

# MEDICINE MANUAL

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## Ischemic Heart Disease

The major goals for the treatment of IHD are to:

- Prevent acute coronary syndromes and death
- Alleviate acute symptoms of myocardial ischemia
- Prevent recurrent symptoms of myocardial ischemia and
- Avoid or minimize adverse treatment effects.

### Non- pharmacological therapy

Lifestyle modifications include smoking cessation, dietary modifications, increased physical activity, and weight loss.

### Pharmacological Therapy

Since chronic stable angina usually results from increased myocardial oxygen demand in the face of a relatively fixed reduction in oxygen supply, drug treatment is primarily aimed at reducing oxygen demand.

### Pharmacotherapy to Prevent Acute Coronary Syndromes and Death

- 1- **Short- acting nitrates** are indicated to acutely relieve angina. All patients with a history of angina should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms at the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually, and repeated every 5 minutes until symptoms resolve.
  - 2- Antiplatelet therapy with aspirin should be considered for all patients without contraindications, particularly in patients with a history of myocardial infarction. Aspirin doses of 75 to 325 mg daily have been shown to be cardioprotective. If aspirin is contraindicated (e.g., aspirin allergy, active peptic ulcer disease, or active internal bleeding) or is not tolerated by the patient, other antiplatelet agents such as clopidogrel should be considered.
  - 3- ACE inhibitors should be considered in ischemic heart disease patients who also have diabetes mellitus, left ventricular dysfunction, history of myocardial infarction, or any combination of these.
  - 4- Patients with chronic stable angina should receive **statin** therapy unless contraindicated.
- statins and angiotensin-converting enzyme (ACE) inhibitors are believed to provide vasculoprotective effects (properties that are generally protective of the vasculature, which may

include anti-inflammatory effects, antiplatelet effects, improvement in endothelial function, and improvement in arterial compliance and tone), and in addition to aspirin, have been shown to reduce the risk of acute coronary events as well as mortality in patients with IHD

**5-** B Blockers, calcium channel blockers (CCBs), and long acting nitrates are traditionally used to prevent ischemic symptoms, reduce the frequency of angina and improve exercise tolerance.

- ✓ B-Blockers are first-line therapy for preventing ischemic symptoms, particularly in patients with a history of myocardial infarction.
- ✓ - b-Blockers have been shown to decrease morbidity and improve survival in patients who have suffered an MI.
- ✓ Calcium channel blockers are recommended as initial treatment in IHD when B-blockers are contraindicated or not tolerated. In addition, CCBs may be used in combination with b-blockers when initial treatment is unsuccessful.
- ✓ Treatment with long-acting nitrates should be added to baseline therapy with either a B-blocker or calcium channel blocker or a combination of the two.

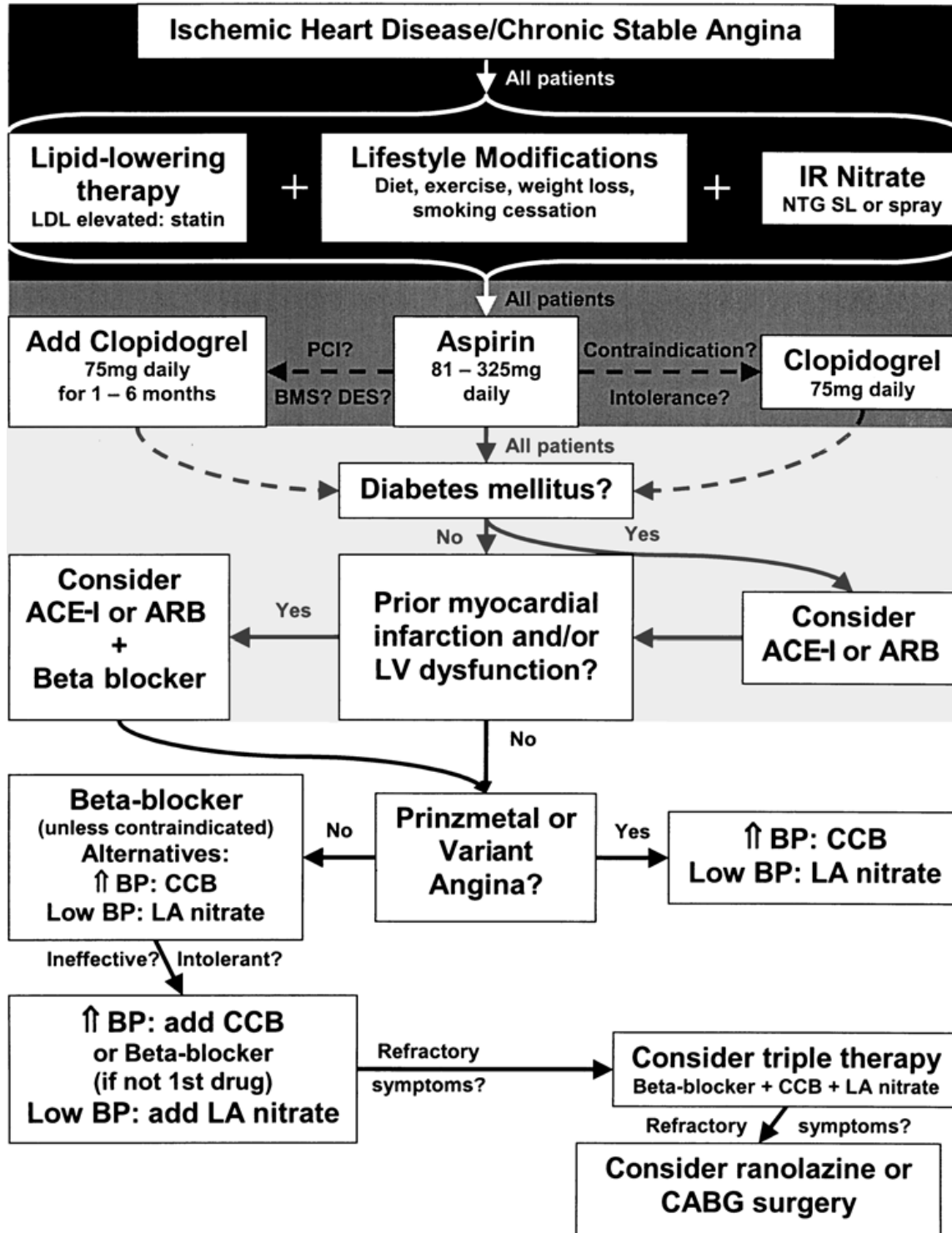
### **Interventional Approaches**

- In most patients with IHD, the most effective treatments to improve myocardial oxygen supply are invasive mechanical interventions: **percutaneous coronary intervention (PCI)** and **coronary artery bypass graft (CABG) surgery**.

Percutaneous Coronary Intervention When drug therapy fails or if extensive coronary atherosclerosis is present, PCI is often performed to restore coronary blood flow, relieve symptoms, and prevent major adverse cardiac events. Patients with one or more critical coronary stenoses (i.e., greater than 70% occlusion of the coronary lumen) detected during coronary angiography may be candidates for PCI. Several catheter-based interventions may be used during PCI, including:

- Percutaneous transluminal coronary angioplasty (PTCA);
- Intracoronary bare metal stent placement;
- Intracoronary drug-eluting stent placement; and
- Rotational atherectomy.
  - ✓ In chronic stable angina, percutaneous coronary intervention is reserved for patients who remain symptomatic despite optimal medical therapy, patients unable to tolerate adverse effects of medications, and those with high-risk findings on noninvasive imaging.
  - ✓ Patients with stable angina who undergo percutaneous coronary intervention should receive clopidogrel for 6 months following placement of a drug-eluting stent and for 2 weeks to 1 month following placement of a bare-metal stent; aspirin should be continued indefinitely.

- ✓ Coronary Artery Bypass Graft Surgery As an alternative to PCI, CABG surgery, or open-heart surgery, may be performed if the patient is found to have extensive coronary atherosclerosis (generally greater than 70% occlusion of three or more coronary arteries) or is refractory to medical treatment. In the former case, CABG surgery has been shown to reduce mortality from IHD.



The treatment algorithm for ischemic heart disease

## Acute Coronary Syndromes

### Reperfusion therapy

- Early reperfusion therapy with either primary percutaneous coronary intervention (PCI) or administration of a fibrinolytic agent within 3 hours of symptom onset is the recommended therapy for patients presenting with STE ACS.
- Fibrinolytic therapy is preferred over primary PCI in patients presenting within 3 hours of symptom onset where there is a delay in “door-to-primary PCI” less than 90 minutes. either alteplase, reteplase, or tenecteplase are acceptable as first-line agents.
- It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy

❖ **Early Pharmacologic Therapy for ST-Segment Elevation Acute Coronary Syndromes:** in addition to reperfusion therapy, early pharmacotherapy of STE should include:

1- **intranasal oxygen** (if oxygen saturation is less than 90%),

2- **Nitrates:** One sublingual nitroglycerin tablet should be administered every 5 minutes for up to three doses in order to relieve myocardial ischemia.

3- aspirin, initial dose of 160 to 325 mg is required to achieve rapid platelet inhibition, long-term therapy with doses of 75 to 150 mg daily are as effective as higher doses.

4- **Thienopyridines :** Administration of clopidogrel is recommended for all patients with STE ACS

#### 5- Anticoagulants

- Unfractionated heparin, administered as a continuous infusion, is a first-line anticoagulant for treatment of patients with STE ACS, both for medical therapy and for patients undergoing PCI.

- Unfractionated heparin should be initiated in the emergency department and continued for 48 hours or longer in patients who will be bridged over to receive chronic warfarin
- Morphine** is administered as an analgesic and a venodilator that lowers preload. This agent should be administered early, while the patient is still in the emergency department.

#### 6- Beta-Blockers

Intravenous or oral doses of a  $\beta$ -blocker should be administered early in the care of a patient with STE ACS, and then oral agents should be continued indefinitely.

#### 8- Glycoprotein IIb/IIIa Receptor Inhibitors

Abciximab is a first-line glycoprotein IIb/IIIa receptor inhibitor for patients undergoing primary PCI who have not received fibrinolytics. It should not be administered for medical management of the STE ACS patient who will not be undergoing PCI

## Early Pharmacotherapy for Non–ST-Segment Elevation Acute Coronary Syndromes

According to the ACC/AHA non–ST-segment elevation ACS practice guidelines, in the absence of contraindications, early pharmacotherapy of NSTEMI ACS should include

- 1- intranasal oxygen (if oxygen saturation is low),
- 2- **Nitrates** Sublingual NTG followed by intravenous NTG should be administered to patients with NSTEMI ACS and ongoing ischemia
- 3- **Aspirin.** aspirin reduces the risk of death or developing MI by about 50% (compared to no antiplatelet therapy) in patients with NSTEMI ACS. Therefore, aspirin remains the cornerstone of early treatment for all ACS. Dosing of aspirin for NSTEMI ACS is the same as that for STEMI ACS . Aspirin is continued indefinitely.

### 4- **Thienopyridines**

For patients with NSTEMI ACS, clopidogrel started on the first day of hospitalization as a 300 to 600 mg loading dose and followed the next day by 75 mg orally per day for 9 to 12 months.

### 5- **Beta-Blockers**

Intravenous  $\beta$ -blockers followed by oral  $\beta$ -blockers should be administered to all patients with NSTEMI ACS in the absence of contraindications.

### 6- **Anticoagulants**

Either UFH or LMWH should be administered to patients with NSTEMI ACS. Therapy should be continued for up to 48 hours or until the end of the angiography or PCI procedure.

7- Morphine is also administered to patients as described previously.

**8- Fibrinolytic Therapy:** Fibrinolytic therapy is not indicated in any patient with NSTEMI ACS, as increased mortality has been reported with fibrinolytics compared to controls in clinical trials in which fibrinolytics have been administered to patients with NSTEMI ACS (patients with normal or ST-segment depression ECGs).

### 9- **Glycoprotein IIb/IIIa Receptor Inhibitors**

Administration of tirofiban or eptifibatid is recommended for high-risk NSTEMI ACS patients as medical therapy without planned revascularization and for patients with continued or recurrent ischemia despite treatment with aspirin and an anticoagulant. In these patients, the benefit of glycoprotein IIb/IIIa inhibitors appears to be limited to those undergoing PCI.

Abciximab should not be used in this setting, because its use in such a setting has not been shown to be beneficial.

### 10- **Calcium Channel Blockers**

calcium channel blockers should not be administered to most patients with ACS. Their role is a second-line treatment for patients with certain contraindications to  $\beta$ -blockers and those with continued ischemia despite  $\beta$ -blocker and nitrate therapy. Administration of either amlodipine, diltiazem, or verapamil is preferred. Agent selection is

based on heart rate and left ventricular dysfunction (diltiazem and verapamil are contraindicated in patients with bradycardia, heart block, or systolic heart failure).

### **Secondary Prevention Following Myocardial Infarction**

Pharmacotherapy, which has been proven to decrease mortality, heart failure, reinfarction, or stroke, should be initiated prior to hospital discharge. for secondary prevention, Guidelines from the ACC/AHA suggest that in the absence of contraindications, following MI from either STE ACS or NSTEMI ACS, patients should receive indefinite treatment with aspirin, a b-blocker, and an ACE inhibitor. For NSTEMI ACS, most patients should receive clopidogrel, in addition to aspirin, for up to 9 months.

Most patients will receive a statin to reduce low-density lipoprotein cholesterol to less than 100 mg/dL.

Selected patients will also be treated with long term warfarin anticoagulation. For all ACS patients, treatment and control of modifiable risk factors such as hypertension, dyslipidemia, and diabetes mellitus is essential.



## **Acute heart failure**

Acute heart failure syndromes (AHFS) may be defined as new-onset, gradual, or rapidly worsening HF signs and symptoms that require urgent therapy. These symptoms reflect congestion behind the failing ventricle and/or hypoperfusion. Patients can be categorized into hemodynamic subsets based on assessment of physical signs and symptoms of congestion and/or hypoperfusion. Patients can be described as “wet” or “dry” depending on volume status, as well as “warm” or “cool” based on adequacy of tissue perfusion.

Patients with AHFS can be further classified as having new-onset or worsening chronic HF. Approximately 80% of patients with AHFS have chronic HF. Patients with advanced HF have low blood pressure (BP), renal impairment, and signs or symptoms refractory to standard medical therapy and represent up to 10% of hospitalized patients with AHFS.

### **Clinical presentation of acute heart failure**

#### **Subset I (Warm and Dry)**

- Patients considered well compensated and perfused, without evidence of congestion
- No immediate interventions necessary except optimizing oral medications and monitoring

#### **Subset II (Warm and Wet)**

- Patients adequately perfused and display signs and symptoms of congestion
- Main goal is to reduce preload (PCWP) carefully with loop diuretics and vasodilators

#### **Subset III (Cool and Dry)**

- Patients are inadequately perfused and not congested
- Hypoperfusion leads to increased mortality, elevating death rates fourfold compared with those who are adequately perfused
- Treatment focuses on increasing CO with positive inotropic agents and/or replacing intravascular fluids
- Fluid replacement must be performed cautiously because patients can rapidly become congested

#### **Subset IV (Cool and Wet)**

- Patients are inadequately perfused and congested
- Classified as the most complicated clinical presentation of AHF with the worst prognosis
- Most challenging to treat; therapy targets alleviating signs and symptoms of congestion by increasing CI as well as reducing PCWP while maintaining adequate mean arterial pressure
- Treatment involves a delicate balance between diuretics, vasodilators, and inotropic agents
- Use of vasopressors is sometimes necessary to maintain blood pressure.

### **Laboratory Assessment**

BNP, electrolytes and blood glucose, serum creatinine and blood urea nitrogen to assess renal function. Complete blood cell count is measured to determine if anemia or infection is present. Creatine kinase and/or troponin concentrations are used to diagnose ischemia, and hepatic transaminases are measured to assess hepatic congestion. Thyroid function tests are measured to

assess hyperthyroidism or hypothyroidism as causes of AHF. A urinalysis is attained in patients with an unknown history of renal disease to rule out nephrotic syndrome.

## **TREATMENT OF ACUTE HEART FAILURE**

### **Desired Therapeutic Outcomes**

The goals of therapy for AHF are to (a) correct the underlying precipitating factor(s); (b) relieve the patient's symptoms; (c) improve hemodynamics; (d) optimize a chronic oral medication regimen; and (e) educate the patient, reinforcing adherence to lifestyle modifications and the drug regimen.

The ultimate goal for a patient hospitalized for AHF is the return to a compensated HF state and discharge to the outpatient setting on oral medications. Only through aggressive management to achieve all of these goals will a patient's prognosis be improved and future hospitalizations for acute decompensations be prevented.

Oral agents such as  $\beta$ -blockers, ACE inhibitors or ARBs, and aldosterone antagonists should be initiated as soon as possible during the hospitalization. These chronic oral medications not only improve mortality and prevent readmissions, acutely they also contribute to improvement in hemodynamics. Patient education prior to discharge from the hospital is recommended to assist in minimizing adverse effects and nonadherence.

### **Pharmacologic Approaches to Treatment**

Treatment of AHF targets relief of congestion and optimization of CO utilizing oral or IV diuretics, IV vasodilators, and, when appropriate, inotropes, based on presenting hemodynamics. Current treatment strategies in AHF target improving hemodynamics while preserving organ function.

### ***Diuretics***

#### ***1. Mechanism and onset***

Loop diuretics, including furosemide, bumetanide, and torsemide, are the diuretics of choice in the management of AHF. Furosemide is the most commonly used agent. Diuretics decrease preload by functional venodilation within 5 to 15 minutes of administration and subsequently by an increase in sodium and water excretion. This provides rapid improvement in symptoms of pulmonary congestion.

#### **2. Route**

Diuretics is recommended to be administered by intravenous route in AHF due to concern about adequate absorption of oral administration due to bowel oedema Bolus injection should be administered at a rate not exceeding 4 mg per minute to avoid ototoxicity

### 3. Dose and renal function

Patients who received double their regular oral diuretic dose by intravenous route experienced more weight loss, diuresis and subsequent symptom relief compared to those who receive intravenous doses equivalent to their oral doses. Relatively higher doses of diuretics are needed in patients with renal impairment because they need adequate glomerular filtration to reach their site of action. For example if creatinine clearance is more than 75 ml/min, infusion rate of intravenous furosemide is 10 mg/hour. However, in patients with creatinine clearance less than 25 ml/min, the dosing rate would be 20 mg increased to 40 mg/hour. Lower doses are needed if the patient improves.

### 6. Diuretic resistance

Occasionally, patients with HF do not respond to a diuretic, defined as failure to achieve a weight reduction of at least 0.5 kg (or negative net fluid balance of at least 500 mL) after several increasing bolus doses can be managed by either increasing the dose of the diuretics, switching to intravenous infusion or addition of oral diuretic with a different mechanism of action such as thiazide (hydrochlorothiazide, bendroflumethiazide) or thiazide like diuretics (metolazone) to counteract diuretic resistance. The addition of these diuretics provide synergistic diuretic effect by preventing sodium uptake from the distal tubule. It should be noted that this co-administration of these diuretics increase the risk of electrolyte abnormalities (hypokalaemia, hyponatremia) and renal dysfunction. Therefore, the renal function and electrolytes should be closely monitored. Combining diuretics should be used with caution due to an increased risk for cardiovascular collapse due to rapid intravascular volume depletion. Strict monitoring of electrolytes, vital signs, and fluid balance is warranted.

### 7. Monitoring

Careful use of diuretics is recommended to avoid overdiuresis. Monitoring parameters for diuretics includes: ↓HF symptoms, weight (loss or gain), Signs of volume depletion (Weakness Hypotension, dizziness Orthostatic changes in BP, ↓Urine output ↑BUN), Serum potassium and magnesium (avoid hypokalemia and hypomagnesemia), ↑Uric acid, ↑Glucose, Weight loss. Finally, poor CO may contribute to diuretic resistance. In these patients, it may become necessary to add vasodilators or inotropes to enhance perfusion to the kidneys. Care must be taken because vasodilators can decrease renal blood flow despite increasing CO through dilation of central and peripheral vascular beds.

### *Vasodilators*

IV vasodilators cause a rapid decrease in arterial tone, resulting in a decrease in SVR and a subsequent increase in SV and CO. Additionally, vasodilators reduce ventricular filling pressures (PCWP) within 24 to 48 hours, reduce myocardial oxygen consumption, and decrease ventricular workload. Vasodilators are commonly used in patients presenting with AHF accompanied by moderate to severe congestion. This class includes nitroglycerin, nitroprusside, and nesiritide.

Usual Doses and Monitoring of Commonly Used Hemodynamic Medications: BP, HR, urinary output and kidney function, ECG, extremity perfusion.

IV nitroglycerin is primarily used as a preload reducer for patients exhibiting pulmonary congestion or in combination with inotropes for congested patients with severely reduced CO. Continuous infusions of nitroglycerin should be initiated at a dose of 5 to 10 mcg/min and increased every 5 to 10 minutes until symptomatic or hemodynamic improvement. Effective doses range from 35 to 200 mcg/min.

### ***Inotropic Agents***

There are several practical considerations to dobutamine therapy in AHF. First, owing to its vasodilatory potential, monotherapy with dobutamine is reserved for patients with systolic blood pressures greater than 90 mm Hg. However, it is commonly used in combination with vasopressors in patients with lower systolic blood pressures.

In patients on  $\beta$ -blocker therapy, it is recommended that consideration be given to the use of phosphodiesterase inhibitors such as milrinone, which do not depend on  $\beta$ -receptors for effect. Dopamine is most commonly reserved for patients with low systolic blood pressures and those approaching cardiogenic shock. As with other inotropes, dopamine is associated with a risk for arrhythmias.

## **CHRONIC HEART FAILURE**

### **KEY CONCEPTS**

1. The most common causes of heart failure are coronary artery disease (CAD), hypertension, and dilated cardiomyopathy.
2. Development and progression of heart failure involves activation of neurohormonal pathways, including the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).
3. The clinician must identify potential reversible causes of heart failure exacerbations, including prescription and nonprescription drug therapies, dietary indiscretions, and medication nonadherence.
4. Symptoms of left-sided heart failure include dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (PND), whereas symptoms of right-sided heart failure include fluid retention, GI bloating, and fatigue.
5. General therapeutic management goals for chronic heart failure focus on preventing onset of clinical symptoms or reducing symptoms, preventing or reducing hospitalizations, slowing or preventing disease progression, improving quality of life, and prolonging patient survival.
6. Nonpharmacologic treatment involves dietary modifications such as sodium and fluid restriction, risk factor reduction including smoking cessation, timely immunizations, and supervised regular physical activity.
7. Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia.

8. Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic heart failure target neurohormonal blockade; these include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs),  $\beta$  adrenergic blockers, and aldosterone antagonists.
9. Combination therapy with hydralazine and isosorbide dinitrate is an appropriate substitute for angiotensin II antagonism in those unable to tolerate an ACE inhibitor or ARB or as add-on therapy in African Americans.
10. Treatment of acute heart failure targets relief of congestion and optimization of cardiac output utilizing oral or IV diuretics, IV vasodilators, and when appropriate, inotropes. Current treatment strategies in acute heart failure target improving hemodynamics while preserving organ function.

Table 6-4

#### Drugs That May Precipitate or Exacerbate Heart Failure

##### Agents Causing Negative Inotropic Effect

Antiarrhythmics (e.g., disopyramide, flecainide, and others)  
 $\beta$ -Blockers (e.g., propranolol, metoprolol, atenolol, and others)  
 Calcium channel blockers (e.g., verapamil and others)  
 Itraconazole  
 Terbinafine

##### Cardiotoxic Agents

Doxorubicin  
 Daunomycin  
 Cyclophosphamide

##### Agents Causing Sodium and Water Retention

Nonsteroidal anti-inflammatory drugs  
 COX-2 inhibitors  
 Glucocorticoids  
 Androgens  
 Estrogens  
 Salicylates (high dose)  
 Sodium-containing drugs (e.g., carbenicillin disodium, ticarcillin disodium)  
 Thiazolidinediones (e.g., pioglitazone)

## NYHA Functional Classification

<b>I</b>	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
<b>II</b>	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
<b>III</b>	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
<b>IV</b>	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

				Transplant/VAD evaluation
				ARB added to ACEI if hypertensive Spironolactone if renal function, potassium stable Isordil/hydralazine if African-American Digoxin if symptomatic with spironolactone CRT if QRS > 130 msec
				Diuretic therapy Beta-blockers once euvolemic Defibrillators if life expectancy > 1 year
ACEI ARB if ACEI-related cough				
NYHA Class I	NYHA Class II	NYHA Class III	NYHA Class IV	

**Treatment of chronic heart failure according to the stage**

## **TREATMENT OF CHRONIC HEART FAILURE**

### **Desired Therapeutic Outcomes**

There is no cure for HF. The general therapeutic management goals for chronic HF include preventing the onset of clinical symptoms or reducing symptoms, preventing or reducing hospitalizations, slowing progression of the disease, improving quality of life, and prolonging survival.

### **Nonpharmacologic Interventions**

Non pharmacologic treatment involves dietary modifications such as sodium and fluid restriction, risk factor reduction including smoking cessation, timely immunizations, and supervised regular physical activity.

- Patient education regarding monitoring symptoms, dietary and medication adherence, exercise and physical fitness, risk factor reduction, and immunizations are important for the prevention of AHF exacerbations. Home monitoring should include daily assessment of weight and exercise tolerance. Daily weights should be done first thing in the morning upon arising and before any food intake to maintain consistency.
- Nonadherence is an important issue because it relates to acute exacerbations of HF. Ensuring an understanding of the importance of each medication used to treat HF, proper administration, and potential adverse effects may improve adherence. Stressing the rationale for each medication is important, especially for NYHA FC I or ACC/AHA stage B patients who are asymptomatic yet started on drugs that may worsen symptoms initially.
- Dietary modifications in HF consist of initiation of an AHA step II diet as part of cardiac risk factor reduction, sodium restriction, and sometimes fluid restriction. Exercise, although discouraged when the patient is acutely decompensated to ease cardiac workload, and is recommended when patients are stable.
- Modification of classic risk factors, such as tobacco alcohol consumption, is important to minimize the potential for further aggravation of heart function. Patients with HF should be counseled to receive yearly influenza vaccinations. Additionally, a pneumococcal vaccine is recommended.

### **Pharmacologic Treatment**

#### ***Diuretics***

Diuretics have been the mainstay for HF symptom management for many years. Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia. In more milder HF, diuretics may be used on an as-needed basis. However, once the development of edema is persistent, regularly scheduled doses will be required.



**Therapeutic options**

Two types of diuretics are used for volume management in HF: thiazides and loop diuretics. Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and metolazone block sodium and chloride reabsorption in the distal convoluted tubule. Thiazides are weaker than loop diuretics in terms of effecting an increase in urine output and therefore are not utilized frequently as monotherapy in HF. They are optimally suited for patients with hypertension who have mild congestion. Additionally, the action of thiazides is limited in patients with renal insufficiency (creatinine clearance less than 30 mL/min [0.50 mL/s]) due to reduced secretion into their site of action. An exception is metolazone, which retains its potent action in patients with renal dysfunction. Metolazone is often used in combination with loop diuretics when patients exhibit diuretic resistance, defined as edema unresponsive to loop diuretics alone. Oral torsemide can be considered an alternative to the IV route of administration for patients who do not respond to oral furosemide in the setting of profound edema

**Home monitoring**

Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement and daily body weight. Because body weight changes are a sensitive marker of fluid retention or loss, patients should continue to weigh themselves daily. Once a patient reaches a euvolemic state, diuretics may be cautiously tapered and then withdrawn in appropriate patients. In stable, educated, and adherent patients, another option is self-adjusted diuretic dosing. Based on daily body weight, patients may temporarily increase their diuretic regimen to reduce the incidence of overt edema. This also avoids overuse of diuretics and possible complications of overdiuresis such as hypotension, fatigue, and renal impairment.

**Mechanism of diuretic resistance**

The maximal response to diuretics is reduced in HF, creating a “ceiling dose” above which there is limited added benefit. This diuretic resistance is due to a compensatory increase in sodium reabsorption in the distal tubules, which decreases the effect of blocking sodium reabsorption in the loop of Henle. Apart from increasing diuretic doses, strategies to improve diuretic efficacy include increasing the frequency of dosing to two or three times daily, utilizing a continuous infusion of a loop diuretic, and/or combining a loop diuretic with a thiazide diuretic. The latter strategy theoretically prevents sodium and water reabsorption at both the loop of Henle and the compensating distal convoluted tubule. Metolazone is used most often for this purpose because it retains its activity in settings of a low creatinine clearance. Metolazone can be dosed daily or as little as once weekly. This combination is usually maintained until the patient reaches his or her baseline weight. The clinician must use metolazone cautiously because its potent activity predisposes a patient to metabolic abnormalities as outlined next.

**Diuretics side effects**



Diuretics cause numerous adverse effects and metabolic abnormalities, with severity linked to diuretic potency. A particularly worrisome adverse effect in the setting of HF is hypokalemia. Low serum potassium can predispose patients to arrhythmias and sudden death. Hypomagnesemia often occurs concomitantly with diuretic-induced hypokalemia, and therefore both should be assessed and replaced in patients needing correction of hypokalemia. Magnesium is an essential cofactor for movement of potassium intracellularly to restore body stores. Patients taking diuretics are also at risk for renal insufficiency due to overdiuresis and reflex activation of the renin-angiotensin system. The potential reduction in renal blood flow and glomerular pressure.

### *Neurohormonal Blocking Agents*

#### *ACE inhibitors*

Numerous clinical studies show ACE inhibitor therapy is associated with improvements in clinical symptoms, exercise tolerance, NYHA FC, LV size and function, and quality of life as compared with placebo. ACE inhibitors significantly reduce hospitalization rates and mortality regardless of underlying disease severity or etiology.

#### **Role in MI**

ACE inhibitors are also effective in preventing HF development in high-risk patients. Studies in acute MI patients show a reduction in new-onset HF and death with ACE inhibitors whether they are initiated early (within 36 hours) or started later. In addition, ACE inhibition decreases the risk of HF hospitalization and death in patients with asymptomatic LV dysfunction. All patients with documented LV systolic dysfunction, regardless of existing HF symptoms, should receive ACE inhibitors unless a contraindication or intolerance is present.

#### **Contraindications**

Despite their clear benefits, ACE inhibitors are still underutilized in HF. One reason is undue concern or confusion regarding absolute versus relative contraindications for their use. Absolute contraindications include a history of angioedema, bilateral renal artery stenosis, and pregnancy. Relative contraindications include unilateral renal artery stenosis, renal insufficiency, hypotension, hyperkalemia, and cough. Relative contraindications provide a warning that close monitoring is required, but they do not necessarily preclude their use.

#### **Use in renal impairment**

In general, ACE inhibitors can be used in patients with serum creatinine less than 2.5 to 3 mg/dL (221 to 265  $\mu\text{mol/L}$ ). In HF, their addition can result in improved renal function through an increase in CO and renal perfusion. Although a small increase in serum creatinine (less than 0.5 mg/dL [44  $\mu\text{mol/L}$ ]) is possible with the addition of an ACE inhibitor, it is usually transient or becomes the patient's new serum creatinine baseline level.

However, ACE inhibition can also worsen renal function because glomerular filtration is maintained in the setting of reduced CO through angiotensin II's constriction of the efferent arteriole. Patients most dependent on angiotensin II for maintenance of glomerular filtration

pressure, and hence most susceptible to ACE inhibitor worsening of renal function, include those with hyponatremia, severely depressed LV function, or dehydration. The most common reason for creatinine elevation in a patient without a history of renal dysfunction is overdiuresis. Therefore, clinicians should consider decreasing or holding diuretic doses if an elevation in serum creatinine occurs concomitantly with a rise in blood urea nitrogen.

**Side effects: (hypotension, cough)**

Hypotension occurs commonly at the initiation of therapy or with dosage increases but may happen anytime. Therefore, in euvolemic patients, diuretic doses may often be decreased or withheld during ACE inhibitor dose titration. Initiating at a low dose and titrating slowly can also minimize hypotension. It may be advisable to initiate therapy with a short-acting ACE inhibitor, such as captopril, and subsequently switch to a longer-acting agent, such as lisinopril or enalapril, once the patient is stabilized.

It can be challenging to distinguish an ACE inhibitor– induced cough from cough caused by pulmonary congestion. A productive or wet cough usually signifies congestion, whereas a dry, hacking cough is more indicative of a drug-related etiology. If a cough is determined to be ACE inhibitor– induced, its severity should be evaluated before deciding on a course of action. If the cough is truly bothersome, a trial with a different ACE inhibitor or switching to an ARB is warranted.

### **Angiotensin Receptor Blockers**

Angiotensin receptor blockers are considered an equally effective replacement for ACE inhibitors in patients who are intolerant or have a contraindication to an ACE inhibitor.

The addition of an ARB to ACE inhibitor therapy can be considered in patients with evidence of disease progression despite optimal ACE inhibitor therapy. Many of the other considerations for the use of ARBs are similar to those of ACE inhibitors, including the need for monitoring renal function, blood pressure, and potassium. Contraindications are similar to those of ACE inhibitors. In patients truly intolerant or contraindicated to ACE inhibitors or ARBs, the combination of hydralazine and isosorbide dinitrate should be considered.

### **Hydralazine and Isosorbide Dinitrate**

The combination of hydralazine and isosorbide dinitrate was the first therapy shown to improve long-term survival in patients with systolic HF, but it has largely been supplanted by angiotensin II antagonist therapy (ACE inhibitors and ARBs). Therefore, until recently, this combination therapy was reserved for patients intolerant to ACE inhibitors or ARBs secondary to renal impairment, angioedema, or hyperkalemia.

### **$\beta$ -Adrenergic Antagonists value in HF**

Chronic  $\beta$ -blockade reduces ventricular mass, improves ventricular shape, and reduces LV end-systolic and diastolic volumes.  $\beta$ -Blockers also exhibit antiarrhythmic effects, slow or reverse catecholamine-induced ventricular remodeling, decrease myocyte death from catecholamine-induced necrosis or apoptosis, and prevent myocardial fetal gene expression. Consequently,  $\beta$ -blockers improve EF, reduce all-cause and HF-related hospitalizations, and decrease all-cause mortality in patients with systolic HF.

### **Introduction of beta blockers**

The key to utilizing  $\beta$ -blockers in systolic HF is initiation with low doses and slow titration to target doses over weeks to months. It is important that the  $\beta$ -blocker be initiated when a patient is clinically stable and euvolemic. Volume overload at the time of  $\beta$ -blocker initiation increases the risk for worsening symptoms.  $\beta$ -Blockade should begin with the lowest possible dose after which the dose may be doubled every 2 to 4 weeks depending on patient tolerability.

### **Side effects**

$\beta$ -Blockers may cause an acute decrease in left ventricular ejection fraction (LVEF) and short-term worsening of HF symptoms upon initiation and at each dosage titration. After each dose titration, if the patient experiences symptomatic hypotension, bradycardia, orthostasis, or worsening symptoms, further increases in dose should be withheld until the patient stabilizes. After stabilization, attempts to increase the dose should be reinstated. If mild congestion ensues as a result of the  $\beta$ -blocker, an increase in diuretic dose may be warranted. If moderate or severe symptoms of congestion occur, a reduction in  $\beta$ -blocker dose should be considered along with an increase in diuretic dose.

Dose titration should continue until target clinical trial doses are achieved (Table 6–7) or until limited by repeated hemodynamic or symptomatic intolerance. Patient education regarding the possibility of acutely worsening symptoms but improved long-term function and survival is essential to ensure adherence.

### **Selection of B blockers**

Apart from possible clinical differences between the  $\beta$ -blockers approved for HF, selection of a  $\beta$ -blocker may also be affected by pharmacologic differences. **Carvedilol** exhibits a more pronounced blood pressure lowering effect, and thus causes more frequent dizziness and hypotension as a consequence of its  $\beta_1$  and  $\alpha_1$ -receptor blocking activities.

Therefore, in patients predisposed to symptomatic hypotension, such as those with advanced LV dysfunction (LVEF less than 20% [0.20]) who normally exhibit low systolic blood pressures, **metoprolol succinate** may be the more desirable first-line  $\beta$ -blocker. In patients with uncontrolled hypertension, carvedilol may provide additional antihypertensive efficacy.

*B-Blockers* may be used by those with reactive airway disease or peripheral vascular disease but should be used with considerable caution or avoided if patients display active respiratory symptoms. Care must also be used in interpreting shortness of breath in these patients because the etiology could be either cardiac or pulmonary. A selective  $\beta_1$ -blocker such as metoprolol is a reasonable option for patients with reactive airway disease. The risk versus benefit of using any  $\beta$ -blocker in peripheral vascular disease must be weighed based on the severity of the peripheral

disease, and a selective  $\beta$ 1-blocker is preferred. During acute heart failure admission, the dose of B-Blocker should be haved.

## **Aldosterone Antagonists**

### **Value**

Currently, the aldosterone antagonists available are spironolactone and eplerenone. Each agent (spironolactone and eplerenone) has been studied in a defined population of patients with HF. Both Effective in reducing HF hospitalizations, improving functional class, reducing sudden cardiac death, and improving all-cause mortality.

### **Introduction, dosing and monitoring**

The major risk related to aldosterone antagonists is hyperkalemia. Before and within 1 week of initiating therapy, two parameters must be assessed: serum potassium and creatinine clearance (or serum creatinine).

Aldosterone antagonists should not be initiated in patients with potassium concentrations greater than 5.5 mEq/L (5.5 mmol/L). Likewise, these agents should not be given when creatinine clearance is less than 30 mL/minute (0.50 mL/s) or serum creatinine is greater than 2.5 mg/dL (221  $\mu$ mol/L).

In patients without contraindications, spironolactone is initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days for patients with baseline renal insufficiency.

Eplerenone is used at a dose of 25 mg daily, with the option to titrate up to 50 mg daily. Doses should be halved or switched to alternate-day dosing if creatinine clearance falls below 50 mL/min (0.83 mL/s).

Potassium supplementation is often decreased or stopped after aldosterone antagonists are initiated, and patients should be counseled to avoid high potassium foods. At any time after initiation of therapy, if potassium concentrations exceed 5.5 mEq/L (5.5 mmol/L), the dose of the aldosterone antagonist should be reduced or discontinued. In addition, worsening renal function dictates consideration for stopping the aldosterone antagonist.

### **Adverse effects**

Other adverse effects observed mainly with spironolactone include gynecomastia for men and breast tenderness and menstrual irregularities for women. Gynecomastia leads to discontinuation in up to 10% of patients on spironolactone. Eplerenone is a CYP3 A4 substrate and should not be used concomitantly with strong inhibitors of 3A4.

## **Digoxin**

### **Value**

The exact role of digoxin in therapy remains controversial largely due to disagreement on the risk versus benefit of routinely using this drug in patients with systolic HF. Digoxin was shown to decrease HF-related hospitalizations but did not decrease HF progression or improve survival.

Moreover, digoxin was associated with an increased risk for concentration-related toxicity and numerous adverse effects.

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,  $\beta$ -blocker, and diuretic. In patients with concomitant atrial fibrillation, digoxin may be added to slow ventricular rate regardless of HF symptomatology.

### **Dosing**

Digoxin is initiated at a dose of 0.125 mg to 0.25 mg daily depending on age, renal function, weight, and risk for toxicity. The lower dose should be used if the patient satisfies any of the following criteria: older than 65 years, creatinine clearance less than 60 mL/min (1.0 mL/s), or ideal body weight less than 70 kg (154 lb). The 0.125-mg daily dose is adequate in most patients.

## ***Antiplatelets and Anticoagulation***

### ***Indication***

Aspirin is generally used in HF patients with an underlying ischemic etiology, a history of ischemic heart disease, or other compelling indications such as history of embolic stroke. If aspirin is indicated, the preference is to use a low dose (81 mg daily).

Current consensus recommendations support the use of warfarin in patients with reduced LV systolic dysfunction and a compelling indication such as atrial fibrillation or prosthetic heart valves. In addition, warfarin is empirically used in patients with echocardiographic evidence of a mural thrombus or severely depressed (LVEF less than 20% [0.20]) LV function.

## **Heart Failure with Preserved Left Ventricular Ejection Fraction**

### **Treatment goal**

- (a) Correction or control of underlying etiologies (including optimal treatment of hypertension and CAD and maintenance of normal sinus rhythm).
- (b) Reduction of cardiac filling pressures at rest and during exertion.
- (c) Increased diastolic filling time. Diuretics are frequently used to control congestion.

### **Therapeutic options**

Recent studies failed to show significant reductions in mortality or hospitalizations with the use of ARBs. *B-Blockers* and calcium channel blockers can theoretically improve ventricular relaxation through negative inotropic and chronotropic effects. Unlike in systolic HF, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may be especially useful in improving diastolic function by limiting the availability of calcium that mediates contractility.

## **Outcome Evaluation of Chronic Heart Failure**

1. If diuretic therapy is warranted, monitor for therapeutic response by assessing weight loss and improvement of fluid retention, as well as exercise tolerance and presence of fatigue.

2. Once therapy for preventing disease progression is initiated, monitoring for symptomatic improvement continues.
3. It is important to keep in mind that patients' symptoms of HF can worsen with  $\beta$ -blockers, and it may take weeks or months before patients notice improvement
4. Monitor blood pressure to evaluate for hypotension caused by drug therapy.

Drug	Starting dose (mg)	Target dose/day	Doses /day	Mean total daily dose achieved in clinical trials
<b>Angiotensin-Converting enzyme inhibitors (ACEI)</b>				
Ramipril	1.25	10 daily	1 or 2	8.7 mg
Perindopril	2.5 od	10 daily		
Enalapril	2.5	20-40 mg	2	16.6 mg
<b>Angiotensin Receptor 2 blockers</b>				
Candesartan	4	32	1	24mg
<b>Beta Blockers</b>				
Carvedilol	3.125 bd	50-100 mg	2	37 mg
Bisoprolol	1.25 od	10	1	6.2 mg
Metoprolol CR/XL	12.5 or 25	200	1	159 mg
<b>Aldosterone Blockers</b>				
Spironolactone	12.5 mg	50 mg	1	26 mg
Eplerenone	25	50	1	43 g

### Patient Care and Monitoring

1. Educate the patient on lifestyle modifications such as salt restriction (maximum 2 to 4 g/day), fluid restriction if appropriate, limitation of alcohol, tobacco cessation, participation in a cardiac rehabilitation and exercise program, and proper immunizations such as the pneumococcal vaccine and yearly influenza vaccine.
2. Develop a treatment plan to alleviate symptoms and maintain euolemia with diuretics. Daily weights to assess fluid retention are recommended.

3. Develop a medication regimen to slow the progression of HF with the use of neurohormonal blockers such as vasodilators (ACE inhibitors, ARBs, or hydralazine/ isosorbide dinitrate),  $\beta$ -blockers, and aldosterone antagonists. Utilize digoxin if the patient remains symptomatic despite optimization of the therapies just described.

4. Is the patient at goal or maximally tolerated doses of vasodilator and  $\beta$ -blocker therapy?

5. Are aldosterone antagonists utilized in appropriate patients with proper electrolyte and renal function monitoring?

6. Stress the importance of adherence to the therapeutic regimen and lifestyle changes for maintenance of a compensated state and slowing of disease progression.

7. Evaluate the patient for presence of adverse drug reactions, drug allergies, and drug interactions.

8. Provide patient education with regard to disease state and drug therapy, and reinforce self-monitoring for symptoms of HF that necessitate follow-up with a healthcare practitioner.

## Atrial Fibrillation (AF) or Flutter – Recent Onset

Requiring admission, or onset during admission for other problem e.g. post-surgery.

- Haemodynamic compromise is an indication for rapid DC cardioversion - always use sedation or general anaesthesia.
- If the patient is haemodynamically stable (no reduced conscious level, systolic BP >90mmHg, no chest pain and no heart failure) and onset <48 hours, consider chemical cardioversion.

Chemical cardioversion

Options include:

**Amiodarone IV 300mg infused over 1 hour then 900mg over 24 hours through a central line (preferable) or large peripheral line or**

**Flecainide IV 2mg/kg, up to 150mg, over 30 minutes if no structural or coronary heart disease.**

- Control ventricular rate with oral beta-blocker or rate-limiting calcium channel blocker (or digoxin if heart failure is present).
- Remember – many cases of new onset AF or flutter will spontaneously revert to sinus rhythm – particularly if there is an obvious precipitating cause such as pneumonia, alcohol intoxication, hyperthyroidism or surgery.
- Cardioversion is much less successful in established AF or flutter than in new onset, and, if being considered, should not be delayed. Anticoagulant cover required if onset >48 hours, so 4 – 6 week delay required.



## Maintenance of Sinus Rhythm

Options include beta-blocker, sotalol, flecainide and amiodarone depending upon circumstances and patient factors.

Amiodarone loading regime is **amiodarone oral 200mg three times daily for 1 week then 200mg twice daily for 1 week then 200mg daily**.

**N.B.** Ideally, check baseline thyroid and liver function tests before starting. Interactions include digoxin and simvastatin (see BNF Appendix 1 for more details).

**N.B.** Deal with precipitants of AF: Infection, alcohol, hyperthyroidism, heart failure

## Atrial Fibrillation (AF) – Persistent

### Objectives

### Therapeutic:

1. Relieve symptoms – often only rate control required; diuretic may also be needed (often only on temporary basis).
2. Target ventricular (apex or ECG) rate <110bpm. If still symptomatic, aim for lower rate, <80bpm.
3. Assess thromboembolic risk and anticoagulate as appropriate (see flow chart further on).
4. In some cases, consider restoration of sinus rhythm by electrical or pharmacological cardioversion (only attempt chemical or electrical cardioversion after adequate anticoagulation with warfarin; risk of thromboembolism if not anticoagulated; limited long-term success).
5. Treat concomitant LV systolic dysfunction / heart failure.

### Ventricular rate control

1. Target ventricular (apex or ECG) rate <110bpm. If still symptomatic then aim for lower rate, <80bpm.
2. Patients without heart failure should be started on either:
  - A beta-blocker – choice includes:
    - **Bisoprolol oral 2.5mg daily and up-titrate to 5mg once daily** if ventricular rate is still >110bpm or
    - **Atenolol oral 25mg twice daily and up-titrate to 50mg twice daily** if ventricular rate is still >110bpm. In frail or elderly patients consider starting dose of **atenolol oral 25mg once daily**.



**Or**

- A rate-limiting calcium-channel blocker (CCB) i.e. verapamil or diltiazem (but avoid if LV systolic dysfunction)- **Start with verapamil (slow release) oral 120mg once daily and titrate up to 240mg once daily if ventricular rate still >110bpm.**

**N.B.** Beta-blockers and rate-limiting CCBs must not be combined except under specialist supervision.

Digoxin has a limited role as first-line treatment for ventricular rate control. It can be used in combination with a beta-blocker / rate-limiting CCB when control of the ventricular rate is difficult.

3. Patients **with** heart failure should be started on digoxin and follow the NHSGGC Heart Failure guideline.

### ***Heart failure / LV Systolic Dysfunction***

. ACE inhibitors and beta-blockers are strongly recommended. Beta-blockers must be initiated under direction of a hospital physician. Rate-limiting CCBs should be avoided.

### Prevention of stroke / thromboembolism

- Patients with both recurrent paroxysmal AF and sustained AF have a high risk of thromboembolism, particularly stroke. Compared to subjects without AF the absolute risk of stroke is, on average, increased by about 4-fold and the risk of stroke is about 4% per annum.
- This risk is greatest in patients with certain risk factors (see flow diagram below).
- For primary prevention, anticoagulants can substantially reduce risk of thromboembolism.
- Patients with AF and a previous stroke or transient ischaemic attack (TIA) have an absolute risk of a further stroke of the order of 10–12% per annum and an absolute benefit of approximately 80 fewer strokes per 1000 patient years of treatment.
- Advanced age is not a contraindication to anticoagulation.
- In patients with 'lone' AF, i.e. AF in a structurally normal heart and no other risk factors for thromboembolic disease ( $CHA_2DS_2-VASC = 0$ ), no anti-thrombotic or anticoagulant therapy is recommended.

### Who should receive anticoagulant therapy

- Patients with clinical risk factors or echocardiographic risk factors (see flow diagram below).
- Patients without contraindications to anticoagulant therapy.

### Cautions / contraindications to anticoagulant therapy

- Absolute contraindications include: active bleeding, pregnancy, stroke <14 days.

- Relative contraindications include: significant bleeding risk e.g. active peptic ulcer or recent head injury; bleeding in the last 6 months; previous cerebral haemorrhage.
- Cautions include: recurrent falls, alcohol abuse.

Choice of agent: new oral anticoagulant agents (NOACs) vs warfarin

Pros of NOACs

- More stable anticoagulation
- No requirement for anticoagulant monitoring
- Fewer food and drug interactions
- Fewer intracranial bleeds

Cons of NOACs

- No specific antidote
- More gastrointestinal bleeding with dabigatran and rivaroxaban, especially in the elderly

**Remember:** NOACS are indicated only in those patients who have non-valvular AF; not those with mitral stenosis or a mechanical valve.

Combined anticoagulant and antiplatelet therapy

Adding aspirin to warfarin in AF does not reduce the risk of stroke (except with prosthetic heart valves) but substantially increases the risk of bleeding. The combination is generally not indicated in stable coronary disease, but there are some circumstances, such as after an acute coronary event or PCI, when short-term combined double or triple therapy is used according to cardiologist advice.

CHADS <sub>2</sub> -> CHA <sub>2</sub> DS <sub>2</sub> VASc			
CHADS2 Risk	Score	CHA2DS2-VASc Risk	Score
CHF	1	CHF or LVEF ≤ 40%	1
Hypertension	1	Hypertension	1
Age > 75	1	Age ≥ 75	2
Diabetes	1	Diabetes	1
Stroke or TIA	2	Stroke/TIA/Thromboembolism	2
		Vascular Disease	1
		Age 65 - 74	1
		Female	1

From ESC AF Guidelines  
<http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf>

**Table 1 – CHADS<sub>2</sub> scoring table**

Non-valvular Atrial fibrillation (paroxysmal, persistent or permanent)



Determine risk of thromboembolism (use CHADS<sub>2</sub>, table 1 above)



If CHADS<sub>2</sub> = 0 or 1 – Use CHA<sub>2</sub>DS<sub>2</sub>-VASC scoring table [here](#)

If CHADS<sub>2</sub> ≥ 2 – continue below



**Warfarin or direct thrombin inhibitor or factor Xa inhibitor (NOAC)**

(if no contraindications, outlined above)

**pixaban oral 5mg twice daily**

- **Dabigatran oral 150mg twice daily**
- **Rivaroxaban oral 20mg once daily**

Doses may need to be reduced in some patients who have either low body weight ( $\leq 60\text{kg}$ ), renal impairment or age  $\geq 80$  years and another risk factor. For details see NOAC Prescribing in Patients with Non-Valvular AF

*Figure 1 –  
Prevention  
of stroke /  
thromboemb  
olism in AF  
stroke  
algorithm*

New  
anticoagulant  
s (direct  
thrombin and  
Factor Xa  
inhibitors)

- New  
anticoagulant  
s:

○

**A**

## Digoxin

In frail elderly patient or patients with very low body weight, lower loading and maintenance doses than those advised below may be required.

### Loading dose – normal renal function:

- **Digoxin oral** (preferred route) **500micrograms followed 6 hours later by 500–1000micrograms in divided doses > 6 hours apart or**
- **Digoxin IV 500micrograms followed 6 hours later by 250–500micrograms in divided doses 4–6 hours apart.**

### Loading dose – renal impairment (creatinine clearance <30ml/minute):

- **Digoxin oral** (preferred route) **500micrograms followed 6 hours later by 250–375micrograms in divided doses >6 hours apart or**
- **Digoxin IV 250–500micrograms**

**N.B.** Digoxin injection: 25micrograms = 0.1ml. Additional loading doses may be required; give according to ventricular (heart rate) response.

**Maintenance daily dose:** The tables below outline digoxin daily maintenance dosing for patients <60kg (see table 2) and >60kg (see table 3).

Drugs to be reviewed in bnf:

1. Bisoprolol
2. Furosemide
3. Amiodarone

## Diabetes Mellitus

### Management of Diabetic Emergencies

- ❖ Patients with diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar non ketotic coma are treated with intravenous fluids and insulin and Potassium supplement if required.
- ❖ Both DKA and hyperglycaemic hyperosmolar non ketotic coma are often precipitated by another illness, frequently infection. An attempt should be made to search for and treat any precipitating illness.
- ❖ When treating patients with hyperglycaemic hyperosmolar non ketotic coma, it is important to follow sodium and serum osmolality measurements to document return to normal values.

### Diabetic Ketoacidosis

**Definition:** Severe uncontrolled diabetes with ketonaemia / ketonuria, metabolic acidosis, usually with hyperglycaemia.

### Goals of therapy

Treatment goals of DKA consist of reversing the underlying metabolic abnormalities, rehydrating the patient, and normalizing the serum glucose

### Management of Diabetic Ketoacidosis

1. Confirm diagnosis ( $\uparrow$  plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH less than 7.0 or unconscious.
3. Assess: Serum electrolytes ( $K^+$ ,  $Na^+$ ,  $Mg^{2+}$ ,  $Cl^-$ , bicarbonate, phosphate) Acid-base status—pH,  $HCO_3^-$ ,  $PCO_2$ , *b*-hydroxybutyrate, Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 hours (5–10 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/hour; change to 5% glucose and 0.45% saline at 100–200 mL/hour when plasma glucose reaches 250 mg/dL (14 mmol/L).
5. Administer regular insulin: IV (0.1 units/kg) or IM (0.4 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 hours. If initial serum potassium is less than 3.3 mmol/L (3.3 mEq/L), do not administer insulin until the potassium is corrected to greater than 3.3 mmol/L (3.3 meq/L).

### Insulin infusion rate: on hourly blood glucose check

- If  $> 14$  mmol/L, increase insulin rate by 1 unit/hour
- If  $< 9$  mmol/L, decrease insulin rate by 1 unit/hour
- If  $< 3.5$  mmol/L, stop insulin for an hour, restart at 1 unit/hour if  $> 3.5$  mmol/L
- If persistently above 14 mmol/L, despite increasing insulin to 6 units/hour, ask for medical review and check pump devices, IV lines and IV cannulae to ensure patient is getting prescribed insulin dose.

6. Assess patient: What precipitated the episode (non-compliance, infection, trauma, infarction, cocaine)? Initiate appropriate work-up for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 hours; measure electrolytes (especially K<sup>+</sup>, bicarbonate, phosphate) and anion gap every 4 hours for first 24 hours.
8. Monitor blood pressure, pulse, respirations, mental status, and fluid intake and output every 1–4 hours.
9. Replace K<sup>+</sup>: 10 mEq/hour when plasma K<sup>+</sup> less than 5.5 mEq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 mEq/hour when plasma K<sup>+</sup> less than 3.5 mEq/L or if bicarbonate is given.
10. Continue above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

### **Key steps in the management of DKA**

1. Ensure all paediatric / adolescent patients are managed using a paediatric protocol.
2. Confirm the diagnosis (H<sup>+</sup> > 45 mEq/L or HCO<sub>3</sub><sup>-</sup> < 18 mmol/L or pH < 7.3 on venous gas with ketonaemia or ketonuria).
3. Initiation of IV fluids within 30 minutes of arrival.
4. Initiation of IV insulin within 1 hour of arrival.
5. Regular monitoring of K<sup>+</sup> level and appropriate replacement.
6. Commence IV glucose infusion once BG < 14 mmol/L.
7. Convert back to usual mealtime SC insulin regimen when HCO<sub>3</sub><sup>-</sup> within normal reference range and patient is eating normally (stop IV fluids and IV insulin 30 minutes after usual injection of pre-meal SC insulin).
8. **WBC count:** This is often raised in DKA. Only give antibiotics if there is clear evidence of infection
9. **Cerebral oedema:** Children and adolescents are at the highest risk. Consider if: headaches, or reduced conscious level. Monitoring for signs of cerebral oedema should start from the time of admission and should continue until up to at least 12 hours after admission. If there is a suspicion of cerebral oedema or the patient is not improving as expected, within 4 hours of admission, call the consultant. Check arterial blood gases and administer **Mannitol IV (100 ml of 20% over 20 minutes) or dexamethasone IV 8 mg (discuss with Consultant)** and undertake CT scan to confirm findings.

### **Hyperglycemic Hyperosmolar Non Ketotic coma**

In hyperglycemic hyperosmolar non ketotic coma, the average fluid deficit is 8- 12 L. Use 0.9 NS for the initial resuscitation (1 L). Switch to 0.45 NS at a rate of 200-500 mL/hr. Goal is 3-4 L over the initial 4-hour period. The corrected serum sodium and the serum osmolarity should be gradually returned to normal over a 24- to 36-hour period. Insulin infusion can be started after initiating infusion of fluids. A total of 0.1 U/kg/hr of regular insulin is given if the K >3.3 mEq/L. Potassium replacement is similar to that in patients with DKA. Frequent monitoring of

glucose and electrolytes is necessary to avoid iatrogenic electrolyte abnormalities, such as hypokalemia.

## Peptic ulcer diseases

### Desired Outcomes

The goals of PUD therapy are to:

- (1) resolve symptoms
- (2) reduce acid secretion
- (3) promote epithelial healing
- (4) prevent ulcer-related complications
- (5) prevent ulcer recurrence. For HP-related PUD, eradication of HP is an additional outcome.

### Non-pharmacologic Therapy

Patients with PUD should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence. Patients should be advised to reduce psychological stress and avoid cigarette smoking, alcohol consumption, foods or beverages that exacerbate ulcer symptoms, and NSAID or aspirin use. surgical interventions are generally reserved for complicated or refractory PUD.

### Pharmacologic Therapy

#### Treatment of *Helicobacter pylori*-Associated Ulcers

The HP regimen that is chosen should have a per-protocol cure rate of greater than or equal to 80%-90%. In addition to proven efficacy, the optimal treatment regimen should cause minimal adverse events, have low risk for the development of bacterial resistance, and be cost effective.

Eradication therapy with a PPI-based three-drug regimen should be considered for all patients who test positive for HP and have an active ulcer or a documented history of either an ulcer or ulcer-related complication. Different antibiotics should be used if a second course of HP eradication therapy is required.

**First line –Omeprazole oral 20 mg twice daily (or lansoprazole oral 30 mg twice daily) and Clarithromycin oral 500 mg twice daily and Amoxicillin\* oral 1 g twice daily. \*In penicillin allergy use tetracycline oral 500 mg twice daily.**

**Second line – Substitute: Clarithromycin for metronidazole oral 400 mg twice daily.**

- ❖ Patients should be counselled on the importance of compliance before starting treatment and in those patients taking metronidazole on the avoidance of alcohol because of the risk of a disulfiram-like reaction.
- ❖ After 1 week's treatment all medication can be stopped, except where ulcers have bled or perforated, when a PPI will be continued.
- ❖ A breath test should be carried out 28 days after completion of treatment to check that eradication has been successful if the patient is still symptomatic.

**N.B.** Healing of gastric ulcers must be confirmed by endoscopy after 6 - 8 weeks

### **Drug Regimens to Eradicate *Helicobacter pylori***

#### **Treatment Regimen**

#### **Cure Rates**

#### **Two Drugs**

Amoxicillin 1 g three times a day + omeprazole 20 mg twice a day

Poor

Clarithromycin 500 mg three times a day + omeprazole 40 mg every day

Poor

Clarithromycin 500 mg three times a day + RBC 400 mg twice a day

Fair

#### **Three Drugs**

Clarithromycin 500 mg twice a day + metronidazole 500 mg twice a day + omeprazole 20 mg twice a day            Good–excellent

Clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day + lansoprazole 30 mg twice a day            Good–excellent

Clarithromycin 500 mg twice a day + metronidazole 500 mg twice a day + RBC 400 mg twice a day            Good

Amoxicillin 1 g twice a day + clarithromycin 500 mg twice a day + RBC 400 mg twice a day            Good

#### **Four Drugs**

BSS 525 mg four times a day + metronidazole 250 mg four times a day + tetracycline 500 mg four times a day + H2RA (conventional ulcer-healing dose)<sup>c</sup>            Good–excellent

BSS 525 mg four times a day + metronidazole + amoxicillin + PPI<sup>d</sup>            Good

#### **Rescue Therapy<sup>e</sup>**

BSS 525 mg four times a day + metronidazole 500 mg four times a day + tetracycline 500 mg four times a day + omeprazole 20 mg twice a day<sup>d</sup>            Good–excellent

Furazolidone 200 mg twice a day + amoxicillin 1 g twice a day + omeprazole 20 mg twice a day<sup>f</sup>            Good

Amoxicillin 1 g twice a day + rifabutin 300 mg every day + pantoprazole 40 mg twice a day<sup>g</sup>            Good–excellent

<sup>a</sup>These regimens based on efficacy for a 14-day treatment duration unless otherwise noted.

<sup>b</sup>Cure rates based on intention-to-treat analysis from references 3, 12, 14, and 35, where: poor = less than 70% eradication, fair =

70–80%, good = 80–90%, and excellent = greater than 90%.

<sup>c</sup>H2RA therapy should be continued for an additional 2 weeks.

<sup>d</sup>Duration of therapy is 7–10 days.

<sup>e</sup>Data based on refractory treatment data.

<sup>f</sup>Given for 7 days.

<sup>g</sup>Given for 10 days.



BSS, bismuth subsalicylate; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor; RBC, ranitidine bismuth citrate (not available in the United States).

### **On discharge**

- Arrange 13C Urea Breath Test in 8 weeks if H. pylori eradication therapy given.
- Continue PPI for 6 weeks and then change to H2 antagonist prior to breath test.
- Repeat OGD (Oesophagogastroduodenoscopy) in 8 weeks if gastric ulcer found.

### **Treatment of NSAID-Induced Ulcers**

Choice of regimen in a patient with PUD related to NSAID use depends on whether NSAID use is to be continued. NSAIDs should be discontinued if possible and replaced with alternatives (such as acetaminophen) although this may not be desirable or feasible in some patients. For patients discontinuing NSAID therapy, PPIs, H2RAs, or sucralfate are all effective for ulcer healing. PPI therapy heals NSAID ulcers faster than H2RAs.

### **Prevention of NSAID-Induced Ulcers**

Prophylactic regimens against PUD are often required in patients who require long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardioprotection. Misoprostol, H2RAs, PPIs, have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD. PPIs at standard doses reduce the risk of both gastric and duodenal ulcers as effectively as misoprostol and are generally better tolerated

### **IV proton pump inhibitors**

- ❖ If the patient is unable to take oral therapy give: **omeprazole 40 mg by slow IV bolus injection**
- ❖ If patient has had endoscopic haemostasis for a bleeding ulcer give: **omeprazole infusion**, initial 80 mg dose (give 80 mg in 100 ml sodium chloride 0.9% infused over 40 - 60 mins). **followed by: continuous infusion of 8 mg/hour for 72 hours** (make up 80 mg in 100 ml sodium chloride 0.9%, infuse at 10 ml (8 mg) per hour over 10 hours for a total of 72 hours) **followed by maintenance dose: omeprazole oral 20 mg each day for 8 weeks**

### **Persisting symptoms**

Omeprazole oral treatment dose 40 mg once daily for 4 - 8 weeks, then maintenance dose 20 mg once daily or Lansoprazole oral treatment dose 30 mg once daily for 4 - 8 weeks, then maintenance dose 15 mg once daily.

### **Long-term maintenance**

- Aim for lowest dose proton pump inhibitor (PPI) needed to control symptoms.

**Note:** Low-dose maintenance therapy with a PPI or H2RA is only indicated for patients who fail HP eradication, have HP-negative ulcers, or develop severe complications related to ulcer disease.

### **Patient Care and Monitoring**

#### **General Recommendations: HP-Associated and NSAID Induced Ulcers**

1. Assess the severity of signs and symptoms. Identify the presence of any alarm signs and symptoms.
2. Educate the patient on monitoring for alarm signs and symptoms.
3. Obtain a history of prescription medication, over-the counter medication, and dietary supplement use.
4. Encourage lifestyle modifications such as reducing tobacco use and ethanol ingestion and decreasing psychological stress.
5. Determine the appropriate duration of therapy for acid-suppressive therapy.
6. Define the current impact of PUD on the patient's quality of life and the improvement in these outcomes sought with drug therapy.
7. Evaluate current drug therapy for potential adverse drug reactions and drug interactions.

#### **Helicobacter pylori–Associated Ulcers**

1. Recommend an appropriate drug regimen that will eradicate the organism.
2. Identify the patient's drug allergies and avoid drug classes a patient is allergic to.
3. Avoid regimens with tetracycline in children.
4. Educate patients on specific adverse drug effects, particularly with metronidazole (avoidance of alcohol) and bismuth (change in stool color).
5. Assess the potential for drug interactions, particularly in patients taking regimens containing metronidazole, clarithromycin, and/or cimetidine.
6. Recommend different antibiotics if this treatment regimen is a result of failure of a prior HP regimen.
7. Educate the patient on the importance of adherence to eradication therapy.

#### **NSAID-Associated Ulcers**

1. Assess for risk factors for NSAID ulcers and recommend an appropriate strategy to reduce ulcer risk.
2. Monitor for signs and symptoms of complications associated with NSAID-related ulceration.
3. Recommend an appropriate treatment regimen to achieve the desired outcomes.
4. Assess and counsel patients on potential adverse drug events and drug interactions.
5. Inform patients who are receiving prophylactic therapy on the importance of its use, potential adverse drug events, and the possible alarm symptoms associated with PUD.

**(Omeprazole, Misoprostol, cimetidine, metronidazole, and clarithromycin)**

## ***Acute Asthma***

### ***Staging the severity***

In acute asthma, the severity of an exacerbation does not depend on the classification of the patient's chronic asthma because even patients with intermittent asthma can have life-threatening acute exacerbations. Severity at the time of the evaluation can be estimated by signs and symptoms or presenting peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV1).

The exacerbation is considered ***mild*** if the patient is only having dyspnea with activity and the PEF is at least 70% of the personal best value, ***moderate*** if the dyspnea limits activity and the PEF is 40% to 69% of the personal best, and ***severe*** with PEF less than 40% and dyspnea interferes with conversation or occurs at rest. When the patient is not able to speak and the personal best PEF is less than 25% of the personal best predicted value, it is a ***life-threatening exacerbation***.

## **TREATMENT OF ASTHMA**

### **Desired Outcomes**

#### ***Acute Asthma***

Acute or worsening asthma can be a life-threatening situation and requires rapid assessment and appropriate intensification of therapy. Mortality associated with asthma exacerbations is usually related to inappropriate assessment of the severity of the exacerbation resulting in insufficient treatment or referral for medical care. The goals of therapy are to:

- (a) Correct significant **hypoxemia**.
- (b) Reverse airflow obstruction rapidly.
- (c) Reduce the likelihood of exacerbation relapse or recurrence of severe airflow obstruction in the future.

#### ***Factors Associated with Worsening Asthma Control***

1. Exercise is one of the most common precipitants of asthma symptoms. Pretreatment with a SABA 5 minutes prior to exercise is the treatment of choice

and will protect against bronchospasm for 2 to 3 hours. Regular treatment with an inhaled corticosteroid (ICS) also prevents bronchospasm associated with exercise.

2. A yearly influenza vaccine is recommended for patients 6 months and older with asthma to decrease the risk of complications from **influenza**. The pneumococcal vaccine may decrease the risk of invasive pneumococcal disease in patients with asthma and is recommended as a one-time immunization before the age of 65 years and again after age 65. In patients older than 11 years, providing a booster vaccine to protect against pertussis is becoming standard practice. The varicella vaccine is also highly recommended.
3. Nonselective  $\beta$ -blockers, such as carvedilol, labetalol, nadolol, pindolol, propranolol, and timolol (including those in ophthalmic preparations) may worsen asthma control. These agents are avoided in patients with asthma unless the benefits of therapy outweigh the risks. In patients with asthma requiring  $\beta$ -blocker therapy, a  $\beta_1$ -selective agent such as metoprolol or atenolol is the best option. Because selectivity is dose related, the lowest effective dose is used.
4. Patients with aspirin-sensitive asthma are usually adults and often present with the triad of rhinitis, nasal polyps, and asthma. In these patients, acute asthma may occur within minutes of receiving aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). These patients are counseled against using NSAIDs. Although acetaminophen is generally safe, doses larger than 1 g may cause acute asthmatic reactions in some patients.

### **Treatment of Acute Asthma**

Early and aggressive treatment is necessary for quick resolution. The optimal treatment of acute asthma depends on the severity of the exacerbation.

Based on the initial response to SABA therapy, the severity of the exacerbation is assessed, and treatment is appropriately intensified. Patients deteriorating quickly or not responding to quick-relief medications should go to the emergency department for assessment and treatment of the asthma exacerbation. Patients responding to therapy in the emergency department with a sustained response to a SABA are discharged home. Patients are discharged with an SABA, a 3-

to 10-day course of oral corticosteroid, an ICS, and perhaps other appropriate long-term controller medications.

### **Oxygen saturation target**

Patients with oxygen saturation less than 90% (less than 95% in children, pregnant women, and patients with coexisting heart disease) receive oxygen with the dose adjusted to keep oxygen saturation above these levels. Administration of low oxygen concentrations (less than 30% of the fraction of inspired air) by nasal cannula or facemask is usually sufficient to reverse hypoxemia in most patients.

## **TREATMENT OF ASTHMA**

### *Chronic Asthma*

Treatment goals are to:

- (a) Prevent chronic and troublesome symptoms,
- (b) Require infrequent use (2 or fewer days/week) of SAB for quick relief of symptoms,
- (c) Prevent exacerbations of asthma and the need for emergency department visits or hospitalizations,
- (d) Provide optimal pharmacotherapy with minimal or no adverse effects.

### **Pharmacologic Therapy**

#### *B<sub>2</sub>-Adrenergic Agonists*

##### *Mechanism of action*

*B<sub>2</sub>-Agonists* relax airway smooth muscle by directly stimulating  $\beta_2$ -adrenergic receptors in the airway. They also increase mucociliary clearance and stabilize mast cell membranes. The early-phase response to antigen in an asthma exacerbation is blocked by pretreatment with inhaled SABAs. Short-acting  $\beta_2$ -agonists have significantly better bronchodilating activity in acute asthma than theophylline or anticholinergic agents.

##### **Adverse effects**

Adverse effects of  $\beta_2$ -agonists include tachycardia, tremor, and hypokalemia, which are usually not troublesome with inhaled dosage forms. Oral  $\beta_2$ -agonists have increased adverse effects and are not used in the treatment of asthma. Inhaled  $\beta_2$ -agonists are classified as either short- or **longacting based on duration of action.**

### **Short-Acting Inhaled $\beta$ 2-Agonists**

*Value:* Are the drugs of choice for treating acute asthma and symptoms of chronic asthma as well as preventing exercise-induced bronchospasm. Inhaled SABAs have an onset of action of less than 5 minutes and a duration of action of 4 to 6 hours.

Scheduled chronic daily dosing of SABAs is not recommended for two reasons. **First**, the need to use an inhaled SABA is one key indicator of uncontrolled asthma. Therefore, patients are educated to record SABA use. **Second**, scheduled SABA use decreases the duration of bronchodilation provided by the SABA.

### **Long-Acting Inhaled $\beta$ 2-Agonists**

#### **Indication, onset, duration**

Salmeterol and formoterol are LABAs that provide up to 12 hours of bronchodilation after a single dose. Because of the long duration of bronchodilation, these agents are useful for patients experiencing nocturnal symptoms. Salmeterol is a partial agonist with an onset of action of approximately 30 minutes. Formoterol is a full agonist that has an onset of action similar to that of albuterol, but it is not currently approved for the treatment of acute bronchospasm.

#### **Value**

LABAs are indicated for chronic treatment of asthma as add-on therapy for patients not controlled on low to medium doses of ICS. Adding an LABA is at **least as effective** in improving symptoms and decreasing asthma exacerbations as doubling the dose of an ICS or adding an LTRA to ICS. Adding an LABA to ICS therapy also **reduces the amount of ICS** necessary for asthma control.

#### **Add on only reason**

Although both formoterol and salmeterol are effective as add-on therapy for moderate persistent asthma, neither agent should be used as monotherapy for chronic asthma. There may be an increased risk of severe asthma exacerbations and asthma-related deaths when LABAs are used alone. The labeling for all drugs containing LABAs includes a black box warning against their use without an ICS.

Salmeterol and formoterol are available in fixed-ratio combination products containing fluticasone, budesonide, or mometasone. Combination products may increase adherence because of the need for fewer inhalers and inhalations.

### *Corticosteroids*

Corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma and are available in inhaled, oral, and injectable dosage forms. Corticosteroids also improve the response to  $\beta_2$ -agonists.

### **Inhaled Corticosteroids**

#### **Value**

*ICS are the preferred therapy for all forms of persistent asthma in all age groups. ICS are more effective* than LTRA and theophylline in improving lung function and preventing emergency department visits and hospitalizations due to asthma exacerbations. The **primary advantage** of using ICS compared with systemic corticosteroids is the targeted drug delivery to the lungs, which decreases the risk of systemic adverse effects. Product selection is based on preference for dosage form, delivery device, and cost.

#### **Frequency, smoking effect, Onset**

The ICS are more effective when given twice daily rather than once daily. Cigarette smoking decreases the response to ICS, and smokers require higher doses of ICS than nonsmokers. Although some beneficial effect is seen within 12 hours of administration of an ICS, 2 weeks of therapy is necessary to see significant clinical effects. Longer treatment may be necessary to realize the full effects on airway inflammation.

#### **Side effects and management, drug interaction, response rate**

For most delivery devices, the majority of the drug is deposited in the mouth and throat and swallowed. Local adverse effects of ICS include oral candidiasis, cough, and **dysphonia**. The incidence of local adverse effects can be reduced by using a VHC and by having the patient rinse the mouth with water and expectorate after using the ICS. Decreasing the dose reduces the incidence of hoarseness.

Systemic absorption occurs via the pulmonary and oral routes. Systemic adverse effects are dose dependent and rare with low to medium doses. However, high-dose ICS have been associated with adrenal suppression, decreased bone mineral density, skin thinning, cataracts, and easy

bruising. Nonprogressive growth suppression in children occurs primarily in the first month of treatment and is reported with low- and medium-dose ICS. A significant drug interaction causing Cushing's syndrome and adrenal insufficiency occurs when potent inhibitors of CYP3A4 (ritonavir, itraconazole, ketoconazole) are administered with high doses of ICS. Considerable variability in response to ICS exists, with up to 40% of patients not responding to ICS.

## **Systemic Corticosteroids**

### **Indication, onset, duration, route**

Prednisone, prednisolone, and methylprednisolone are systemic corticosteroids used in asthma treatment. These medications are the cornerstone of treatment for acute asthma not responding to a SABA. The onset of action for systemic corticosteroids is 4 to 12 hours. For this reason, systemic corticosteroids are started early in the course of acute exacerbations. The oral route is preferred in acute asthma; there is no evidence that IV corticosteroid administration is more effective. Therapy with systemic corticosteroids is continued until the PEF is 70% or more of the personal best measurement and asthma symptoms are resolved.

The duration of therapy usually ranges from 3 to 10 days. Tapering the corticosteroid dose in patients receiving short bursts (up to 10 days) is usually not necessary because any adrenal suppression is transient and rapidly reversible. Because of serious potential adverse effects, systemic corticosteroids are avoided as long-term controller medication for asthma, if possible. Systemic corticosteroids are only used in patients who have failed other therapies, including immunomodulators. If systemic therapy is necessary, once daily or every-other-day therapy is used with repeated attempts to decrease the dose or discontinue the drug.

## ***Anticholinergics***

### ***Mechanism of action, onset, duration, indication***

Two anticholinergic medications are available: ipratropium bromide and tiotropium bromide. Anticholinergic agents act by inhibiting the effects of acetylcholine on muscarinic receptors in the airways and protecting against cholinergic mediated bronchoconstriction. The bronchodilating effects are not as effective as SABAs in asthma. Ipratropium bromide (Atrovent) is available as an MDI and solution for nebulization. Its onset of action is approximately 30 minutes, and the duration of action is 4 to 8 hours. The addition of ipratropium bromide to



SABAs during a moderate to severe asthma exacerbation improves pulmonary function and decreases hospitalization rates in both adult and pediatric patients. Combining an SABA with ipratropium is only indicated in the emergency department setting. There is no evidence to support continued use of ipratropium during hospitalization or for chronic asthma treatment.

### ***Leukotriene Receptor Antagonists***

The LTRAs are anti-inflammatory medications that either inhibit 5-lipoxygenase (zileuton) or competitively antagonize the effects of leukotriene D4 (montelukast and zafirlukast).

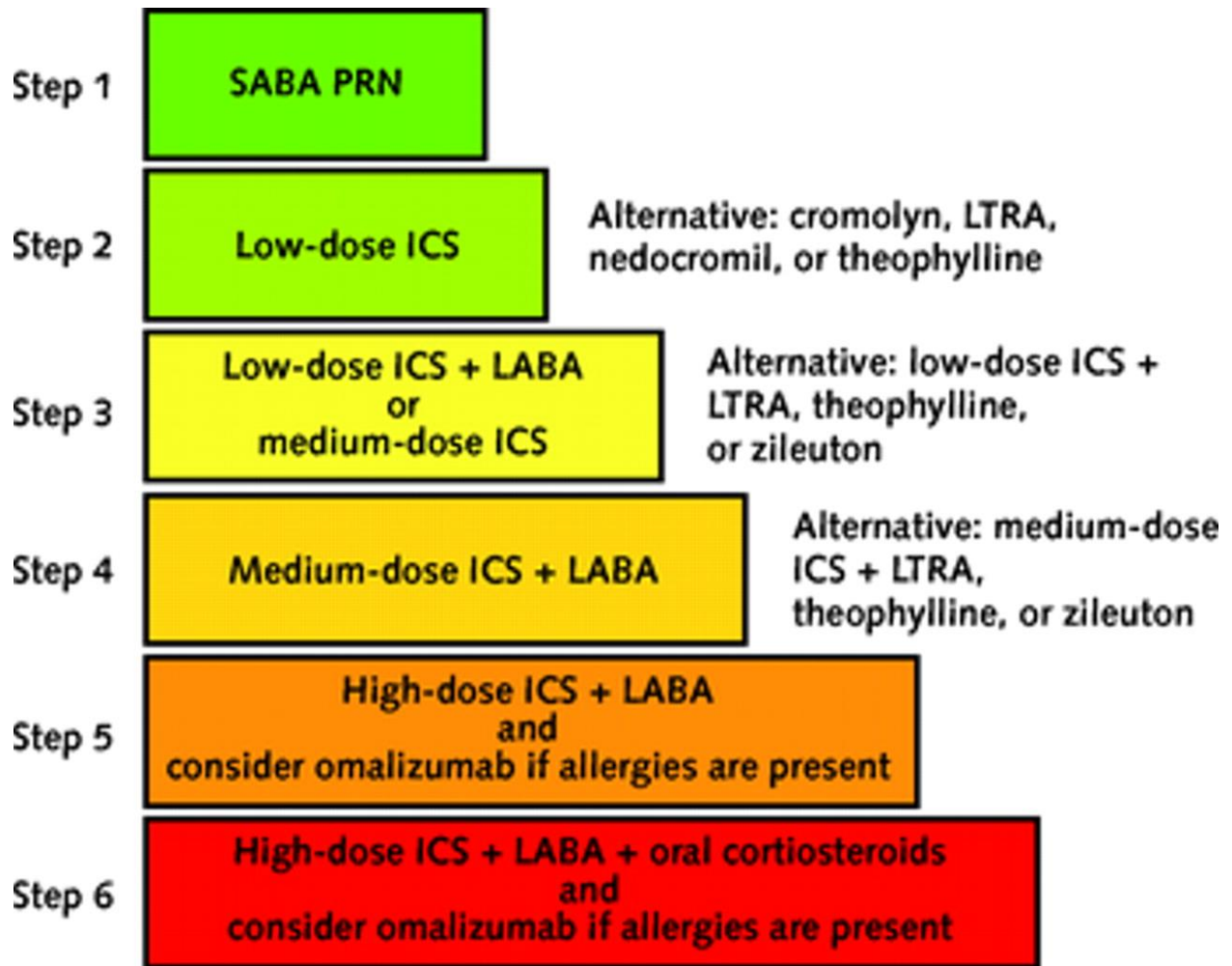
These agents improve FEV1 and decrease asthma symptoms, SABA use, and asthma exacerbations. Although these agents offer the convenience of oral administration, they are significantly less effective than low ICS doses. Combining an LTRA with an ICS or LABA is not as effective as an ICS plus an LABA. LTRA are beneficial for asthma patients with allergic rhinitis or aspirin sensitivity. Montelukast (Singulair) is generally well tolerated with minimal need for monitoring and few drug interactions. Zileuton (Zyflo) and zafirlukast (Accolate) are not commonly used because of the risk of hepatotoxicity. Both zileuton and zafirlukast require liver function monitoring at baseline and every 3 months for the first year of use and then periodically thereafter. Zileuton and zafirlukast are metabolized through the CYP 2C9 hepatic pathway and have significant drug interactions. All three agents have reports of neuropsychiatric events, such as sleep disorders, aggressive behavior, and suicidal thoughts that need to be monitored.

### ***Methylxanthines***

Theophylline has anti-inflammatory properties and causes bronchodilation by inhibiting phosphodiesterase and antagonizing adenosine. Its use is limited because of inferior efficacy as a long-term controller medication compared with ICS, a narrow therapeutic index with potentially life threatening toxicity, and multiple clinically important drug interactions.

## Classification of Asthma Severity in Children(5yrs) to Adults [Symptom Based]

Components of Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
1.Symptoms	=<2 days/week	>2 days/week but not daily	Daily	Throughout the day
2.Nighttime awakenings	=<2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
*3.Using Short-acting Beta2-agonists for symptom control	=<2 days/week	>2 days/week But not daily	Daily	Several times per day
4.Interference with normal activity	None	Minor Limitation	Some Limitation	Extremely Limited



# Chronic Obstructive Pulmonary Disease

## Therapy of COPD Exacerbations

### Definition

An exacerbation is acute worsening of the patient's symptoms from his or her usual stable state that is beyond normal day to-day variations; an exacerbation warrants a change in medications. Common symptoms are worsening of dyspnea, increased sputum production, and change in sputum color.

The most common causes of an exacerbation are respiratory infection and air pollution, but the cause cannot be identified in about one-third of severe exacerbations. Treatment depends on the symptoms and severity of the exacerbation.

### Severity

**Mild exacerbations** can often be treated at home with short-acting inhaled bronchodilators with or without oral corticosteroids. Antibiotics are indicated when there are specific signs of airway infection (e.g., change in color of sputum and/or increased sputum production or dyspnea) or when mechanical ventilation is needed. **Moderate to severe exacerbations** require management in the emergency department or hospital. Management should consist of controlled oxygen therapy, bronchodilators, oral or IV corticosteroids, antibiotics if indicated, and consideration of mechanical ventilation (noninvasive or invasive).

### Bronchodilators

Albuterol is the preferred bronchodilator for treatment of acute exacerbations because of its rapid onset of action. Ipratropium can be added to allow for lower doses of albuterol, thus reducing dose-dependent adverse effects such as tachycardia and tremor.

Delivery can be accomplished through MDI and spacer or nebulizer. The nebulizer route is preferred in patients with severe dyspnea and/or cough that would limit delivery of medication through an MDI with spacer. If response is inadequate, theophylline can be considered; however, clinical evidence supporting its use is lacking.

### Oral Corticosteroids

Systemic corticosteroids shorten the recovery time, help to restore lung function more quickly, and reduce the risk of early relapse. The GOLD guidelines recommend oral prednisolone 30 to 40 mg/day for 10 to 14 days. Shorter courses (7 days or fewer) may be as effective, but further studies are needed. Prolonged treatment and/or higher doses do not result in greater efficacy and increase the risk of adverse effects. If

inhaled corticosteroids are part of the patient's usual treatment regimen, they should be continued during systemic therapy.

### **Antibiotics**

The predominant bacterial organisms in patients with mild exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In patients with more severe underlying COPD, other bacteria such as enteric gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*) and *Pseudomonas aeruginosa* may be more common. A risk stratification approach has been advocated to help guide antibiotic selection.

This approach is based on risk factors found to be predictive of treatment failure or early relapse. Patients at risk for poor outcome are candidates for more aggressive initial antibiotic treatment. Table 15–5 provides recommended antibiotic treatment based on this risk stratification approach. Antibiotic treatment for most patients should be maintained for 5 to 10 days. Exacerbations due to certain infecting organisms (*P. aeruginosa*, *E. cloacae*, and methicillin resistant *Staphylococcus aureus*), although not common, require more lengthy courses of therapy (21 to 42 days). If there is worsening clinical status or inadequate clinical response in 48 to 72 hours, reevaluate the patient, consider sputum Gram stain and culture if not already obtained, and adjust antimicrobial therapy. If Gram stain and culture results are available, narrow the antibiotic therapy according to cultured organism(s) and sensitivities. If no cultures have been obtained, or cultures remain negative, consider additional antibiotics and/or change to antibiotics with a broader spectrum of activity.

**Table 15-5**  
**Recommended Antibiotic Therapy in Acute Exacerbations of COPD**

Patient Characteristics	Likely Pathogens	Recommended Antibiotics <sup>a,b</sup>
<b>Mild Exacerbation Without Risk Factors for Poor Outcome</b>		
Not requiring hospitalization Less than three exacerbations per year No comorbid illness FEV <sub>1</sub> greater than 50% predicted No recent antibiotic therapy	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Chlamydia pneumoniae</i> Viruses	<b>Oral First-Line Therapy:</b> β-Lactam (high-dose amoxicillin) <sup>c</sup> β-Lactam/β-lactamase inhibitor (amoxicillin-clavulanate) Tetracycline Trimethoprim/sulfamethoxazole <b>Alternative Oral Therapy:</b> Macrolides (azithromycin, clarithromycin) Second- or third-generation cephalosporins (cefuroxime, cefpodoxime, cefdinir, cefprozil) <b>IV Therapy:</b> Not recommended
<b>Moderate Exacerbation With Risk Factors for Poor Outcome</b>		
FEV <sub>1</sub> less than 50% predicted Comorbid diseases Three or more exacerbations per year Antibiotic therapy in the previous 3 months	Above organisms plus: Resistant pneumococci (β-lactamase producing, penicillin-resistant), <i>Escherichia coli</i> , <i>Proteus</i> spp, <i>Enterobacter</i> spp, <i>Klebsiella pneumoniae</i>	<b>Oral First-Line Therapy:</b> β-Lactam/β-lactamase inhibitor (amoxicillin-clavulanate) <b>Alternative Oral Therapy:</b> Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, moxifloxacin) <b>IV Therapy:</b> β-lactam/β-lactamase inhibitor (ampicillin-sulbactam) Second- or third-generation cephalosporin (cefuroxime, ceftriaxone) Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, moxifloxacin)
<b>Severe Exacerbation With Risk Factors for <i>Pseudomonas aeruginosa</i></b>		
Recent hospitalization Four or more courses of antibiotics in the last year Very severe COPD (GOLD 4) Previous isolation of <i>P. aeruginosa</i>	Above organisms plus: <i>P. aeruginosa</i>	<b>Oral First-Line Therapy:</b> Antipseudomonal fluoroquinolone (ciprofloxacin, high-dose levofloxacin) <b>IV Therapy:</b> Antipseudomonal β-lactamase-resistant penicillin (piperacillin-tazobactam) Third- or fourth-generation cephalosporin with antipseudomonal activity (ceftazidime, cefepime) Antipseudomonal fluoroquinolone (ciprofloxacin, high-dose levofloxacin)

## Oxygen

The goal of oxygen therapy is to maintain Pao<sub>2</sub> above 60 mm Hg (7.98 kPa) or Sao<sub>2</sub> above 90% to prevent tissue hypoxia and preserve cellular oxygenation. The GOLD guidelines recommend a target Sao<sub>2</sub> of 88% to 92%. Increasing the Pao<sub>2</sub> much further confers little added benefit and may increase the risk of CO<sub>2</sub> retention, which may lead to respiratory acidosis. ABGs should be obtained after 30 to 60 minutes to assess for hypercapnia and acidosis.

In advanced COPD, caution should be used because overly aggressive administration of oxygen to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. In these patients, mild hypoxemia, rather than CO<sub>2</sub> accumulation, triggers their drive to breathe.

## Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible. It is caused by exposure to noxious particles or gases, most commonly cigarette smoke. It is a major cause of morbidity and mortality and a leading cause of

disability in the United States. Previous definitions of COPD included chronic bronchitis and emphysema.

A suspected diagnosis of COPD should be based on the patient's symptoms and history of exposure to risk factors. **Spirometry** is required to confirm the diagnosis, using the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC).

In advanced COPD, airflow obstruction, damaged bronchioles and alveoli, and pulmonary vascular abnormalities lead to impaired gas exchange. This results in **hypoxemia** and eventually **hypercapnia**. Hypoxemia is initially present only during exercise but occurs at rest as the disease progresses. Pulmonary hypertension develops late in the course of COPD, usually after the development of severe hypoxemia. It is the most common cardiovascular complication of COPD and can result in **cor pulmonale**, or right-sided heart failure.

## **TREATMENT**

### **Desired Outcomes**

The goals of COPD management include: (a) smoking cessation, (b) reducing symptoms, (c) improving exercise tolerance, (d) minimizing the rate of decline in lung function, (e) maintaining or improving the quality of life, (f) preventing and treating exacerbations, and (g) limiting complications.

### **General Approach to Treatment**

An integrated approach of health maintenance (e.g., smoking cessation), drug therapy, and supplemental therapy (e.g., oxygen and pulmonary rehabilitation) should be used in a stepwise manner. Symptom severity and risk of COPD exacerbations can be used to guide therapy decisions.

### **Non pharmacologic Therapy**

#### **1. *Smoking Cessation***

Smoking cessation slows the rate of decline in pulmonary function in patients with COPD. Stopping smoking can also reduce cough and sputum production and decrease

airway reactivity. Therefore, it is a critical part of any treatment plan for patients with COPD.

## 2. *Surgery*

**Bullectomy**, lung volume reduction surgery, and lung transplantation are surgical options for very severe COPD.

## **Pharmacologic Therapy of Stable COPD**

### ***Bronchodilators***

#### ***Value***

*Bronchodilators are the mainstay of treatment for symptomatic COPD. They reduce symptoms and improve exercise tolerance and quality of life.* They can be used as needed for symptoms or on a scheduled basis to prevent or reduce symptoms. Bronchodilator drugs commonly used in COPD include  $\beta$ 2-agonists, anticholinergics, and theophylline.

#### **Selection: long versus short**

Long-acting bronchodilators are more expensive than short-acting bronchodilators but are **superior** on important clinical outcomes, including frequency of exacerbations, degree of dyspnea, and health related quality of life. Monotherapy with long-acting bronchodilators is preferred; combination therapy may be appropriate in symptomatic patients with an FEV1 less than 60% predicted, although it is unclear when combination therapy provides added benefit.

Most COPD patients need continuous bronchodilator therapy on a scheduled basis every day. For these patients, short acting  $\beta$ 2-agonists are **inconvenient** because of the need for frequent dosing. In addition, short-acting  $\beta$ 2-agonists have been associated with a slight, but statistically significant, **loss of effectiveness** when used regularly longer than 3 months (tachyphylaxis). Patients treated with long-acting  $\beta$ 2-agonists should also have a short-acting  $\beta$ 2-agonist such as albuterol available for as-needed use (“rescue” medication).

**Anticholinergics** Ipratropium and tiotropium are inhaled anticholinergic medications commonly used for COPD. They produce bronchodilation by competitively blocking muscarinic receptors in bronchial smooth muscle. They may also decrease mucus secretion, although this effect is variable. Tiotropium dissociates from receptors extremely slowly, resulting in a half-life longer



than 36 hours, allowing for once-daily dosing. Ipratropium has an elimination half-life of about 2 hours, necessitating dosing every 6 to 8 hours.

Tiotropium significantly decreases exacerbations and related hospitalizations, reduces symptoms, and improves quality of life compared with placebo or ipratropium. Tiotropium may be **more effective** than salmeterol for reducing exacerbations in patients with moderate to very severe COPD.

Patients using tiotropium as maintenance therapy should be prescribed albuterol as their rescue therapy. The combination of ipratropium and tiotropium is **not recommended** because of the risks of excessive anticholinergic effects.

### **Side effects**

Inhaled anticholinergics are well tolerated with the most common adverse effect being dry mouth. Occasional metallic taste has also been reported with ipratropium. Other anticholinergic adverse effects include constipation, tachycardia, blurred vision, and precipitation of narrow angle glaucoma symptoms. Urinary retention could be a problem, especially for those with concurrent bladder outlet obstruction.

### **Methylxanthines**

#### **Place in treatment**

Theophylline is a nonspecific phosphodiesterase inhibitor that increases intracellular cAMP within airway smooth muscle resulting in bronchodilation. It has a modest bronchodilator effect in patients with COPD, and its use is limited due to a narrow therapeutic index, multiple drug interactions, and adverse effects. Theophylline should be reserved for patients who cannot use inhaled medications or who remain symptomatic despite appropriate use of inhaled bronchodilators.

#### **Adverse effects and monitoring**

Theophylline's bronchodilatory effects depend on achieving adequate serum concentrations, and therapeutic drug monitoring is needed to optimize therapy because of wide interpatient variability. The most common adverse effects include heartburn, restlessness, insomnia, irritability, tachycardia, and tremor. Dose-related adverse effects include nausea and vomiting, seizures, and arrhythmias. Smoking leads to increased clearance and subsequently decreased plasma levels of the drug. Because most patients with COPD are current or past smokers, it is

important to assess current tobacco use and adjust the theophylline dose as required based on altered plasma theophylline levels if tobacco use changes.

## ***Corticosteroids***

### ***Role***

Inhaled corticosteroids improve symptoms, lung function, quality of life, and exacerbation rates in patients with an FEV1 less than 60%. They do not appear to modify the rate of decline in pulmonary function or improve mortality.

### **Indication**

Inhaled corticosteroids are recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators.

### **Side effects and comparison with combination therapy**

Monotherapy with inhaled corticosteroids is less effective than when combined with a long-acting  $\beta_2$ -agonist and is therefore not recommended. Combination inhaler devices (Advair [fluticasone/salmeterol], Symbicort [budesonide/formoterol], and Dulera [mometasone/formoterol]) are convenient and ensure patients receive both medications.

Upon discontinuation of inhaled corticosteroids, some patients may experience deterioration in lung function and an increase in dyspnea and mild exacerbations. Long-term use of oral corticosteroids should be avoided due to an unfavorable risk-to-benefit ratio. The steroid myopathy that can result from long-term use of oral corticosteroids weakens muscles, further decreasing the respiratory drive in patients with advanced disease.

## ***Combination Therapy***

### ***Indication***

For patients who remain symptomatic on monotherapy, a combination of bronchodilators can be used. Combining albuterol plus ipratropium, a long-acting  $\beta_2$ -agonist plus theophylline, or a long-acting  $\beta_2$ -agonist plus tiotropium, produces a greater change in spirometry than either drug alone. Administering a long-acting  $\beta_2$ -agonist plus ipratropium leads to fewer exacerbations than either drug alone. Some studies have found an increase in adverse events without added benefit when combinations of bronchodilators are used.

**Example combination**

Triple therapy with inhaled corticosteroid, long-acting  $\beta_2$ -agonist, and tiotropium is commonly used. Triple therapy appears to improve lung function and quality of life but may not further reduce exacerbations or dyspnea. Further studies are needed to determine if the benefits of triple therapy outweigh the increased risk of adverse effects and added cost.

Potential benefits and risks of any combination therapy should be considered on a case-by-case basis. Patients should be monitored closely and therapy should be changed if the combination is not more effective.

***Immunizations***

Serious illness and death in COPD patients can be reduced by about 50% with annual influenza vaccination. The optimal time for vaccination is usually from early October through mid-November. A onetime pneumococcal polysaccharide vaccine should be administered to all adults with COPD.

Patients older than 65 years should be revaccinated if it has been more than 5 years since initial vaccination and they were younger than 65 years at the time.

**Drugs to be reviewed in BNF**

1. Salbutamol
2. Prednisolone
3. montelukast
4. levofloxacin
5. clarithromycin
6. amoxicillin

## **STROKE**

### **DESIRED TREATMENT OUTCOMES**

- The short-term goals of treatment for acute ischemic stroke include reducing secondary brain damage by re-establishing and maintaining adequate perfusion to marginally ischemic areas of the brain and to protect these areas from the effects of ischemia (i.e., neuroprotection).
- The long-term goals of treatment include prevention of a recurrent stroke through reduction and modification of risk factors and by use of appropriate treatments.
- The short-term goals for the treatment of hemorrhagic stroke include rapid neurointensive care treatment to maintain adequate oxygenation, breathing, and circulation. Management of increased intracranial pressure and blood pressure (BP) are important in the acute setting.
- Long-term management includes prevention of complications and prevention of a recurrent bleed and delayed cerebral ischemia. Prevention of long-term disability and death related to them stroke are important regardless of the type of stroke.

### **TREATMENT OF ACUTE ISCHEMIC STROKE**

- 1- Tissue oxygenation should be maintained acutely
- 2- Volume status and electrolytes should be corrected.
- 3- If required, the blood glucose should be corrected, as both hyperglycemia and hypoglycemia may worsen brain ischemia.
- 4- If the patient is febrile, treat with acetaminophen, as fever is associated with brain ischemia and increased morbidity and mortality after stroke.
- 5- Intravenous (IV) and subcutaneous heparin will significantly decrease the risk of developing deep vein thrombosis (DVT) post-stroke .Heparin 5000 units subcutaneously every 12 hours should be given for DVT prophylaxis in patients who are not candidates for intravenous alteplase.
- 6- Blood pressure should be optimized; however, hypertension should generally not be treated initially in acute stroke patients, as this may cause decreased blood flow in ischemic areas, potentially increasing the infarction size.
  - The cautious use of antihypertensive medications may be necessary in patients who are otherwise candidates for thrombolytic therapy, including those with severely elevated blood pressure (systolic BP greater than 220 mm Hg or diastolic BP greater than 120 mm Hg), and those with other medical disorders requiring immediate lowering of BP.
- 7- **Thrombolytic Therapy**  
**Systemic Thrombolytic Therapy:**

The current American Stroke Association guidelines include alteplase as the only Food and Drug Administration (FDA) approved acute treatment for ischemic stroke and strongly encourage early diagnosis and treatment of appropriate patients.

Withhold antiplatelet / antithrombotic medication until CT scan or MRI excludes haemorrhage.

- ✓ If the patient presents **within 3 hours of onset** of focal symptoms, thrombolysis may be appropriate.
- ✓ If patient presents > 3 hours, follow local protocol for stroke admissions.
  - alteplase is effective in limiting the infarct size and protecting brain tissue from ischemia and cell death by restoring blood flow
  - A dose of 0.9 mg/kg (maximum 90 mg) is recommended; the first 10% is given as an IV bolus and the remainder is infused over 1 hour.

Antiplatelet agents, anticoagulants, and invasive procedures such as the insertion of a central line or the placement of a nasogastric tube should be avoided for 24 hours after the infusion of alteplase to prevent bleeding complications. Bladder catheterization should also be avoided for 30 minutes post-infusion.

### **Streptokinase:**

Streptokinase is not indicated for use in acute ischemic stroke treatment. due to a high incidence of hemorrhage in the streptokinase-treated patients.

### **Intra-arterial Thrombolytics**

Intra-arterial thrombolytics are typically avoided except at major stroke centers where there is more experience with this route of administration. Alteplase is the only product currently available; therefore, when intra-arterial thrombolytics are given, alteplase must be used.

Due to the limitations of intra-arterial thrombolysis, current guidelines recommend that treatment with IV alteplase in eligible patients not be delayed by waiting for intra-arterial thrombolytics

#### **8- aspirin therapy**

is recommended in most patients with acute ischemic stroke within the first 24 to 48 hours after stroke onset and should be continued for at least 2 weeks. The administration of anticoagulants and antiplatelet agents should be delayed for 24 hours in those patients receiving alteplase.

## **PREVENTION OF ACUTE ISCHEMIC STROKE**

### **Primary Prevention**

#### ✓ **Aspirin**

The use of aspirin in patients with no history of stroke or ischemic heart disease reduced the incidence of non-fatal myocardial infarction (MI) but not of stroke. A meta-analysis of eight trials found that the risk of stroke was slightly increased with aspirin use, especially hemorrhagic stroke.

#### ✓ **Statin Therapy**

Recent studies show that statin use may reduce the incidence of a first stroke in high-risk patients (e.g., hypertension, coronary heart disease, or diabetes) including patients with normal lipid levels.

✓ **Blood Pressure Management**

Lowering blood pressure in patients who are hypertensive has been shown to reduce the relative risk of stroke, both ischemic and hemorrhagic, by 35% to 45%.<sup>23</sup> Also, the more blood pressure is lowered, the greater the reduction in stroke risk.

**Secondary Prevention:** Secondary prevention of stroke should be considered in all patients as soon as possible after their stroke.

**Nonpharmacologic Therapy**

✓ **Carotid Endarterectomy**

- ✓ **Carotid Angioplasty** Carotid angioplasty with or without **stenting** is typically restricted to patients who are refractory to medical therapy and are not surgical candidates.

**Pharmacologic Therapy**

✓ **Aspirin**

considered to be the first-line secondary prevention agent for ischemic stroke and decreases the risk of subsequent stroke by approximately 25% in both men and women with previous transient ischemic attacks or stroke. The FDA has approved doses of 50 to 325 mg for secondary ischemic stroke prevention.

✓ **Warfarin**

patients with atrial fibrillation usually start oral anticoagulants 10 to 14 days after the acute stroke, long-term anticoagulation with warfarin is recommended and is effective in both primary and secondary prevention of stroke. The goal International Normalized Ratio (INR) for this indication is 2 to 3.

✓ **Ticlopidine**

Ticlopidine is slightly more beneficial in stroke prevention than aspirin in both men and women. The usual recommended dosage is 250 mg orally twice daily. Ticlopidine is costly, and side effects include bone marrow suppression, rash, diarrhea, and an increased cholesterol level. Neutropenia is seen in approximately 2% of patients.

✓ **Clopidogrel**

Clopidogrel is slightly more effective than aspirin with a relative risk reduction of 7.3% more than that provided by aspirin, and it may be considered as first-line therapy in patients with peripheral arterial disease. The usual dose is 75 mg orally taken on a daily basis. Clopidogrel has a significantly lower incidence of diarrhea and neutropenia than ticlopidine, and laboratory monitoring is typically not required.

✓ **Blood Pressure (BP)**

After the acute phase, all patients with a BP > 130 mmHg systolic or > 80 mmHg diastolic should be considered for a Long-acting angiotensin-converting enzyme inhibitor (ACEI) and a diuretic (such as bendroflumethiazide), if tolerated and not contraindicated. Add additional antihypertensives if BP remains above target level. Even ‘normotensive’ patients (< 130 mmHg systolic or < 80 mmHg diastolic) may benefit from antihypertensive treatment, especially with ACEIs.

- ✓ **Cholesterol:** Unless contraindicated, treat all patients who have had an ischaemic stroke with a statin regardless of baseline cholesterol concentration. Recommended drug of choice is: **Simvastatin oral 40 mg each night.**

## **TREATMENT OF ACUTE HEMORRHAGIC STROKE**

There is no proven treatment for intracerebral hemorrhage. Management is based on neurointensive care treatment and prevention of complications. Treatment should be provided to manage the needs of the critically ill patient including management of increased intracranial pressure, seizures, infections, and prevention of re-bleeding and delayed cerebral ischemia

- ✓ Blood pressure is often elevated after hemorrhagic stroke and appropriate management is important to prevent re-bleeding and expansion of the hematoma. Blood pressure can be controlled with IV boluses of labetalol 10 to 80 mg every 10 minutes up to a maximum of 300 mg or with IV infusions of labetalol (0.5 to 2 mg/minute) or nicardipine (5 to 15 mg/hour).
- ✓ Deep vein thrombosis prophylaxis with intermittent compression stockings should be implemented early after admission.
- ✓ Oral nimodipine is recommended in subarachnoid hemorrhage to prevent delayed cerebral ischemia. Delayed cerebral ischemia occurs 4 to 14 days after the initial aneurysm rupture and is a common cause of neurologic deficits and death.
- ✓ Hemostatic Therapy: Recombinant factor VIIa has been shown to have a benefit in the treatment of ICH.

### **Patient Care and Monitoring**

1. Assess the patient’s signs and symptoms including the time of onset of symptoms and the time of arrival in the emergency department.
2. Perform thorough neurological and physical examinations evaluating for a potential cause of the stroke.
3. Perform a CT scan to rule out a hemorrhagic stroke prior to administering any treatment.
4. Evaluate the inclusion and exclusion criteria for thrombolytic therapy to determine if it is appropriate for the patient.
5. Transfer the patient to a stroke center if available and develop a plan for the acute management of the patient.
6. Determine the patient’s risk factors for stroke.
7. Develop a plan for the long-term management of risk factors in order to prevent a recurrent stroke.

8. Educate the patient on appropriate lifestyle modifications that will reduce stroke risk.
9. Educate the patient on their medication regimen and stress the importance of compliance.

(alteplase, aspirin, warfarin, Clopidogrel, labetalol)

## Chronic kidney disease

### Key points

1. The prevalence of chronic kidney disease (CKD) increases with age and is greater in females and some ethnic populations.
2. CKD is classified according to severity from 1 to 5, where 5 is the most advanced and 1 the least.
3. CKD 1–3 is common and may not cause symptoms. It may progress to end-stage renal disease but frequently remains stable for many years.
4. CKD is an important risk factor for cardiovascular disease.
5. As CKD becomes more advanced (stages 4 and 5), virtually all body systems are adversely affected.
6. Clinical signs and symptoms of severe CKD include oedema, anaemia, hypertension, bone pain, nocturia, neurological changes and disordered muscle function.
7. The aims of treatment are to reverse or arrest the process responsible for CKD, relieve symptoms and reduce cardiovascular morbidity and mortality.
8. To prevent further renal damage, adequate control of blood pressure and reduction of proteinuria are essential.
9. Renal anaemia is common when the glomerular filtration rate (GFR) falls below 30 mL/min but can be corrected by erythropoietin in 90–95% of cases.
10. End-stage renal disease is the point at which life can only be sustained by dialysis or transplantation. This may occur soon after presentation or after several years.
11. The need for dialysis therapy is increasing at about 5% per annum with attendant resource implications.
12. There are two principal types of dialysis: haemodialysis and peritoneal dialysis. In both, waste products and metabolites are transferred from the patient's blood across a semipermeable membrane to a dialysis solution.
13. Renal transplantation remains the treatment of choice for end-stage renal disease. However, up to 60% of patients on dialysis programmes are not fit enough to be put on the transplant list.

### Definition

Chronic kidney disease (CKD) is defined by a reduction in the glomerular filtration rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract. The severity of CKD is



classified from 1 to 5 depending upon the level of GFR (Table 1). It is a common condition affecting up to 10% of the population in Western societies.

## Measurement of renal function

### MDRD glomerular filtration rate equation

The four-variable equation (MDRD) incorporates age, creatinine, gender and ethnicity.

$eGFR \text{ (mL/min/1.73m}^2\text{)} = 186 \times [\text{serum creatinine (}\mu\text{mol/L)/88.4}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African-American}]$

**Table 1. Stages of chronic kidney disease.**

Stage	Description	eGFR (mL/min)	Potential complications of reduced GFR (in alphabetical order)
1	Kidney damage with normal or $\uparrow$ GFR	$\geq 90$	<ul style="list-style-type: none"> <li>• Anemia, including functional iron deficiency</li> <li>• Blood pressure increases</li> <li>• Calcium absorption decreases</li> <li>• Dyslipidemia /heart failure/volume overload</li> <li>• Hyperkalemia</li> <li>• Hyperparathyroidism</li> <li>• Hyperphosphatemia</li> <li>• Left ventricular hypertrophy</li> <li>• Metabolic acidosis</li> <li>• Malnutrition potential (late)</li> </ul>
2	Kidney damage with mild $\downarrow$ GFR	60–89	
3	Moderate $\downarrow$ GFR	30–59	
4	Severe $\downarrow$ GFR	15–29	
5	Kidney failure	<15 or dialysis	

Source: Adapted from Identification, Evaluation and Management of Chronic Kidney Disease ([www.health.gov.bc.ca/gpac/pdf/ckd.pdf](http://www.health.gov.bc.ca/gpac/pdf/ckd.pdf))

## Treatment

The aims of the treatment of CKD can be summarized as follows:

- Reverse or arrest the process causing the renal damage. (this may not be possible)
- Avoid conditions that might worsen renal failure (Box 18.1)
- Treat the secondary complications of CKD (renal anemia and bone disease)
- Relieve symptoms
- Implement regular dialysis treatment and/or transplantation at the most appropriate time.

### **Box 18.1 Factors that might exacerbate established chronic renal failure**

Reduced renal blood flow  
 Hypotension  
 Hypertension  
 Nephrotoxins including drugs  
 Renal artery disease

### **Hypertension**

Optimum control of blood pressure is one of the most important therapeutic measures since there is a vicious cycle of events whereby hypertension causes damage to the intrarenal vasculature resulting in thickening and hyalinisation of the walls of arterioles and small vessels. This damage effectively reduces renal perfusion, contributing to stimulation of the RAAS. Arteriolar vasoconstriction, sodium and water retention result, which in turn exacerbates the hypertension.

Antihypertensive therapy with certain agents might produce a transient reduction in GFR over the first 3 months of treatment as the systemic and glomerular blood pressure drop; this is mainly seen with ACE inhibitors/angiotensin receptor blockers (ARBs). However, it is possible to ultimately halt or slow the decline in many cases.

### **Calcium channel blockers**

#### **Place**

For patients without proteinuria, calcium channel blockers (CCBs) are the agents of choice. They produce vasodilatation principally by reducing Ca<sup>2+</sup> influx into vascular muscle cells. CCBs also appear to promote sodium excretion in hypertension associated with fluid overload.

#### **Therapeutic options**

Both verapamil and diltiazem (non-dihydropyridine CCBs) block conduction across the atrioventricular node and should not be used in conjunction with  $\beta$ -blockers. They are also negative cardiac inotropes. By contrast, dihydropyridines such as nifedipine and amlodipine produce less cardiac depression and differentially dilate afferent arterioles in the kidney. CCBs can produce headache, facial flushing and oedema. The latter can be confused with the symptoms of volume overload but is resistant to diuretics.

### **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**

#### **Role in CKD**

The role of ACE inhibitors in hypertensive patients with renal insufficiency is complicated, the current evidence base supports the principle that all diabetic patients with micro/macroalbuminuria and CKD should be treated with ACE inhibitors or ARBs regardless of blood pressure. There is also evidence that in non-diabetic patients with proteinuria, the use of

these drugs can reduce proteinuria and thus reduce progression of CKD. ACE inhibitors reduce circulating angiotensin II and ARBs block binding to the angiotensin II receptor, which results in vasodilatation and reduced sodium retention.

### **Contraindication**

These agents can produce a reduction in GFR by preventing the angiotensin II mediated vasoconstriction of the efferent glomerular arteriole. This contributes to the high pressure gradient across the glomerulus, which is responsible for filtration and intra-glomerular hypertension. This problem may only be important in patients with renal vascular disease, particularly those with functionally significant renal artery stenoses where they should be avoided.

### **Short versus long**

For long-term management, it is usually preferable to use an agent with a duration of action that permits once-daily dosing. It has been reported that ACE inhibitors may reduce thirst, which may be useful in those patients who have a tendency to fluid overload as a result of excessive drinking. ACE inhibitors are potassium sparing and therefore serum potassium should be monitored carefully. A low-potassium diet may be necessary.

### **ARB**

ARBs have properties similar to ACE inhibitors with the advantage that, since they do not inhibit the breakdown of kinins such as bradykinin, they do not cause the dry cough associated with the ACE inhibitors.

## **Diuretics**

### **Choice**

Diuretics are of use in patients with salt and volume overload, which is usually indicated by the presence of oedema. This type of hypertension may be particularly difficult to treat. The choice of agent is generally limited to a **loop diuretic**. **Potassium sparing diuretics** are usually contraindicated owing to the risks of developing hyperkalaemia, and **thiazides** become ineffective as renal failure progresses. In combination with ACE inhibitors, spironolactone can significantly reduce proteinuria; however, the combination of these agents clearly raises the risk of significant hyperkalaemia and care must be taken. The combination should be avoided when the eGFR falls to <30 mL/min.

### **Dosing and monitoring**

As loop diuretics need to be filtered to exert an action, progressively higher doses are required as CKD worsens. Doses of more than 250 mg/day of furosemide may be required in advanced renal failure. Patients who do not respond to oral loop diuretic therapy alone may benefit from concomitant administration of metolazone, which acts synergistically to produce a profound diuresis. Alternatively, the loop diuretic may be given intravenously. Care must be taken to avoid hypovolaemia (by monitoring body weight) and electrolyte disturbances such as hypokalaemia and hyponatraemia. Thiazide diuretics, with the notable exception of metolazone, are ineffective at a low GFR and may accumulate, causing an increased incidence of side effects.

## **B-Blockers**

B-Blockers are commonly used in the treatment of hypertension in CKD. They exhibit a range of actions including a reduction of renin production. Consequently,  $\beta$ -blockers have a particular role in the rational therapy of hypertension without fluid overload.

### **Choice between Bblockers**

However,  $\beta$ -blockers can reduce cardiac output, cause peripheral vasoconstriction and exacerbate peripheral vascular disease. It is advisable to use the more cardioselective B-blockers atenolol or metoprolol. Atenolol is excreted renally and consequently should require dosage adjustment in renal failure. In practice, however, atenolol is effective and tolerated well by renal patients at standard doses. However, metoprolol is theoretically a better choice since it is cleared by the liver and needs no dosage adjustment, although small initial doses are advised in renal failure since there may be increased sensitivity to its hypotensive effects.

## **Management of symptoms associated with CKD**

### **1. Gastro-intestinal symptoms**

#### **Therapeutic options**

- **Nausea and vomiting** may persist after starting a low protein diet. Metoclopramide is useful to treat this, but sometimes accumulation of the drug and its metabolites may occur, leading to extrapyramidal side effects. Patients should be started on a low dose, which should then be increased slowly. Prochlorperazine or cyclizine may also be useful. The 5-HT<sub>3</sub> antagonists such as ondansetron have also been shown to be effective. The anaemic patient often becomes less nauseated when treated with an erythropoiesis stimulating agent.
- **Constipation** is a common problem in patients with renal disease, partly as a result of fluid restriction and anorexia and partly as a consequence of drug therapy with agents such as phosphate binders. It is particularly important that patients managed with peritoneal dialysis do not become constipated, as this can reduce the efficacy of dialysis. Conventional laxative therapy may be used, such as bulk-forming laxatives or increased dietary fibre for **less severe constipation**.
- Alternatively, a stimulant such as senna with enemas or glycerine suppositories may be used for **severe constipation**. Higher doses of senna, typically 2–4 tablets at night, may be required. It should be noted that certain brands of laxatives that contain ispaghula husk may also contain significant quantities of potassium, and should be avoided in renal failure because of the risk of hyperkalaemia. Sterculia preparations are an effective alternative.

## 2. Pruritus

### Cause

Itching associated with renal failure can be extremely severe, distressing and difficult to treat. It can also be disfiguring as a result of over-enthusiastic scratching. The exact mechanism responsible for the itching is not clear and several possibilities have been suggested including: xerosis (dry skin), skin micro-precipitation of divalent ions, elevated PTH levels and increased dermal mast cell activity. Generally, however, no underlying cause is found and it is likely that a multifactorial process is responsible.

### Management

Sometimes correction of serum phosphate or calcium levels improves the condition, as does parathyroidectomy. Conventionally, oral antihistamines are used to treat pruritus; however, topical versions should not be used owing to the risk of allergy. Non-sedating antihistamines such as loratidine are generally less effective than sedating antihistamines such as chlorphenamine or alimemazine which may be useful, particularly at night. Topical crotamiton lotion and creams may also be useful in some patients. Other non-drug therapies include either warming or cooling the skin using baths, three times weekly, UVB phototherapy and modified electrical acupuncture.

## 3. Anaemia

### Type, options

The normochromic, normocytic anaemia of CKD does not respond to iron or folic acid unless there is a coexisting deficiency. Traditionally, the only treatment available was to give red blood cell transfusions, but this is time-consuming, expensive, an infection risk, may lead to fluid and iron overload and promotes antibody formation, which may give problems if transplantation is subsequently attempted. The introduction of ESAs, initially as recombinant human erythropoietins (epoetin alfa and beta) have transformed the management of renal anaemia.

### Rare side effect

Epoetin alfa and beta were thought to be indistinguishable in practical terms, as well as being immunologically and biologically indistinguishable from physiological erythropoietin. However, it has now been recognized that epoetins can be associated with the production of antierythropoietin antibodies leading to a severe anaemia which is unresponsive to exogenous epoetin. This is known as **pure red cell aplasia (PRCA)** and is more commonly associated with epoetin alfa when given by the subcutaneous route.

### Route of administration

The subcutaneous route is preferred as it provides equally effective clinical results while using similar or smaller doses (up to 30% less) when given three times a week. Most patients report a dramatically improved quality of life after starting epoetin therapy.

### Long acting epoetin

Darbepoetin alfa is a novel erythropoiesis-stimulating protein (NESP) that is a recombinant hyperglycosylated analogue of epoetin which stimulates red blood cell production by the same mechanism as the endogenous hormone. The terminal half-life in man is three times longer than that of epoetin and consequently requires a once weekly or alternate weekly dosing schedule. Recently, a longer acting ESA has been introduced (methoxy polyethylene glycol-epoetin beta, pegzerepoetin alfa). This is a continuous erythropoietin receptor activator (CERA), which can be used in a once monthly dosing schedule.

#### **Iron and folate supplementation, monitoring**

Iron and folate deficiencies must be corrected before therapy is initiated, while patients receiving epoetin generally require concurrent iron supplements because of increased marrow requirements. Supplemental iron is often given intravenously owing to bioavailability problems with oral forms. Maintaining iron stores ensures the effect of epoetin is optimized for minimum cost, as with insufficient iron stores a patient will not respond to treatment with epoetin. Epoetin therapy should aim to achieve a slow rise in the haemoglobin concentration to avoid cardiovascular side effects associated with a rapidly increasing red cell mass, such as hypertension, increased blood viscosity/volume, seizures and clotting of vascular accesses. Blood pressure should be closely monitored.

#### **Dosing, target Hb level**

An initial subcutaneous or intravenous epoetin dose of 50 units/kg body-weight three times weekly, increased as necessary in steps of 25 units/kg every 4 weeks, should be given to produce a haemoglobin increase of not more than 2 g/dL per month. The target haemoglobin concentration is commonly 10.5–12.5 g/dL with most aiming for a target around 11.5 g/dL. Once this has been reached, a maintenance dose of epoetin in the region of 33–100 units/kg three times a week or 50–150 units/kg twice weekly should maintain this level. There have been several studies of ESAs which have shown an increased risk of cardiovascular morbidity and overall mortality in people treated to a target >12.5 g/Dl

This has led to more conservative dosing strategies and prompt discontinuation or reduction of dose in patients with Hb >12.5 g/dL. Correcting anaemia usually helps control the symptoms of lethargy and myopathy, and often greatly reduces nausea. Improved appetite on epoetin therapy can, however, increase potassium intake, and may necessitate dietary control.

#### **4. Acidosis**

Since the kidney is the main route for excreting H<sup>+</sup> ions, CKD may result in a metabolic acidosis. This will cause a reduction in serum bicarbonate that may be treated readily with oral doses of sodium bicarbonate of 1–6 g/day. As the dose of bicarbonate is not critical, it is easy to experiment with different dosage forms and strengths to suit individual patients. If acidosis is severe and persistent then dialysis may be required. Correction of acidosis may slow the decline in renal function.

#### **5. Neurological problems**

Neurological changes are generally caused by uraemic toxins and improve on the treatment of uraemia by dialysis or diet. Muscle cramps are common and are often treated with quinine sulphate. Restless legs may respond to low doses of clonazepam or co-careldopa.

## **6. Osteodystrophy**

The osteodystrophy of renal failure is due to three factors: hyperphosphataemia, vitamin D deficiency and hyperparathyroidism.

## **7. Hyperphosphataemia**

### **Difficulty in management of hyperphosphatemia**

The management of hyperphosphataemia depends initially upon restricting dietary phosphate. This can be difficult to achieve effectively, even with the aid of a specialist dietician, because phosphate is found in many palatable foods such as dairy products, eggs, chocolate and nuts. Phosphate-binding agents can be used to reduce the absorption of orally ingested phosphate in the gut, by forming insoluble, non-absorbable complexes when taken a few minutes before or with meals.

Traditionally, phosphate-binders were usually salts of a di- or trivalent metallic ion, such as aluminium, calcium or occasionally magnesium.

- Calcium acetate is widely used as a phosphate binder. The capacity of calcium acetate and calcium carbonate to control serum phosphate appears similar. However, phosphate control is achieved using between half and a quarter of the dose of elemental calcium when calcium acetate is used.
- Calcium carbonate has been used as a phosphate binder. Unfortunately, it is less effective as a phosphate binder than aluminium, and sometimes requires doses of up to 10 g daily. Calcium carbonate has advantages, however, in that correction of concurrent hypocalcaemia can be achieved.
- Sevelamer, a hydrophilic but insoluble polymeric compound is used increasingly as a phosphate binder. Sevelamer binds phosphate with an efficacy similar to calcium acetate but with no risk of hypercalcaemia.
- Lanthanum, like sevelamer, is a non-calcium containing phosphate binder; there is therefore no resultant risk of hypercalcaemia but there are gastro-intestinal side effects and the drug is significantly more expensive than the alternatives
- Historically, aluminium hydroxide was widely used as a phosphate binder owing to the avid binding capacity of aluminium ions. However, a small amount of aluminium may be absorbed by patients with CKD owing to poor clearance of this ion, which can produce toxic effects including encephalopathy, osteomalacia, proximal myopathy and anaemia.

### **Side effects of aluminium hydroxide**

Dialysis dementia was a disease observed among haemodialysis patients associated with aluminium deposition in the brain and exacerbated by aluminium in the water supply and the use of aluminium cooking pans. Desferrioxamine (4–6 g in 500 mL of saline 0.9% per week) has been used to treat this condition by removing aluminium from tissues by chelation. The tendency of aluminium to cause constipation is an added disadvantage. Therefore, aluminium as a phosphate binder in CKD should be used with caution.

## 8. Vitamin D deficiency and hyperparathyroidism

### Treatment options

Vitamin D deficiency may be treated with the synthetic vitamin D analogues 1 $\alpha$ -hydroxycholecalciferol (**alfacalcidol**) at 0.25–1  $\mu$ g/day or 1,25-dihydroxycholecalciferol (**calcitriol**) at 1–2  $\mu$ g/day. The serum calcium level should be monitored, and the dose of alfacalcidol or calcitriol adjusted accordingly. Hyperphosphataemia should be controlled before starting vitamin D therapy since the resulting increase in the serum calcium concentration may result in soft tissue calcification. The rise in 1,25-dihydroxycholecalciferol 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. This surgical procedure was once commonly performed on CKD patients, but is now less frequent owing to effective vitamin D supplementation.

**Cinacalcet** is a calcimimetic which increases the sensitivity of calcium sensing receptors to extracellular calcium ion, this results in reduced PTH production. The benefit of this treatment is the suppression of PTH without resultant hypercalcaemia. It is recommended for use as an alternative to parathyroidectomy for patients who are not fit enough to undergo this procedure.

### Table 18.4 Common therapeutic problems in chronic renal failure with Problem Comment

1. **Drug choice:** Care with choice/dose of all drugs. Care to avoid renotoxic agents pre-dialysis to preserve function. Beware herbal therapies as some contain immune system boosters (reverse immunosuppressant effects) and some are nephrotoxic
2. **Drug excretion:** CKD will lead to accumulation of drugs and their active metabolites if they are normally excreted by the kidney
3. **Dietary restrictions:** Restrictions on patient often severe. Fluid allowance includes foods with high water content, for example, gravy, custard, and fruit
4. **Hypertension:** Frequently requires complex multiple drug regimens. CCBs can cause oedema that might be confused with fluid overload
5. **Analgesia:** Side-effects are increased. Initiate with low doses and gradually increase. Avoid pethidine as metabolites accumulate. Avoid NSAIDs unless specialist advice available



6. Anaemia: Epoetin requires sufficient iron stores to be effective. Absorption from oral iron supplements may be poor and i.v. iron supplementation might be required. Care required to make sure that epoetin use does not produce hypertension
7. Immunosuppression: Use of live vaccines should be avoided (BCG, MMR, mumps, oral polio, oral typhoid, smallpox, yellow fever)
8. Pruritis (itching): Can be severe. Treat with chlorphenamine; less sedating antihistamines often less effective. Some relief with topical agents, for example, crotamiton
9. Restless legs: Involuntary jerks can prevent sleep. Clonazepam 0.5–1 mg at night may help

### 1. The emergency treatment of hyperkalemia should include:

1. Stabilisation of the myocardium by intravenous administration of 10–30 mL calcium gluconate 10% over 5–10 min. The effect is temporary but the dose can be repeated.
2. Intravenous administration of 10–20 units of soluble insulin with 50 mL of 50% glucose to stimulate cellular potassium uptake. The dose may be repeated. The blood glucose should be monitored for at least 6 h to avoid hypoglycaemia.
3. Acidosis may be corrected with an intravenous dose of sodium bicarbonate, preferably as an isotonic solution. Correction of acidosis stimulates cellular potassium re-uptake.
4. Intravenous salbutamol 0.5 mg in 100 mL 5% dextrose administered over 15 min has been used to stimulate the cellular Na-K ATPase pump and thus drive potassium into cells. This may cause disturbing muscle tremors at the doses required to reduce serum potassium levels.

### 2. ACE Inhibitors: U&E Monitoring

- Worsening Renal Function
  - Generally Cr ↑ <50% or <266 μmol/L- **acceptable.**
  - If Cr ↑ >265 μmol/L but <310 μmol/L- **halve dose of ACE and monitor.**
  - If Cr ↑ >310 μmol/L- **stop ACE immediately and monitor more closely.**

Drugs to be reviewed in BNF

1. Valsartan
2. Lisinopril
3. Erythropoietin alpha

