] to prevent recurrent thrombosis [7] 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**) [8].

Complications of Anticoagulants

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 [5].

2- If rapid reduction of an elevated INR is required for hemorrhagic complications due to **warfarin**, **vitamin K** can be given [1].

3-**Heparins**, particularly UFH, may also cause **thrombocytopenia** (low platelet count). This may occur in two forms [9].

A-Heparin-associated thrombocytopenia (HAT) is a benign, transient, and mild that usually occurs within the first few days of treatment [1].

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].

4-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** [5].

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) [10].

2-As compared to warfarin, these oral anticoagulants have a **more rapid onset**, **shorter half-life**, **wider therapeutic window**, and **more predictable pharmacokinetics** [10].

3-These features allow for sole oral therapy without **the need for an overlapping parenteral agent** (with the exception of edoxaban for VTE), **no need for titration or dose adjustments in patients with normal renal function**, and **no need for routine monitoring** [10].

4-Compared to warfarin, the target-specific anticoagulants have **a lower risk of intracranial hemorrhage** [10].

5-Issues of concern include the **lack of antidotes**, **and risk of thrombosis due to missed doses** [10]. (**Note: Idarucizumab** is a monoclonal antibody fragment used to reverse dabigatran Anticoagulation) [11].

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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

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].

2-**Brain edema** develops between the second and fifth day after stroke onset, 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 [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].

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].

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.

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.

5-**Disadvantages of dabigatran** include the fact that, in cases of dabigatran-associated bleeding, there is no antidote to reverse dabigatran's effects [8].

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

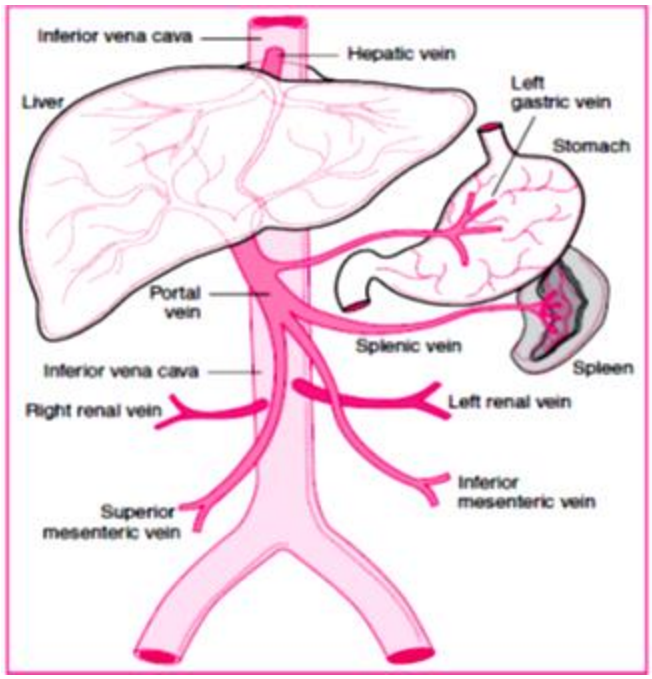


Figure -1-The portal venous system

Etiology:

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

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** or **neomycin** is reserved for patients who have not responded to lactulose [2].

C-Spontaneous Bacterial Peritonitis (SBP):

1-Antibiotics: **Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy** [2] [**Third-generation cephalosporins,** 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 [9].

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 [8].

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, 8, 9].

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].

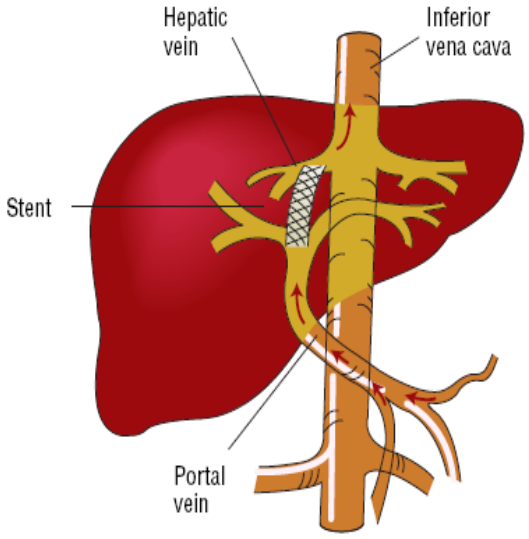


Figure 2:TIPS

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].

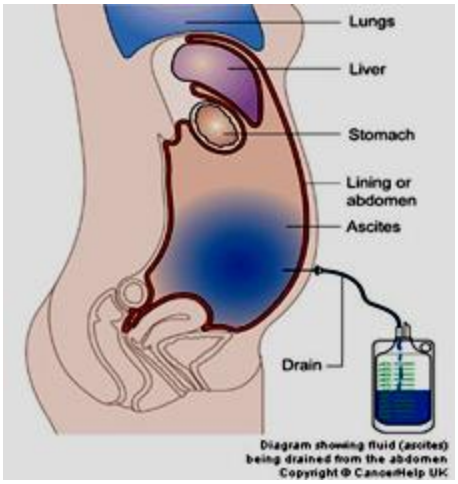
2-Because of the role of hyperaldosteronism in ascites, **spironolactone** is the drugs of choice [5].

Loop diuretics (**furosemide**) may be added to the regimen [1, 8]. Diuretic therapy in cirrhosis is typically lifelong [5].

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] [9].

Liver Transplantation

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

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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

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) [5, 6].

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 [10].

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 [10].

Pharmacotherapy of type 1 diabetes mellitus [2, 5].

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

A-Basal-bolus regimens involve the administration of fast-acting insulin (**regular insulin, lispro, aspart,** or **glulisine)** prior to meals and once or twice daily injections of long- or intermediate-acting insulins. 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 insulins provide a convenience for many patients. (Two-thirds of the daily dose given in the morning and one-third in the evening).

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.

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
Amylin agonist	Pramlintide
Bile Acid Sequestrant	Colesevalem
Dopamine Agonist	Bromocriptine
sodium-glucose cotransporter 2 (SGLT-2) Inhibitor	Canagliflozin

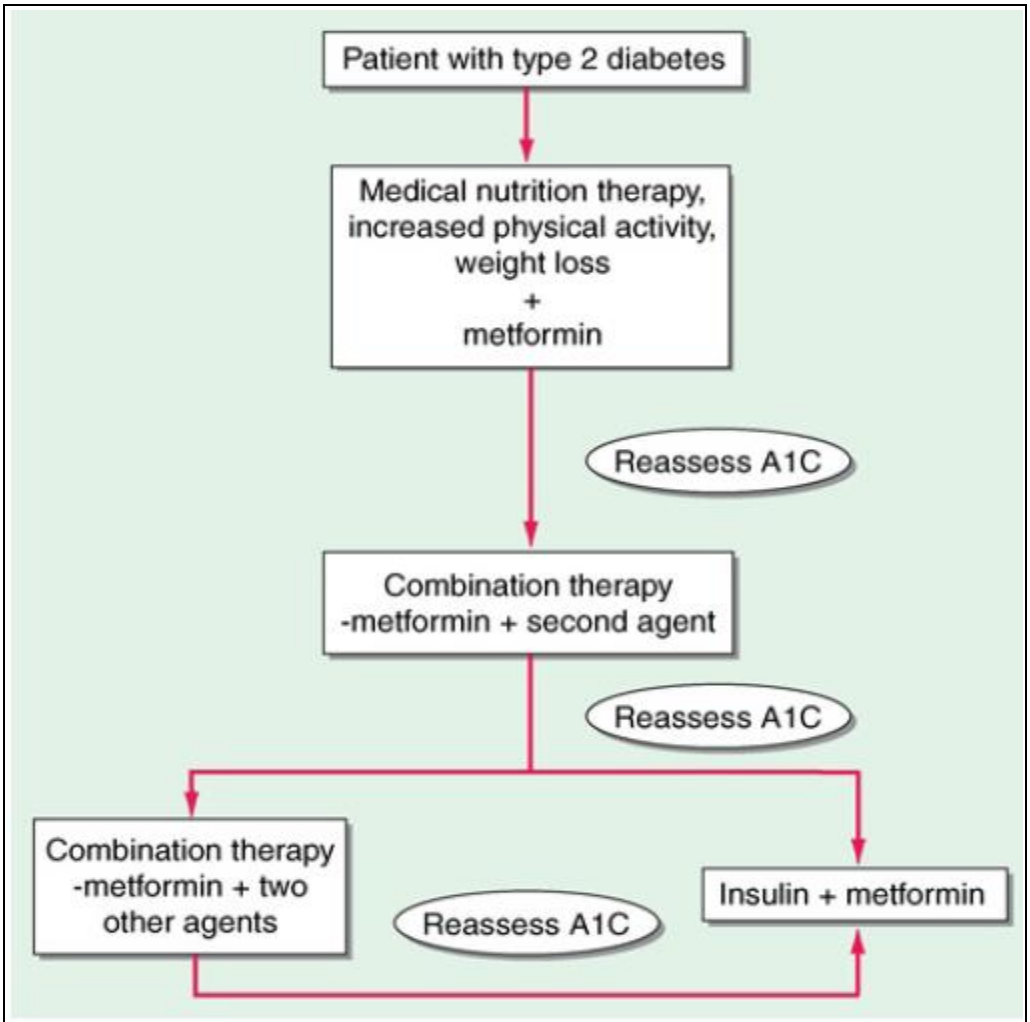

Figure 1 : Glycemic management of type 2 diabetes. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, and GLP-1 receptor agonists.

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 low-dose **TCAs,** anticonvulsants (e.g., **gabapentin, pregabalin**), **duloxetine, 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].

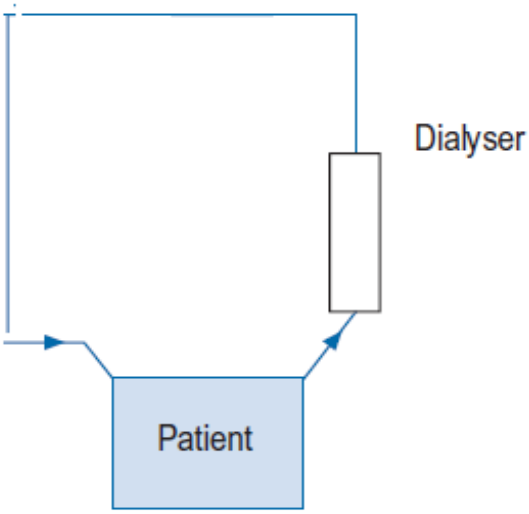

Figure 1: haemodialysis

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].

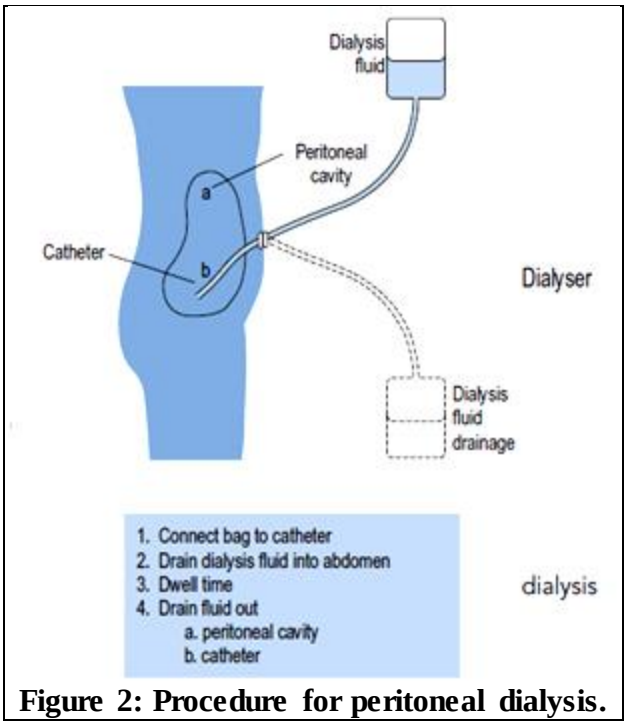

Figure 2: Procedure for peritoneal dialysis.

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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.

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 Aapprov

ed 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-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].

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