CARDIOVASCULAR DISEASES

INFECTIVE ENDOCARDITIS

Bacterial endocarditis is a life-threatening infectious disease. Infection of the endothelial surface of the heart with its attendant complications. Acute bacterial endocarditis (ABE) is usually caused by *S. aureus*, *Group A haemolytic Streptococci*, *Pneumococci* or *Gonococci*. Subacute bacterial endocarditis (SABE) is usually caused by *S. viridans* or other *streptococci*, rarely by other organisms. Prosthetic valvular endocarditis (PVE) develops in 2-3% of patients within 1 year, more in aortic valve than mitral and least with porcine valves. Early onset infections (<2 months) are caused by resistant *S. epidermidis*, *coliforms*, *candida*, etc. while late infections are caused by low virulence organisms. ABE may affect normal valves, especially in intravenous drug addicts while SABE complicates deformed/damaged valves or congenital heart disease (CHD).

SALIENT FEATURES

- Clinical manifestations of bacterial endocarditis are highly variable and frequently non-specific. The diagnosis of bacterial endocarditis is based on clinical, laboratory and echocardiographic criteria. Classification and definitions of infective endocarditis are given in Table 3.1.
- Fever, toxaemia, clubbing, splenomegaly, anaemia, microscopic haematuria, a new onset or changing murmur, evidence of immune phenomena and metastatic infection.
- Complications such as congestive heart failure (CHF), mycotic aneurysm, embolic cardiovascular accident (CVA) or other phenomena may be the presenting features.
- Definitive diagnosis requires positive blood cultures aided by positive echocardiogram (transoesophageal positive in >90%).

Table 3.1. Classification and definitions of infective endocarditis (IE)

IE according to localization of infection and presence or absence of intracardiac material

- · Left sided native valve IE
- Left sided prosthetic valve IE (PVE)
 - Early PVE: <1 year after valve surgery; late PVE: >1 year after valve surgery
 - Right-sided IE Device-related i.e., (permanent pacemaker or cadioverter-defibrillator)

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IE according to the mode of acquisition:

- Health care-associated IE:
 - Nosocomial IE: Developing in a patient hospitalized >48 hours prior to the onset of signs/ symptoms consistent with IE
 - Non-nosocomial IE: Signs and/or symptoms of IE starting <48 hours after admission in a
 patient with health care contact defined as:
 - 1. Home-based nursing or intravenous therapy, haemodialysis, or intravenous chemotherapy <30 days before the onset of IE; or
 - 2. Hospitalized in an acute care facility < 90 days before the onset of IE
 - 3. Resident in a nursing home or long-term care facility
- Community-acquired IE: Signs and/or symptoms of IE starting <48 hours after admission in a patient not fulfilling the criteria for health care associated infection
- Intravenous drug abuse associated IE: IE in an active injection drug user without alternative source of infection.

Active IE

- IE with persistent fever and positive blood cultures or
- · Active inflammatory morphology found at surgery or
- · Patient still under antibiotic therapy or
- · Histopathological evidence of active IE

Recurrence

- Relapse: Repeat episodes of IE caused by same microorganism < 6 months after the initial episode
- Reinfection: Infection with different microorganism or repeat episodes of IE caused by the same microorganism > 6 months after the initial episode

Treatment (infective endocarditis should be treated as a medical emergency)

Treatment should be started on clinical suspicion. Subsequent changes in the antibiotic regimen should be based on the results of cultures and sensitivity testing. The choice of antibiotic therapy for bacterial endocarditis is determined by the identity and antibiotic susceptibility of the infecting organism, the type of cardiac valve involved (native or prosthetic) and characteristics of the patient, such as drug allergies.

Presumptive initial treatment for SABE should cover *S. viridans*, microaerophilic and anaerobic *streptococci*.

Inj. Crystalline Penicillin-G 12-18 MU/24 h after test dose + Inj. Gentamicin 3 mg/kg/day IV (or IM) 8 hourly for 2 weeks.

Enterococci.

Inj. Crystalline Penicillin-G 18-30 MU/day after test dose (divided into 6 doses) + Inj. Gentamicin 1 mg/kg 8 hourly IV for 4-6 weeks.

Or

Inj. Ampicillin 12 g/day, given 4 hourly may be substituted for crystalline penicillin-G

In acute bacterial endocarditis, cover for staphylococci:

Inj. Nafcillin 2 g IV 4 hourly for 4-6 weeks.

In penicillin sensitive individuals

Inj. Cefazolin IV 8 hourly for 4-6 weeks.

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Or

Inj. Vancomycin 15 mg/kg IV 12 hourly for 4-6 weeks.

Methicillin resistant Staphylococcus aureus (MRSA)

Inj. Vancomycin as above for 6-8 weeks + Inj. Gentamicin 1 mg/kg IV 8 hourly for 2 weeks + Cap. Rifampicin 300 mg orally 8 hourly for 6-8 weeks.

(For treatment of congestive heart failure see section on Congestive Heart Failure).

Follow-up

Patients with bacterial endocarditis should be monitored carefully. Clinical response occurs in 3-7 days. Change the antibiotics as per culture/sensitivity report, if required. Blood cultures should be obtained to ensure eradication of the organism. Gentamicin blood levels should be monitored with dosage adjustments as indicated and renal function should be assessed frequently when an aminoglycoside is administered. If a prolonged course of gentamicin is planned, a hearing assessment should be performed. Fever usually resolves within several days of initiation of effective antibiotic treatment, although fever may persist longer with *S. aureus* infection. Persistent fever after the first week of treatment suggests a septic embolic complication or inadequate antibiotic therapy. The recurrence of fever after an initial defervescence suggests a septic or nonseptic embolic event, a drug hypersensitivity reaction or the emergence of a resistant strain.

Cardiac surgery is required if:

- 1. No response to medical treatment (especially in prosthetic valve endocarditis).
- 2. Worsening heart failure and the lesion is correctable.
- 3. Acute onset cardiac complication due to infection, e.g. septal perforation/valvular damage/stroke perivalvular extension of infection.
- 4. Large (> 1 cm diameter) hypermobile vegetation with increased risk of embolism.

Antibiotic prophylaxis in high-risk patients

Antibiotic prophylaxis should only be considered in patients at higher risk of IE:

- Prosthetic valve or a prosthetic material used for cardiac valve repair, patients with previous IE
- High-risk patients
- Patients with congenital heart disease
- Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa; prophylaxis is not recommended for local anaesthetic injections in non-infected tissue, removal of sutures, dental X-ray, placement or adjustment of removal prosthodontics or orthodontic appliances or braces. Prophylaxis is also not recommended following the shedding of deciduous or trauma to the lips and oral mucosa.

Assess individual risk and develop an appropriate management plan with following:

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- Cap. Amoxycillin 3 g orally 1 hour preoperatively or Cap. Clindamycin 600 mg 1 hour preoperatively (for details see section on Antibiotic Prophylaxis in Chapter 18).
- Higher risk patients with prosthetic valves, genitourinary procedures Inj. Amoxycillin
 2 g IV + Inj. Gentamicin 120 mg IV before procedure followed by Cap. Amoxycillin
 1 g orally 6 hours postoperatively.

Substitute Vancomycin 1 g IV infusion over 100 min in case patient is allergic to penicillin.

Patient education

Good oral hygiene, including daily flossing, is an important preventive measure. If
you have a history of structural heart disease or believe that you are at risk for the
development of endocarditis. Discuss this potential risk with dentist or other health
care providers that may be performing invasive procedures (dental extraction, upper
respiratory tract) to take prophylactic treatment.

References

- 1. Management of Bacterial Endocarditis. Am Fam Physician. 2000; 61:1725-1732.
- 2. Bacterial Endocarditis: The Disease, Treatment, and Prevention. Circulation 2003; 107: e185-e187.
- Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009). The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). European Heart Journal 2009; 30: 2369–2413.

ACUTE PERICARDITIS

Inflammation of pericardium, which may be acute or chronic and may result in pericardial effusion. It may be caused by viruses, bacteria, mycobacteria, connective tissue disorders, uraemia, myocardial infarction (MI), malignancies, radiation and trauma.

SALIENT FEATURES

• Chest pain, dyspnoea, presence of friction rub, tamponade and serial ECG changes.

Treatment

Nonpharmacological

Bed rest.

Pharmacological

1. Tab. Aspirin 650 mg orally every 3 to 4 hours.

Or

Tab. Ibuprofen 400 mg orally every 6-8 hours for 1 week.

2. In the absence of relief within 48 hours (non-infective cases only) Tab. Prednisolone 20-60 mg per day for 3-4 days.

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- 3. Antibiotics should be used only in case of documented purulent pericarditis empirically to cover *pneumococci*, *meningococci*, *staphylococci*, *H. influenzae* (Ampicillin + Gentamicin may be used).
- 4. Anticoagulants are not to be used except in case of prosthetic valves when Heparin may be used.
- 5. Treatment of primary disease causing pericarditis.

Complications of the pericarditis are pericardial effusion, constrictive pericarditis and recurrent pericarditis.

Pericardial effusion

Pericardial effusion occurs when pericarditis leads to accumulation of fluid in pericardial cavity. Echocardiography is diagnostic.

Treatment

- As above for pericarditis.
- Diagnostic tap for effusion.
- Pericardiocentesis in case of a large effusions or tamponade.
- Pericardiostomy with drainage for large effusions with rapid refilling.

Constrictive pericarditis

It is the restriction induced by a thickened fibrous pericardium as sequelae of pericarditis. Tuberculosis is the commonest cause. Treatment is surgical excision. Pericardiectomy for recurrent pericarditis or constrictive pericarditis.

Treatment

- 1. Antitubercular therapy (for details see section on Tuberculosis in Chapter 1).
- 2. Tab. Prednisolone 1 mg/kg for 2 weeks and then taper off in next 4 weeks.

Recurrent pericarditis

It may require intravenous methyl prednisolone pulses, colchicine 1 mg daily or pericardiectomy.

Monitoring

Monitor symptomatic relief so as to stop NSAIDs or taper steroids.

Watch for complications (clinical course, echocardiography, chest roentgenograms) and refer to a higher centre for appropriate management.

Ensure treatment of the underlying cause.

Patient education

 Reassurance that viral pericarditis is self-limiting and monitoring for complications is sufficient.

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- Patients with tubercular or purulent aetiology must be educated to ensure adequate therapy and compliance.
- Myxoedema must be adequately treated and emphasize the need for follow-up and compliance.
- Uraemia, malignancy, etc. require referral for specialized care and management.
- Rheumatic fever patients must receive prophylaxis and follow-up at a higher centre for management of valvular involvement.
- Drug induced pericarditis must be prevented by educating the patient against future use.
- Emphasize the need for post-myocardial infarction prophylaxis, follow-up with echocardiography and other measures including lifestyle modification, drugs, revascularization, etc.

Reference

1. Pericardial Disease. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 1488-1495.

CARDIOMYOPATHY

Any structural or functional abnormality of the ventricular myocardium, excluding congenital/valvular structural defects, vascular (systemic/pulmonary), pericardial, nodal or conductive system diseases.

Dilated congestive cardiomyopathy

Commonest type of cardiomyopathy usually caused by ischaemia and characterized by ventricular dilatation and systolic dysfunction. The other important causes include alcohol, endocrinopathies (diabetes, thyrotoxicosis), myocarditis or idiopathic.

SALIENT FEATURES

- Features of biventricular failure resulting in oedema and dyspnoea.
- Diagnosis is clinical supported by ECG, chest X-ray and echocardiography.
- Carries a poor prognosis with 5-year survival of <70%.

Treatment

Symptomatic, management as in congestive heart failure (see respective section). Treat any underlying treatable cause.

Reference

 The Cardiomyopathy and Myocarditis. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 1951-1970.

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HYPERTENSION

Usually asymptomatic and discovered on routine measurement of blood pressure. Secondary hypertension (HT) presents as a part of a symptom complex as in acromegaly, Cushing's disease, renovascular or renal parenchymal disease, connective tissue disorders (SLE, scleroderma, etc.), or coarctation of aorta.

SALIENT FEATURES

- Nonspecific symptoms are fatigue, headache, epistaxis.
- Uncontrolled hypertension can lead to target organ damage (TOD) such as coronary artery disease (CAD), left ventricular hypertrophy (LVH), cerebrovascular accidents (CVA), transient ischaemic attacks (TIA), retinopathy, peripheral vascular diseases including dissecting aneurysm, renal disease.
- Associated risk factors are age >55 years in males and >65 years in females, smoking, diabetes mellitus, microalbuminuria or GFR <60 ml/min, hyperlipidaemia, family history, obesity, sedentary lifestyle and ethnic group.
- Routine laboratory tests recommended before initiating therapy include an
 electrocardiogram; urinalysis; blood glucose and haematocrit; serum potassium,
 creatinine (or the corresponding estimated GFR) and calcium; and a lipid profile
 (after a 9-12-hour fast) that includes high-density lipoprotein, cholesterol,
 low-density lipoprotein cholesterol, and triglycerides. Optional tests include
 measurement of urinary albumin excretion or albumin/creatinine ratio. More
 extensive testing for identifiable causes is not indicated generally unless BP
 control is not achieved.

Precautions to be taken while measuring BP

The auscultatory method of BP measurement with a properly calibrated and validated instrument should be used. BP should be measured using an appropriate size cuff in both upper limbs and at least one lower limb in both supine and erect posture. Patient should have been resting for at least 5 minutes and should not have consumed coffee, smoked during the last 30 minutes before measuring the blood pressure. At least 2 measurements should be made. Systolic BP is the point at which the first of 2 or more sounds are heard (phase 1) and diastolic BP is the point before the disappearance of sounds (phase 5).

Treatment

Nonpharmacological

- Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).
- Adopt DASH eating plan-diet rich in fruits, vegetables, with low fat dairy products with a reduced content of saturated and total fat.

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- Lifestyle modification exercise consisting of vigorous aerobic exercise like brisk walking, swimming or jogging at least 20 to 30 minutes on most days of the week with the heart rate reaching 65-70% of maximal heart rate.
- Weight control using a combination of dietary and exercise measures to maintain normal body weight (body mass index 18.5-24.9 kg/m²).
- Moderation of alcohol consumption limit alcohol to no more than 2 drinks (1 oz or 30 ml ethanol; e.g. 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.
- Cessation of smoking.
- Yoga.
- Control of other risk factors.

Pharmacological

Table 3.2. Classification and management of blood pressure for adults aged 18 years or older

BP Classifica- tion	Systolic BP		Diastolic BP mmHg*	Life- style modifi- cation	Management* Initial drug therapy	
	mmHg*				Without compelling indication	With compelling indications§
Normal	<120	and	<80	Encourage		
Prehyper- tension	120-139	Or	80-89	Yes	No antihypertensive drug	Drug(s) for the compelling indication**
Stage 1 hypertension	140-159	Or	90-99	Yes	Thiazide type diuretic for most; may consider ACEI, ARB, beta blocker, CCB or combination	Drug(s) for the com- pelling indication Other antihyperten- sive drugs as needed
Stage 2 hypertension	≥ 160	Or	≥ 100	Yes	2-drug combination for most (usually thiazide type diuretic and ACEI or ARB or beta blocker or CCB)*	Drug(s) for the com- pelling indication Other antihyperten- sive drugs as needed

ACEI: Angiotensin converting enzyme inhibitor; ARB:Angiotensin receptor blocker; CCB: Calcium channel blocker

Antihypertensive drug choices: Additional considerations

- (a) Diuretics—elderly, obese, congestive heart failure (CHF).
- (b) Beta-blockers—young, coronary artery disease (CAD), vascular headache, associated atrial fibrillation (AF).

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^{*} Treatment determined by highest BP category

^{**} Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mmHg

[§] Compelling indications — heart failure, post-myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, recurrent stroke prevention (for details see respective section).

[♣] Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

- (c) Calcium channel blockers (CCB)—old age, CAD, atrial fibrillation (AF), paroxysmal supraventricular tachycardia (PSVT).
- (d) Angiotensin converting enzyme inhibitors (ACEI)—young, left ventricular failure (LVF), diabetes.
- (e) Angiotensin II receptor antagonists (ARB)—same as ACEI.
- (f) Alpha-blockers—prostatism, diabetes, dyslipidaemia.
- (g) Combined alpha and beta blockers—pregnancy.
- (h) Old drugs—alpha-methyl dopa (pregnancy), clonidine-refractory cases.

Thiazide diuretics should be used with caution in patients with gout or history of hyponatraemia.

Beta blockers should be avoided in patients with bronchial asthma, reactive airways disease, or second- or third-degree heart block.

ACEI should not be used in patients with a history of angioedema.

Aldosterone antagonists and potassium sparing diuretics can cause hyperkalaemia and should generally be avoided in patients who have serum potassium values of more than 5.0 mEq/L while not taking medications.

Drug combination used for

- Additive effect—use drugs acting by different mechanisms.
- Minimization of the side effects:
 - Block opposing effects on homeostatic mechanism.
 - Block predictive sideeffects.
 - Permits use of lower dose (less side effects).

Fully additive drug combinations

- Diuretic + beta-blocker.
- Diuretic + ACEI.
- CCB + beta-blocker.
- CCB + ACEI.

Questionable drug combinations

- (a) Nonadditive
 - beta-blocker + ACEI
 - -ARB + ACEI.
- (b) Side effects additive
 - beta blocker + Verapamil/Diltiazem (older CCB).
 - alpha blocker + CCB.

Drug combinations for patients with associated conditions

 $\begin{array}{lll} \text{HT with angina} & & -\text{ Beta blocker} + \text{CCB} \\ \text{HT with heart failure} & & -\text{ Diuretic} + \text{ ACEI} \\ \text{HT with diabetes mellitus} & & -\text{ ACEI} + \text{ CCB} \\ \text{HT with COAD} & & -\text{ Diuretic} + \text{ CCB} \\ \end{array}$

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Isolated systolic hypertension (systolic BP ≥ 160 mmHg)

Drugs of choice in order of preference are:

- Diuretics.
- Beta blocker.
- Diuretic + beta blocker.
- Diuretic + CCB.
- ACEI + CCB.

Hypertension in pregnancy

Alpha-methyldopa, beta blockers and vasodilators are preferred medications for safety of the foetus. **ACEI and Angiotensin II receptor blockers are contraindicated** (for details see section on Eclampsia in Chapter 15).

Hypertension in children and adolescents

In children and adolescents, hypertension is defined as BP that is, on repeated measurement, at the 95th percentile or greater adjusted for age, height, and gender. The fifth Korotkoff sound is used to define diastolic BP. Be alert for possibility of identifiable causes of hypertension in younger children (i.e. kidney disease, coarctation of aorta). Lifestyle interventions are strongly recommended, with pharmacological therapy instituted for a higher levels of BP or if there is insufficient response to lifestyle modification. Choices of antihypertensive drugs are similar in children and adults, but effective doses for children are often smaller and should be adjusted carefully.

Commonly used antihypertensive drugs

Tab. Hydrochlorothiazide 12.5-25 mg once daily or 2 times a day

Oı

Tab. Frusemide 20-40 mg twice a day

Or

Tab. Frusemide 20 mg + Spironolactone 50 mg 1-2 times a day

Ο.

Tab. Benzthiazide 25 mg + Triamterene 50 mg per day

Or

Tab. Indapamide 2-5 mg daily

Or

Tab. Atenolol 25-100 mg daily or Metoprolol 25-150 mg 2 times a day.

(Caution: Contraindicated in asthma, peripheral arterial disease, moderate to severe congestive heart failure, uncontrolled hypothyroidism, myocardial conduction defects).

Or

Tab. Amlodipine 2.5-20 mg daily or Cap. Nifedipine 20-80 mg as sustained release daily. (**Caution**: May cause peripheral oedema in some individuals)

Or

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Tab. Enalapril 2.5 mg and may be increased to 40 mg daily or Lisinopril 2.5 to 20 mg daily or Ramipril 1.25 mg to 10 mg daily (**Caution:** May cause dry cough in some individuals).

Or

Tab. Losartan 25-50 mg once or twice daily.

Or

Tab. Prazosin 1-20 mg/day first dose to be given at bedtime.

Oı

Tab. Terazosin 1-10 mg daily in 2 divided doses. First dose to be given at bed-time.

Or

Tab. Clonidine 0.05-0.6 mg 2 times a day.

Oı

Tab. Methyldopa 250-1000 mg 2 times a day.

Accelerated hypertension

Patients presenting with BP 200/140 mmHg or more without papilloedema:

Inj. Enalapril 1.25-5 mg IV 6 hourly

Or

Inj. Nitroprusside 0.25-1.0 mcg/kg/min IV infusion (dose to be titrated with BP, maximum dose for 10 mcg only)

Or

Inj. Nitroglycerine 5-100 mcg/min infusion

Or

Inj. Hydralazine 10-20 mg IV or IM, if no response at 20 mg change the drug

Or

Inj. Labetalol 20-80 mg IV every 5-10 min up to a total of 300 mg, infusion 0.5-2 mg/min, oral 100-600 mg 2 times a day.

Or

Inj. Phentolamine 5-15 mg IV (specially useful in pheochromocytoma)

Malignant hypertension

Patients presenting with BP 200/140 mmHg and evidence of vascular damage like papilloedema, deranged renal function, should be referred to a tertiary care centre.

Resistant hypertension

Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic. Refer these patients to hypertension specialist.

Follow-up

1. Regular BP monitoring to ensure optimal or normal BP in young or middle aged or diabetic subjects (130/80 mmHg) and at least high normal BP in elderly patients (140/90 mmHg).

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- 2. Monitor all risk factors for coronary artery disease.
- 3. Ensure compliance with lifestyle modifications.
- 4. Assess for complications and target organ damage.
- 5. In accelerated or malignant HT, avoid sudden fall in diastolic BP to below 100 mmHg.

Patient education

- Explain consequences of uncontrolled HT and the need for the long-term control with medication.
- Advise regarding control of other risk factors like diabetes, hyperlipidaemia, etc.
- Diuretics should be taken in the morning and if two doses a day are required second dose should be given before 4 PM.
- Manage target organ damage referral to a higher centre for CAD (PTCA/CABG), nephropathy (prepare for dialysis or transplant), carotid Doppler to determine presence of atheroma and possibility of endarterectomy.

References

- 1. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 report. JAMA 2003; 289: 2560-2572.
- 2. Hypertensive vascular disease. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 2042-2059.

ANGINA PECTORIS

Angina is clinical syndrome due to myocardial ischaemia, caused by critical obstruction in coronary arteries due to atherosclerosis, calcific aortic stenosis or rarely due to spasm/embolism.

SALIENT FEATURES

- Typical anginal pain is characterized by precordial or retrosternal discomfort or pressure, usually precipitated by exertion and relieved by rest and sublingual nitroglycerine. Pain may radiate to left shoulder, arm, neck or jaws.
- Atypical symptoms of acute coronory syndrome may be more common in the elderly, women, and diabetic patients, but any patient may present with atypical signs and symptoms.
- If anginal pain occurs at any time without any precipitating factor or increases in intensity or frequency, it is called unstable angina.
- Signs and symptoms cannot be used to confirm or exclude the diagnosis of acute coronary syndrome and may be confirmed, if reversible ischaemic ECG changes are seen during pain, and cardiac biomarkers. Exercise testing may be used to support the diagnosis in other cases. Other investigations include echocardiography, radionuclide studies or coronary angiography.

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Treatment

Nonpharmacological

Avoid heavy exertion and take rest during acute stage, stop smoking, weight reduction, if overweight.

Pharmacological

- 1. Tab. Isosorbide dinitrate 5 mg sublingual during the attack, dose repeated as required. Or
 - Tab. Nitroglycerin 0.3-0.6 mg sublingual during the attack, dose repeated as required.
- 2. If attacks are more than twice a week, regular drug therapy is required.

 Tab. Isosorbide mononitrate 20 mg 2 times a day PO, may be increased to 120 mg per day, if required.
- If no contraindications exist, Tab. Metoprolol 50 mg 2 times a day Or

Tab. Atenolol 50 mg/day orally

- 4. If beta-blockers are contraindicated or angina persists, Tab. Diltiazem 60-120 mg/day PO
- 5. Tab. Aspirin 100-150 mg per day orally

Tab. Ticlopidine 250 mg 2 times a day. If patient cannot tolerate Aspirin, Tab. Clopidogrel 75 mg/day, if available.

6. If still ischaemia is not controlled, Tab. Nicorandil 5 mg 3 times a day can be started.

UNSTABLE ANGINA

Initial management (Patient should be hospitalized)

- 1. Tab. Aspirin 300 mg stat. If aspirin is given before arrival at hospital, note saying that it has been given, should be sent with the patient.
- 2. Tab. Clopidogrel 300 mg stat followed by 75 mg/day, if available and no contraindications to it.
- 3. Inj. Nitroglycerine 5 mcg/min IV infusion, increase dose by 2.5 to 5 mcg every few minutes until pain is controlled (monitor BP).
- 4. Continue other drugs as above.
- 5. Inj. Heparin–unfractionated–1000 U/h or low molecular weight heparin (Enoxaparine) 1 mg/kg (0.6 ml for 60 kg) 12 hourly.
- 6. Angioplasty/CABG may be done, if no relief with medication or disease is progressive.

Follow-up

- Assess the risk factors like diabetes, obesity, hyperlipidaemia, hypertension, smoking and correct these factors.
- Correct anaemia, if present.

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 Worsening angina/unstable angina requires further investigation and should be referred to a higher centre.

MYOCARDIAL INFARCTION (MI)

The term myocardial infarction is used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia.

SALIENT FEATURES

Any one of the following criteria meets the diagnosis:

 Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit-together with evidence of myocardial ischaemia with at least one of the following.

Symptoms of ischaemia:

- Chest pain similar to anginal pain is the commonest symptom, usually begins at rest, no response to nitrates, lasts >20 minutes and patient may have associated dyspnoea, hypotension, sweating, altered sensorium and cyanosis. Diagnosed by typical ECG changes.
- ECG changes indicative of new ischaemia (new ST-T changes (STEMI) or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Sudden unexpected cardiac death:

• Sudden death is 1st manifestation in significant number of patients. Some patients may be asymptomatic and detected on routine ECG.

Prehospital care

- Administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having STEMI unless contraindicated or already taken by patient.
- Perform and evaluate ECG
 Goal of transport time is to keep total ischaemic time within 120 minutes.

Treatment (preferably in CCU)

Nonpharmacological

Diagnosis should be made as soon as possible (within 20 minutes of arrival in hospital). Admit in CCU (if available), supplementary oxygen in patients with respiratory distress and oxygen saturation ≤94%, bed rest, ensure IV access, continuous cardiac monitoring and pulse oximetry, avoid visitors and outside influences, e.g. radio, newspapers; therapeutic lifestyle changes, diet, restrict sodium intake.

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Pharmacological

- 1. Inj. Morphine 2-4 mg IV, repeated 4-6 hourly, if needed.
- 2. Tab. Aspirin 150-325 mg PO administered as soon as possible on admission, if not taken earlier.
- 3. Tab. Clopidogrel 300 mg stat and 75 mg/day for maintenance, if available.
- 4. Tab. Nitroglycerine 0.3-0.6 mg sublingual.

First 24 hours:

- 5. Confirm MI by cardiac enzymes estimation and ECG.
- 6. Thrombolysis should be done within 6-12 hours with the following (There is slightly increased risk of intracranial haemorrhage—if age >65, weight <70 kg, hypertension, and with TPA).
 - Inj. Streptokinase 250,000 units IV as loading dose over 30 min followed by 100,000 units every hour for up to 12-72 hours.

Or

Inj. Urokinase 4400 U/kg IV over 10 min then 4400 U/kg every hour for up to 12-24 hours.

Or

Inj. rt-PA 100 mg continuous IV infusion over 2 hours.

- 7. Primary PTCA may be done as an alternative to thrombolysis.
- 8. Close monitoring as mortality is maximum in the first 24 hours.
- 9. Adequate analgesia.
- 10. Limit physical activities at least for 12 hours.
- 11. Do not use prophylactic antiarrhythmics but should be readily available.
- 12. Inj. Enoxaparin 1 mg/kg subcutaneously 12 hourly for 3-5 days or Inj. Dalteparin 120 IU/kg subcutaneously 12 hourly or Inj. Heparin 1000 units/h IV infusion for 72 h (more useful with TPA).
- 13. Inj. Nitroglycerin as in angina if pain continuing and no hypotension, bradycardia/excessive tachycardia (24-48 h).
- 14. If no contraindication, Inj. Metoprolol 2 mg IV every 2 minutes for 3 injections; if well tolerated follow with 50 mg PO started 15 minutes after last IV dose and given every 12 hourly for 48 hours. Then it may be changed to 100 mg once a day.
- 15. If no hypotension or contraindications and uncomplicated MI given Tab. Enalapril 5 mg 2 times a day PO.
- 16. Measure serum lipids and electrolytes.

After first 24 hours:

- 17. Continue aspirin, beta-blockers, nitroglycerine, heparin, ACEI, analgesia (if required).
- 18. Observe and treat any complication—high-dose aspirin, if pericarditis; diuretics, if congestive heart failure; defibrillation, if haemodynamic compromise in atrial fibrillation; atropine, if heart block/bradycardia; intra-aortic balloon, if severe hypotension.

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Indications for urgent angiography/angioplasty

Ischaemic episodes (spontaneous/provoked) and preserved left ventricular systolic function.

Indications of temporary pacing

Sinus bradycardia unresponsive to drugs, mobitz type II AV block, third degree AV block, bilateral bundle branch block (BBB), newly acquired BBB, and bifascicular or trifascicular block.

Indications for urgent surgery

- Failed PTCA with persistent chest pain or haemodynamic instability.
- Persistent or refractory ischaemia who is not a candidate for catheter intervention.
- Cardiogenic shock and coronary anatomy not amenable to PTCA.
- Mechanical abnormality leading to pulmonary oedema/hypotension, e.g. papillary muscle rupture or acute ventricular septal defect.
- Life-threatening ventricular arrhythmias in the presence of ≥ 50% left main stenosis and/or triple-vessel disease.

Discharge from hospital

• Treadmill test—submaximal at 4-7 days or limited symptom (10-14 days).

Aim

- To assess functional capacity and ability to perform work at home/work.
- Evaluate efficacy of current medical regimen and titrate accordingly.
- Risk stratification for future.

Long-term management (secondary prevention)

- Complete smoking cessation at every visit ask about smoking and assist patient in quitting.
- Initiate or maintain lifestyle modification—weight-control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat diary products.
- BP control goal is < 140/90 mmHg or 130/80 mmHg, if patient has diabetes or chronic kidney disease.
- Maintain LDL-C < 100 mg/L (for very high-risk patients, an LDL-C < 70 mg/dL); if TG are ≥ 200 mg/dl, non-HDL-C should be < 130 mg/dl whereas non-HDL-C should be < 100 mg/dL for very high risk with life style modification, diet, and hypolipidaemic agents.
- Physical activity 30 minutes 7 days/week (minimum 5 days per week).

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- Weight management goal is to maintain body mass index 18.5 to 24.9 kg/m²; waist circumference: men < 40 inches, women < 35 inches.
- Aspirin, beta-blockers and ACEI (selected patients)—indefinite period. Those who do not tolerate aspirin Clopidogrel. For patients undergoing coronary artery bypass grafting, aspirin, (110-325 mg) should be started within 6 hours after surgery to reduce saphenous vein graft closure.
- Warfarin for compelling indication for anticoagulant therapy, such as atrial
 fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous
 thromboembolic disease. Use of warfarin in conjunction with aspirin and/or
 clopidogrel is associated with increased risk of bleeding and monitor closely.

Patient education

- Counsel patient to comply with medication, to stop smoking, reduce weight, regular exercise (20 minutes brisk walk at least 3 times a week), restrict fat intake to control serum lipids.
- Family members of patients experiencing STEMI to immediately activate the Emergency Response Team when symptoms appear and should be advised to take CPR training and familiarize themselves with the use of an automated external defibrillator (AED).

References

- 1. Thygesen et al. Universal Definition of Myocardial Infarction. Expert Consensus Document. Circulation; 2007; Nov 27; 2634-53.
- Coronary Syndromes: 2010 American Heart Association Guideline. Circulation. 2010;122:S787-S817
- 3. Focused Update of the Guidelines for the management of patients with Unstable Angina/Non-ST Elevation Myocardial Infarction. ACCF/AHA 2012.
- 4. Unstable Angina and NSTEMI. NICE Guidelines 2010.
- 5. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. Circulation 2011; 124: 2458-2473.

CONGESTIVE HEART FAILURE (CHF)

Clinical syndrome of inadequate cardiac output resulting in fluid retention in the lungs, abdominal organs and peripheral tissue. Common causes include coronary artery disease, hypertensive heart disease, cardiomyopathy, valvular heart disease, and pulmonary vascular disease.

SALIENT FEATURES

- Dyspnoea and peripheral oedema. Cyanosis may or may not be present.
- Raised JVP, S3 summation gallop and bilateral basal crepitations.
- Profuse pink frothy sputum in severe cases.
- Tender hepatomegaly and ascites.

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Treatment

- Since it is a syndrome, appropriate examination and investigations like chest X-ray, ECG, ABG and echocardiography should be done to identify the cause.
- Identify precipitating factor arrhythmias, fluid overload, thyroid disease, infection, anaemia, pregnancy, pulmonary embolism, dietary or medical noncompliance (for details see respective sections).

Nonpharmacological

- Restrict physical activity and take bed rest in propped up position with a back rest.
- Oxygen inhalation—high flow oxygen 10 liters/min through facemask or 60% venturi mask.
- Dietary sodium restriction (2-3 g/day; no added salt in cooking and no table salt).
- Fluid restriction depending on output and other conditions.
- Dialysis or ultrafiltration or mechanical fluid removal (ascitic tap, paracentesis, etc.).
- Discontinue drugs with negative inotropic action (high dose beta blockers, calcium-antagonists, etc.).

Pharmacological

Treatment consists of a judicious mix of vasodilators, diuretics and inotropic support.

- In severe/acute cases, Inj. Frusemide 40-80 mg IV stat and repeated after 2-3 hours. Individualize the maximum dose up to 200 mg/day. Maintenance dose is 40 mg IV 12 hourly till clinical improvement is seen.
 - High dose of Frusemide infusion, i.e. 10 mg/h undiluted and 1 mg/h as continuous infusion can be used in refractory patient.
- 2. Tab. Spironolactone 25-200 mg daily may be used in combination with above.

Tab. Chlorothiazide 250-500 mg/day.

 Ω r

Tab. Indapamide 2.5-5 mg/day.

Or

Tab. Benzthiazide 25 mg + Tab. Triamterene 50 mg/day.

3. Tab. Enalapril 2.5-20 mg/day may be given as a single or two divided doses.

Tab. Lisinopril 2.5-20 mg/day as a single daily dose.

- 4. Tab. Isosorbide mononitrate 60 mg/day preferably as slow release preparation given at night.
- 5. Digoxin is indicated in fast ventricular rate (e.g. in atrial fibrillation). Inj. Digoxin 1 mg IV, followed by 0.5 mg at 8 and 0.25 mg at 16 hours Or 0.5 mg followed by 0.25 mg PO at 8, 16 and 24 hours (rapid digitalization) followed by 0.125-0.375 mg/day as maintenance dose.

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Or

Tab. Digoxin 0.5 mg first day, followed by 0.25 mg/day (slow digitalization).

- 5. Tab. Carvedilol 3.125 25 mg per day in single/or two divided doses (useful if persistent tachycardia, idiopathic dilated cardiomyopathy) dose to be doubled, if required, only after 2 weeks.
- 6. Inj. Heparin 5000 U 12 hourly SC, if the patient is bed ridden.

Monitoring

- Strict intake-output charting and daily weight as well as abdominal girth.
- Symptomatic relief and resolution of signs and symptoms of failure.
- Serum electrolytes and uric acid.

In case of refractory failure and for management of underlying cause, refer the patient to a higher centre for cardiac repolarization therapy.

Prevention of heart failure

Identifying and preventing illnesses which lead to HF including hypertension, and coronary heart disease should be paramount among the approaches to prevent HF.

Patient education

- Explain need to control salt intake and bed rest or regular compliance with medication.
- Patient should be advised to contact the physician, if symptoms of digitalis toxicity, e.g. anorexia, nausea and vomiting or worsening of heart failure.
- Diuretics should be taken in the morning and if two doses a day are required, second dose should be given before 4 PM.
- Lifestyle changes alcohol moderation, cessation of smoking, management of dyslipidaemia, diabetes, hypertension, ischaemic heart disease; weight reduction in obese patients and physical activity.

(See also Cardiac Failure in Chapter-19).

References

- 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the International Society for Heart and Lung Transplantation. Circulation. 2009;119:1977-2016.
- 2. Heart Failure and Cor Pulmonale. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 1901-1915.

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PULMONARY EMBOLISM/INFARCTION

SALIENT FEATURES

- Pulmonary embolism may pass off unnoticed in case of a small embolism or present with a full blown acute cor pulmonale.
- Patients usually present with dyspnoea, tachypnoea, chest pain, haemoptysis and cough; crepitations, rhonchi and occasionally pleural rub or signs of collapse accompanied by acute cor pulmonale, loud P2, RV S3, right ventricular heave, raised JVP, hepatomegaly, pedal oedema, cyanosis, and dyspnoea.
- ECG changes S1-Q3-T3 pattern, incomplete RBBB or right ventricular ischaemia.
- Predisposing factors for pulmonary embolism are surgery, immobilization, trauma, oral contraceptives, pregnancy, postpartum, cancer, chemotherapy, stroke, indwelling venous catheter.

Investigations

- Chest roentgenogram oligaemia in lung fields and typical wedge-shaped infarction, arterial blood gas analysis.
- Lung scanning and pulmonary angiography, D-Dimer ELISA and latex agglutination, LDH, echocardiography, contrast plethysmography and venous ultrasound for deep vein thrombosis.
- Blood cultures in case of septic emboli.

Treatment

Primary therapy

A. Pharmacological

1. Inj. Streptokinase 250,000 units IV as loading dose over 30 min followed by 100,000 units every hour for up to 12-72 hours.

Or

Inj. Urokinase 4400 U/kg IV over 10 mins—4400 U/kg every hour for up to 12 to 24 hours.

Or

- Inj. rt-PA 100 mg continuous IV infusion over 2 hours.
- 2. Inj. Dobutamine IV infusion at the rate of 5 to 10 mcg/kg/min.
- 3. Oxygen 100% inhalation (except in cases of COPD/cor pulmonale).
- 4. Pain relief with NSAIDs or narcotics.
- B. Catheter-based suction embolectomy, local mechanical dispersion, local pharmacological thrombolysis.

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C. Surgical embolectomy.

D. Secondary prevention

- 1. Inj. Heparin 5000-10,000 IU over 5 minutes followed by an IV infusion at the rate of 15-25 units/kg/hour. Check prothrombin time (PT) after 6 hours and titrate INR to 1.5 to 2.3 times control. Complete blood count (CBC) for heparin associated thrombocytopenia (HAT).
 - (**Caution**: Protamine sulphate is an antidote to overdosage with heparin with 1 mg neutralizing 100 IU of heparin given within 75 minutes (maximum 50 mg).
- 2. Tab. Warfarin is initiated on the first day of documenting PT within therapeutic range in a dose of 10 mg daily for 2 days. The subsequent maintenance dose depends on PT with an overlap of 5 days with heparin (stop heparin, when INR>2). A target INR of 2.0 to 3.0 is achieved and therapy is continued for at least a year. (Caution: Vitamin K 1-10 mg acts as an antidote to warfarin overdose).
- 3. Tab. Aspirin 75 mg/day following a full course of warfarin.
- 4. Inferior vena caval (IVC) obstruction with green field or bird's nest filter to prevent recurrent embolization from deep vein thrombosis (DVT).

Monitoring and follow-up

- 1. Complete course of anticoagulant therapy with INR at regular intervals. First INR after 16 hours of warfarin.
- 2. Inferior vena caval filters for recurrent emboli.
- 3. Evaluate for hypercoagulable states such as protein C and S deficiencies, factor V leiden, antithrombin III deficiency, plasminogen deficiency, and elevated factor VIII.

Patient education

• Prophylaxis against deep vein thrombosis and pulmonary embolism in high-risk settings with graduated compression stockings, pneumatic compression, IVC interruption and heparin therapy.

Reference

 Deep Venous Thrombosis and Pulmonary Thromboembolism. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 2170-2177.

ARRHYTHMIA

SALIENT FEATURES

• Palpitations, anxiety, lightheadedness, angina, syncope or near syncope, hypotension and may lead to cardiac compromise.

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- When severe, these may suggest underlying cardiac disease, ischaemic heart disease (IHD), cardiomyopathy, myocarditis, conduction disorders, etc. or noncardiac (thyroid disorders, electrolyte imbalances or drugs).
- Arrhythmias are frequently intermittent (paroxysmal) and may be classified based on:
 - Ventricular vs supraventricular.
 - Narrow QRS vs wide QRS.
 - Regular vs irregular.
 - Clinically benign vs those associated with haemodynamic compromise (lower the ejection fraction [EF], poorer the prognosis).
- Diagnostic tests include ECG during attack of arrhythmia or 24-hour Holter monitoring (if no abnormality seen in ECG on presentation)

Treatment

Identify and treat precipitating factors.

SUPRAVENTRICULAR TACHYCARDIA

SALIENT FEATURES

- Sustained regular narrow QRS tachycardia with normal appearing QRS (<120 msec) or may be broad QRS, if there is aberrancy.
- Onset is sudden with heart rate being 160-200/min, presents with palpitation. Hypotension may occur in some patients. Polyurea may follow the episode.

Nonpharmacological treatment

- Reassure the patient especially if no haemodynamic disturbance present at a time when the patient has symptoms.
- Vagal stimulation by drinking cold water, Valsalva manoeuvre, carotid massage, etc.

Pharmacological treatment

Acute attack is treated as follows (if no response to vagal stimulation): Inj. Adenosine 3 mg as a rapid IV push into the large peripheral vein, 3 mg over 2 seconds with cardiac monitoring, if necessary followed by 6 mg after 1-2 minutes, and then by 12 mg after a further 1-2 minutes followed by a saline flush.

(Caution: Contraindicated in 2nd and 3rd degree heart block)

Or

Inj. Verapamil 5-10 mg bolus over 2-3 min repeated at 15-30 min, if necessary. Or

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Inj. Diltiazem 0.25 mg/kg slow IV repeated after 15 min. It can be continued as an infusion 10 mg/h up to 24 h.

Or

Inj. Metoprolol 1-2 mg/min IV at 5 min interval up to a total of 5-10 mg. Low energy (25-50 joules) DC shock may be used in resistant cases.

Maintenance treatment

Tab. Atenolol 25-100 mg/day as single or divided doses.

Or

Tab. Metoprolol 50-200 mg/day as a single dose or divided doses.

Or

Tab. Verapamil 40 mg thrice a day.

Or

Tab. Amiodarone 150-200 mg/day (in resistant cases).

Patient should be referred to a higher centre for maintenance treatment/definitive treatment.

VENTRICULAR TACHYCARDIA

SALIENT FEATURES

- Run of three or more consecutive ventricular beats at a rate >120 beats/min. If the rate of consecutive ventricular beats is >100/min, it is called accelerated idioventricular rhythm which is a benign condition, usually occurring following the thrombolytic therapy.
- Diagnosis is made by ECG, suggested by independent P wave, fusion or capture beats, uniformity of QRS wave in the V leads (concordance) and a frontal plain QRS axis > -30.

A. Haemodynamically stable

Inj. Lidocaine 1 mg/kg IV bolus (3 ml) followed by repeated 0.5-1 mg/kg boluses at 5 min intervals up to a total of 3 mg/kg to attain desirable response followed by IV infusion 2-4 mg/min. Endotracheal or IM administration in extreme cases (300 mg).

If no effect of Lidocaine and DC conversion is not available:

Inj. Procainamide 15 mg/kg loading dose followed by 2-5 mg/min maintenance infusion.

NOTE: Lidocaine (class 1B) is the drug of choice for ventricular tachycardia during acute ischaemia and myocardial infarction.

B. Haemodynamically unstable VT or no response to lidocaine

Synchronized DC shock starting with 50-200 Joules.

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C. In ventricular fibrillation

Unsynchronized 200 Joules followed by 360 Joules, if required.

D. Maintenance treatment

Tab. Flecainide (class 1C) 100 mg 8-12 hourly.

Or

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Tab. Procainamide (class 1A) 250-750 mg 4 to 6 hourly.

In refractory cases, Tab. Amiodarone (class III) 200-400 mg/day, starting at a higher dose of 200 mg 8 hourly for first week.

SUSTAINED ATRIAL FIBRILLATION

It is characterized by sustained rapid irregular atrial rhythm. Mostly associated with underlying heart disease, e.g. rheumatic heart disease, coronary heart disease, hypertension. Other non-cardiac causes include thyrotoxicosis and alcohol ingestion.

SALIENT FEATURES

• Usually presents with severe palpitation, chest discomfort, weakness, breathlessness and sometimes signs/symptoms of arterial embolic phenomenon like stroke.

Treatment

Nonpharmacological

Reassurance, oxygen inhalation, propped up position, if patient is dyspnoeic.

Pharmacological

- 1. Rapid digitalization done as in section on CHF followed by maintenance dose.
- 2. Beta blockers (class II) like metoprolol 25-100 mg twice daily are also effective in controlling ventricular rate.
- 3. Tab. Warfarin 5 mg daily with titration as per INR (maintain about 1.5 to 2) in patients with documented clots or thromboembolic episodes. In cases of elective DC cardioversion (100 to 400 Joules), 3 weeks of anticoagulation required.

Treatment of underlying condition like thyrotoxicosis.

BRADYARRHYTHMIAS AND BLOCKS

Treatment

Pharmacological

May be useful initially while pacing is organized.

Inj. Atropine 0.5-2 mg IV repeated 4-6 hourly, if needed.

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And/Or

Inj. Dopamine 5-20 mcg/kg/min infusion,

And/Or

Inj. Isoproterenol 2-10 mcg/min infusion.

Monitor patient for improvement in pulse rate and blood pressure. Definitive treatment is cardiac pacing.

Monitoring

- Shift patient on to appropriate oral drugs once the arrhythmia has been controlled.
- Monitor for drug toxicities and recurrences so as to titrate the dose.
- Evaluate and refer for electrophysiological studies.
- Monitor INR for patients on anticoagulant therapy.
- Evaluate and refer for electrophysiological studies.

Patient education

- Emphasize need for compliance and regular follow-up.
- Prepare for further intervention depending upon the cause. Valvular heart disease
 may be managed by repair or replacement; reentrant tachycardia can be managed
 with radiofrequency ablation; coronary heart block requires temporary often
 followed by permanent pacing; coronary artery disease requires revascularisation.
- Emphasize need for compliance and regular follow-up, including monitoring of anticoagulation.

Reference

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