

## Drug Therapy of Cardiac Diseases in Children

WORKING GROUP ON MANAGEMENT OF CONGENITAL HEART DISEASES IN INDIA

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**Justification:** The indications and doses of most drugs used for heart ailments in children are extrapolated from data in adult patients. Separate guidelines are needed for neonates, infants and children because of the differences in underlying heart diseases and metabolic clearance of some of these drugs.

**Process:** Consensus emerged following expert deliberations at the National Meeting on Management of Congenital Heart Diseases in India, held on 13<sup>th</sup> September 2008, at the All India Institute of Medical Sciences, New Delhi, India, supported by Pediatric Cardiac Society of India.

**Objectives:** To review the literature and frame evidence based guidelines for (i) indications, doses, adverse effects and safety profile of commonly used drugs in pediatric cardiology practice; and (ii) to provide an algorithm for treatment in various clinical settings.

**Recommendations:** Consensus review and recommendations are given for drugs used in children for heart failure, hypertension, thrombosis, supraventricular tachycardia and intensive care. Guidelines are also given for use of intravenous immunoglobulins and sildenafil in children.

**Key words:** *Children, Drug doses, Drug therapy, India, Pediatric cardiology.*

The list of drugs used for various cardiac diseases in children is long and ever increasing. Most of the data for efficacy of these drugs has been generated in adult cardiac patients through randomized trials and observational studies. Conducting such trials in children is difficult, if not impossible, due to logistic problems and ethical issues. Therefore, in most cases the basis of using a drug in pediatric practice is extrapolated from the experience in adult patients.

With this background, the Working Group on Management of Congenital Heart Diseases met on 13th September 2008, at the All India Institute of Medical Sciences, New Delhi, to reach a consensus for evidence based review of drugs used in heart disease in children and formulation of recommendations.

The recommendations are classified into three categories according to their strength of agreement:

*Class I:* General agreement exists that the treatment is useful and effective.

*Class II:* Conflicting evidence or divergence of opinion or both about usefulness/efficacy of treatment.

*IIa:* Weight of evidence/opinion is in favor of usefulness/efficacy.

*IIb:* Usefulness/efficacy is less well established.

*Class III:* Evidence and/or general agreement that the treatment is not useful and in some cases may be harmful.

The following review is based on the presentations and discussion of the Working Group. A consensus was reached to provide recommendations for drug therapy under the sub-headings of various clinical settings. The pharmacokinetics and pharmacodynamics of individual drugs will only be briefly mentioned, as and when necessary.

**HEART FAILURE**

Heart failure is a clinical syndrome characterized by the inability of the heart to supply cardiac output at a pace necessary to meet the metabolic demands of the body. In children, the requirement also includes “growth and development”. Heart failure in children may occur secondary to congenital or rheumatic heart disease. The causes of heart failure in children are summarized in *Table I*.

**A. DRUGS USED FOR TREATMENT OF HEART FAILURE**

**1. Digoxin**

Digoxin is a digitalis glycoside. It inhibits the sodium potassium adenosine triphosphatase (Na-K-ATPase), increasing the intracellular calcium levels, thereby increasing the contractile state of the myocardium. Inhibition of Na-K-ATPase also reduces sympathetic flow from the central nervous system and reduces the renal absorption of sodium in

the kidney(1). This leads to suppression of renin secretion from the kidneys(2). Digoxin increases the vagal tone, thereby increasing the refractory period and slowing the conduction through the sinus node and the atrioventricular node. Digoxin is the only oral inotropic drug.

*Indications:* Digoxin is indicated in heart failure associated with reduced systolic function of heart. In most cases of heart failure, digoxin is combined with a diuretic and an angiotensin converting enzyme inhibitor (ACEi). Its role in heart failure secondary to left to right shunt lesions, where systolic function of the myocardium is preserved, is not well defined. Digoxin is used for slowing ventricular rate in tachyarrhythmias such as supraventricular tachycardia (SVT), atrial flutter and atrial fibrillation (AF).

*Evidence:* Digoxin is shown to improve symptoms in patients with heart failure(3). However, it has not been shown to provide survival benefit in adults or in children(4). Lower dose may reduce the incidence of side effects and toxicity(DIG trial)(5). In a post hoc analysis of DIG trial, higher serum digoxin levels were associated with increased mortality in men with heart failure(6). Scant data exist for digoxin therapy in children with heart failure. Utility of digoxin in heart failure secondary to volume overload of the ventricle, as seen in left to right shunt lesions, is less clear, since the myocardial contractility is normal in such cases(7).

*Dosage:* See (*Table II*). Rapid digitalization is usually not indicated when using digoxin for heart failure(9). Rapid digitalization may be indicated for treatment of acute tachyarrhythmias. The maintenance dose is given in twice daily doses for children under 10 years and once daily for children above 10 years. Digoxin “holiday” is generally not needed in children. The half life of digoxin is markedly prolonged in preterm babies and in those with renal dysfunction. Dose of digoxin should be halved when using amiodarone.

*Side effects:* Digoxin has a narrow therapeutic range and side effects are not uncommon. Heart blocks are more common in children; ectopy is more often seen in adults. Side effects include:

**TABLE I** CAUSES OF HEART FAILURE

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*Volume overload with preserved systolic ventricular function*

Large left to right shunt: VSD, AVSD, PDA

Admixture lesions with high PBF: TGA, TAPVC, Truncus

Regurgitant lesions: MR, AR (Rheumatic/Congenital)

*Myocyte dysfunction with abnormal ventricular contractile function*

Pressure overload: Severe AS, PS

Muscular dystrophy, DCM

Inflammatory: Myocarditis, Chaga’s, HIV

Tachycardiomyopathies secondary to SVT

Abnormal morphology: single ventricle (pre and post op)

Ischemic: ALCAPA

Others: Sepsis, post CPB, hypocalcemia etc.

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*ALCAPA: anomalous left coronary artery from pulmonary artery, AR: aortic regurgitation, AS: aortic stenosis, AVSD: atrioventricular septal defect, CPB: cardiopulmonary bypass, DCM: dilated cardiomyopathy, HIV: human immunodeficiency virus, MR: mitral regurgitation, PBF: pulmonary blood flow, PDA: patent ductus arteriosus, PS: pulmonary stenosis, SVT: supraventricular tachycardia, TAPVC: total anomalous pulmonary venous connection, TGA: transposition of great arteries, VSD: ventricular septal defect.*

**TABLE II** DOSING FOR DIGOXIN IN INFANTS AND CHILDREN(8)

Age	Total digitalizing dose mcg/kg/24 hr		Daily maintenance dose mcg/kg/24 hr	
	PO	IV	PO	IV
Premature newborn	20	15	5	3-4
Full term newborn	30	20	8-10	6-8
<2 yr	40-50	30-40	10-12	7.5-9
2-10 yr	30-40	20-30	8-10	6-8
>10 yrs	0.75-1.5 mg	0.5-1 mg	0.125-0.5mg	0.1-0.4mg

PO: per oral; IV: intravenous.

- Cardiac arrhythmias – Sinus bradycardia, sinoatrial and atrioventricular blocks, atrial and nodal ectopic beats, atrial tachycardia with block, ventricular arrhythmias including ventricular tachycardia (VT).
- Gastrointestinal – nausea, vomiting, abdominal pain and diarrhea.
- Central nervous system – lethargy, confusion, disorientation, vertigo, headache, fatigue, anxiety, depression, delirium, and hallucinations
- Endocrine and Metabolic – Hyperkalemia with acute toxicity.
- Ocular – blurred vision, haloes, yellow/green vision, diplopia, photophobia, flashing lights.

*Contraindications:*

*Absolute:* Hypersensitivity to digoxin, ventricular fibrillation, sick sinus syndrome, atrioventricular blocks and hypertrophic obstructive cardiomyopathy.

*Relative:* Hypoxia, hypothyroidism, acute myocarditis, pre-excitation like WPW syndrome (if >2 years of age), electrolyte disorders and acute myocardial infarction.

The dose of digoxin should be reduced in renal impairment. Concomitant use of calcium channel blockers should be avoided.

*Monitoring:* Heart rate and rhythm should be monitored. Periodic ECGs are recommended when uptitrating the dose or using diuretics. Serum calcium, potassium and renal parameters need to be

monitored. If suspecting toxicity, serum digoxin levels should be measured (sample taken at least 6 hours after the dose). Toxicity is usually seen at >2 ng/mL level.

*Preparations:* Digoxin is available as elixir (60 mL suspension, 50ug/mL) and tablet (0.25 mg tab). Tablets should not be crushed to formulate liquid preparations for children. Injectable digoxin (100 µg/mL, 250 µg/mL) is available for intravenous use. Intramuscular route is not recommended.

**2. Diuretics**

Diuretics are widely used in heart failure because of the symptomatic relief from fluid overload with in minutes of administration. Diuretics are currently recommended for all adult patients with heart failure who have volume overload of the ventricle(10). These drugs can be classified into three categories, according to their site of action on the kidney. Diuretics from different groups can be combined for greater efficacy:

(a) *Loop diuretics:* Act on the ascending limb of loop of Henle, resulting in Na, K<sup>+</sup>, chloride and water excretion. Examples include Furosemide, torsemide.

(b) *Thiazides:* These drugs act at the distal convoluted tubule and also result in Na, K<sup>+</sup> and chloride excretion. Examples include hydrochlorothiazide and metolazone.

(c) *Aldosterone antagonists:* These drugs act primarily by competing for intracellular aldosterone receptors in the distal tubule. The excretion of water and Na is increased, while K<sup>+</sup>

excretion is spared. Examples include spironolactone and eplerenone

**Furosemide**

Furosemide is a loop diuretic and is a preferred agent in heart failure due to its rapid onset of action, high efficacy with greater fluid clearance. Increasing doses have increasing efficacy and it remains effective even at low glomerular infiltration rate (GFR). Furosemide is three times more potent than thiazide diuretics. Furosemide also has a venodilatory effect and increases systemic venous capacitance, thereby reducing preload.

*Indications:* Furosemide is indicated in heart failure, pulmonary edema, hypertension, renal failure, and for fluid overload due to other causes. When using diuretic, one must make sure that there is no hypovolemia (as may be seen in postoperative settings and in newborns)

*Evidence:* Furosemide is proven to be beneficial for symptomatic relief. No survival benefit has been shown for patients with heart failure.

*Dosages and Pharmacodynamics:* Oral: 1-2 mg/kg every 12 hours, maximum of 4 mg/kg/day; intravenous: 1 mg/kg/dose up to 3-4 times a day; Continuous IV infusion: 1-4 mg/kg/day. Continuous infusion may be better and safer in acute heart failure and in postoperative setting. The onset of action starts in 10-20 minutes after an IV dose and 20-30 minutes after oral administration. The duration of action is six hours.

The dose does not need to be adjusted in renal or hepatic impairment. Furosemide may increase chances of digoxin toxicity by producing hypokalemia. It activates the renin angiotensin aldosterone axis (RAAS), producing vasoconstriction, which is detrimental in heart failure. Concomitant use of ACEi (vasodilator) is recommended, whenever possible.

*Preparations:* Furosemide is available as 40 mg tablet and 10 mg/mL (2 mL amp) injections. The cost is quite low. Oral liquid preparation is not available in Indian market.

*Side effects:* These are dose dependent and include the following:

1. Electrolyte imbalance: Most common and most dreaded side effects.
  - (a) *Hyponatremia:* hyponatremia is common, especially with high doses and it results in further drug resistance. It should be managed with fluid restriction.
  - (b) *Hypokalemia:* Hypokalemia may increase chances of digoxin toxicity. It is best managed by combining furosemide with ACEi or spironolactone. Alternatively, potassium supplements may be prescribed.
  - (c) Chloride depletion, leading to metabolic alkalosis. Supplementation with potassium chloride helps.
2. Metabolic alkalosis, hyperuricemia.
3. Impaired glucose tolerance leading to hyperglycemia.
4. Increased low density lipoprotein cholesterol and triglycerides.
5. Ototoxicity: Rapid administration of large doses may cause ototoxicity, rare in children. When furosemide is used along with aminoglycosides, the incidence of ototoxicity increases.
6. Nephrocalcinosis.

*Contraindication:*

*Absolute:* None except hypersensitivity.

*Relative:* Hypotension, hypovolemia, hypokalemia, hyponatremia.

*Alert:* Furosemide may have to be stopped if child develops diarrhoea or vomiting.

To be used with caution when using digoxin (avoid hypokalemia) and aminoglycosides (higher risk of ototoxicity)

*Monitoring parameters:* Serum Na, K<sup>+</sup>, Ca<sup>++</sup> and blood sugar.

**Torsemide**

Is also a loop diuretic similar to furosemide, but is more potent (10 mg of torsemide is equivalent to 40mg of furosemide), has a higher bioavailability and a longer duration of action. In an open label study on children, torsemide was considered better than furosemide for control of heart failure(11). It is more expensive than furosemide.

**Thiazides**

These drugs act on distal convoluted tubule of the nephron. Except for metolazone, thiazides are relatively milder diuretics and are rarely used in the treatment of heart failure. Hydrochlorothiazide is the most often used drug in this category. Primary indications for thiazide diuretics are mild hypertension and edema. The dose of hydrochlorothiazide is 2 mg/kg/day in two divided doses. Like furosemide, it also causes excretion of Na, K<sup>+</sup> and chloride along with water. Hydrochlorothiazide is available as 12.5 gm, 25 mg, 50 mg tab. The drug is quite inexpensive.

Metolazone is ten times more potent than hydrochlorothiazide and is useful in resistant cases of hypertension and heart failure. Intermittent doses of metolazone may help to overcome diuretic resistance which may occur due to fluid overload, mesenteric congestion (inadequate absorption) and low renal blood flow. The dose is 2.5-5 mg/day for adults and 0.2-0.4 mg/kg/day in children. Electrolytes must be monitored closely.

**Spironolactone**

Spironolactone is an aldosterone blocking agent, the other such drug is eplerenone. These act on distal convoluted tubule of the nephron, producing moderate diuresis with Na and chloride excretion and sparing of K<sup>+</sup>. Spironolactone is often used in combination with furosemide for heart failure.

*Evidence:* Spironolactone has been shown to improve survival in adult patients with heart failure(12). No such specific benefit has been shown in children, but the drug is effective.

Two small observational studies using spironolactone(13,14) in children, have shown benefit in controlling heart failure.

*Dosage and preparations:* Neonates 1-3 mg/kg/d in 1-2 divided doses; Children 1.5-3.5 mg/kg/d in 1-4 divided doses; Adult 25-200 mg in 1-2 divided doses. Available as 25 mg, 50 mg and 100 mg tablet.

*Side Effects:* Electrolyte imbalance: hyperkalemia, especially when using with ACEi and in renal impairment; anorexia, gastritis, gastric bleeding, diarrhea, gynaecomastia, irregular menses, and amenorrhea. These side effects are dose and duration related and tend to reverse after discontinuation of the drug. These are not seen with eplerenone.

*Contraindications:* Significant renal failure, hyperkalemia, peptic ulcer

*Monitor:* Serum K<sup>+</sup>, renal functions, especially if renal impairment.

**3. Vasodilators: Angiotensin Converting Enzyme Inhibitors (ACEi)**

ACEi decrease the adrenergic drive and block the heart failure induced activation of renin angiotensin aldosterone axis (RAAS). Increased levels of aldosterone and angiotensin II have been associated with poor outcome in heart failure. ACEi also increase bradykinin which has natriuretic properties. Currently ACEi therapy is recommended as the first line treatment for heart failure, when it is not secondary to an obstructive lesion.

*Indications:*

1. Heart failure due to ventricular dysfunction
2. Hypertension
3. Significant valvular regurgitation (even without heart failure)
4. Heart failure secondary to large left to right shunts: Role of ACEi is less convincing, but is often used.

*Classification:* ACEi are classified into 3 classes;

- I Captopril is the active form of the drug and it is metabolized in liver.
- II Enalapril, ramipril: These are pro-drugs and are metabolized to the active form.

III Lisinopril: Is excreted without being metabolized by the kidney.

*Evidence:* Improvement in symptoms and survival has been shown in adults with symptomatic heart failure on ACEi(15,16). Later, ATLAS trial showed that high dose of lisinopril was more beneficial than a low dose(17). Therefore, one must up titrate the dose to the maximum tolerable permissible doses for maximum benefit.

There are no randomized trials in children, the trials may be considered unethical at this stage. Several small observational studies have proven the efficacy and safety of these drugs in children(18-20). There is one study showing survival benefit with ACEi in children with idiopathic dilated cardiomyopathy(21). ACEi have been found to be useful in valvular regurgitation(22) and large left to right shunts, if the systemic vascular resistance is elevated at the baseline(23).

**Captopril.** Most often used ACEi in pediatric practice, especially in neonates and infants where enalapril may induce renal dysfunction. The starting dose is 0.1 mg/kg/dose; it is gradually increased to 0.5-1 mg/kg/dose three times a day (increase after every 4 to 5 doses). Maximum dose is 2 mg/kg/dose. BP and renal parameters should be monitored when up titrating the dose.

**Enalapril.** Enalapril is useful for older children. It is longer acting and given twice daily. The dose is 0.1-0.5 mg/kg/dose twice a day. The initial dose may be smaller. Monitoring is as for captopril.

Ramipril and lisinopril are other ACEi, both are commonly used for hypertension. The doses for heart failure in children are not defined.

*Side effects:* Hypotension: It usually occurs in the initial phase (4 or 5 doses) and recovers after reduction of the dose. Cough is the most troublesome side effect. It is due to increased levels of bradykinin. Non steroidal anti-inflammatory agents may be helpful. The frequency of cough is lower in infants and children as compared to adults.

*Monitoring:* Blood pressure (BP), renal parameters, serum K<sup>+</sup> should be monitored, initially and

whenever the dose is increased. In a relatively stable patient, ACEi therapy can be initiated in the outpatient department.

*Alert:* Avoid using ACEi with spirinolactone due to possibility of inducing hyperkalemia.

*Contraindications:* Bilateral renal artery stenosis, to be used carefully in coarctation of aorta, renal failure with severe decrease in GFR, hyperkalemia, preterm and sick neonates – avoid ACEi especially enalapril, and pregnancy.

**Hydralazine:** It is a non ACEi peripheral vasodilator, resulting in relaxation of arterial smooth muscles. Hydralazine does not produce hyperkalemia, and is safe in patients with renal impairment. It should be used in patients in whom ACEi or ARB are not tolerated or are contraindicated. Dose is 0.75 mg/kg/day; may be increased gradually up to maximum of 5 mg/kg/day in four divided doses. It is available with difficulty.

#### 4. Angiotension Receptor Blockers (ARB)

ARB are competitive antagonists for the angiotension II receptors, they block the cell surface receptor for angiotension unlike ACEi, which are converting enzyme inhibitors. ARB do not inhibit bradykinin breakdown and hence cough is much rarer. Also ARB are not nephrotoxic. However, a meta analysis of randomized trials in adults did not show any advantage of ARB over ACEi(24).

Side effects are same as for ACEi except that cough does not occur. Other drugs in this group besides the commonly used losartan, are Candesartan and Valsartan. Studies in children are in progress, primarily for treatment of hypertension. A combination of ACEi and ARB is currently not recommended in pediatric patients.

*Dose of Losartan:* 0.75 to 1.4 mg/kg/day

#### 5. Beta blockers

Heart failure results in activation of sympathetic nervous system and increased levels of circulating catecholamines. Chronic activation of sympathetic nervous system leads to worsening of heart failure by inducing myocardial apoptosis and fibrosis.

Circulating catecholamines also induce peripheral vasoconstriction along with renal retention of salt and water. Betablockers antagonize these deleterious effects(25). In addition, betablockers also have antiarrhythmic effect.

*Indications:*

1. Mild, moderate or compensated heart failure, secondary to ventricular dysfunction. Beta-blockers should not be initiated in acute decompensated heart failure.
2. SVT and other tachyarrhythmias
3. Hypertension

*Evidence:* The benefits of betablocker therapy in adult patients with heart failure have been shown in several studies(26). In addition to metoprolol, carvedilol has been shown to decrease all cause mortality and risk of clinical progression of heart failure(27,28). Carvedilol is a non selective beta blocker which also has an anti-oxidant property. Due to its alpha blocking effect, carvedilol exerts a vasodilatory effect. It improves functional class and fractional shortening in children with ventricular dysfunction(29). Side effects include dizziness, hypotension and headache. The first multicentre, randomized, double blind, placebo controlled trial for carvedilol in children is recently published by Shaddy and colleagues(30). There was no statistically significant difference between carvedilol and placebo. Authors postulated that this lack of effect may be due to unexpectedly low rate of events for patients in worsened category and that the trial may have been underpowered.

*Pharmacodynamics:* Dose reduction is required in severe liver dysfunction, but not for renal dysfunction. Carvedilol increases digoxin concentration so dose of digoxin may have to be decreased by 25% when using carvedilol. Combination with calcium channel blockers should be avoided.

*Dosages:*

Metoprolol: 0.2-0.4 mg/kg/day initially, gradually increase to a maximum of 1 mg/kg/day in two divided doses.

Carvedilol: 0.1 mg/kg/day in two divided doses, increase at 1-2 weekly interval to 1 mg/kg/day with a maximum of 2 mg/kg/day.

Metoprolol is available as 12.5 mg, 25 mg, 50 mg, and 100 mg tablet.

Carvedilol is available as 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablet.

*Side effects:* Bronchospasm, bradycardia, heart block, hypotension, hyperglycemia, dizziness. Aggravation of heart failure may occur in some cases, the diuretic dose may have to be increased.

*Contraindications:* Advanced heart block, sick sinus syndrome, acute heart failure, bronchial asthma, cardiogenic shock. Relative contraindications include chronic airway disease, bradycardia, hypotension, hypothyroidism.

Anticoagulation for children with chronic heart failure is discussed later.

**B. ALGORITHM FOR MANAGEMENT OF HEART FAILURE**

Key concepts in management of heart failure in children are listed in **Box 1**. In neonates and infants, active fluid restriction is not recommended. Calorie supplementation, either by increasing the density of milk or giving commercially available high calorie formulas, is recommended. In older children, fluid and salt restriction are generally required. Children should be asked to avoid extra salt as is present in fries, chips, pizzas and other similar food items. Drug therapy has to be individualized as per clinical setting A-D, as described below:

*Clinical setting A:* Patients at increased risk for heart failure, but no volume overload or ventricular dysfunction as seen in exposure to cardiotoxic agents; family history of heritable cardiomyopathy; univentricular hearts (pre and post Fontan); congenitally corrected transposition.

*Therapy consists of the following:* (i) avoid cardiotoxic drugs; (ii) periodic clinical assessment; (iii) periodic echocardiographic evaluation for ventricular function; (iv) maintenance of sinus

**BOX 1** GUIDELINES FOR MANAGEMENT OF HEART FAILURE

<p><i>Do</i></p> <ul style="list-style-type: none"> <li>• Treat the underlying cause of heart failure.</li> <li>• Digoxin has a narrow safety window in children.</li> <li>• Continuous infusion of furosemide may be better in acutely ill cases .</li> <li>• A persistent tachycardia (&gt;180) may indicate “tachycardiomyopathy” as the cause of heart failure.</li> <li>• Rapid digitalization is not required for majority.</li> </ul> <p><i>Do Not</i></p> <ul style="list-style-type: none"> <li>• Combine angiotensin converting enzyme inhibitors (ACEi) with Angiotensin receptor blockers (ARB) (Class III).</li> <li>• Avoid combining ACEi and spironolactone, if necessary, monitor potassium levels (<i>Class II b</i>)</li> <li>• Do not give ACEi in heart failure secondary to pressure overload (<i>Class III</i>)</li> <li>• Avoid using ACEi in acute decompensated heart failure (<i>Class II b</i>)</li> <li>• Betablockers should not be initiated in acute decompensated stage of heart failure (<i>Class III</i>)</li> <li>• Potassium supplements are not required in early infancy</li> </ul>
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rhythm. There is no role of ACE inhibitors/ Betablockers (*Class III*).

*Clinical setting B:* Patients with abnormal cardiac morphology or function, but no symptoms of heart failure as seen in mitral regurgitation (MR) or aortic regurgitation (AR) with left ventricular enlargement; and univentricular heart with dysfunction.

*Therapy and class of recommendation:* See **Table III**.

*Clinical setting C:* Patients with past or current symptoms of heart failure (*commonest group*)

*Therapy and class of recommendation is detailed in Table IV.*

*Clinical setting D:* Treatment for end-stage heart failure requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplantation or hospice care.

*Therapy:* Intravenous infusion of dopamine, dobutamine, milrinone, alone or in combination (details described later in section on “Drugs in ICU setting”). Betablockers and ACEi should not be used (*Class III*).

**TABLE III** DRUG THERAPY AND CLASS OF RECOMMENDATION FOR PATIENTS WITH ABNORMAL CARDIAC MORPHOLOGY OR FUNCTION, BUT NO SYMPTOMS OF HEART FAILURE

	Preserved systolic function		Ventricular Dysfunction
	Left to right shunts	MR/AR	
ACEi	III	IIa	I
Betablockers	III	III	I (IIa if RV morphology)
Digoxin	III	III	III
Diuretics	III	III	III
Anticoag	III	III	IIb

*ACEi: angiotensin converting enzyme inhibitor; AR: aortic regurgitation; MR: mitral regurgitation; RV: right ventricle*

**TABLE IV** DRUG THERAPY AND CLASS OF RECOMMENDATION FOR PATIENTS WITH PAST OR CURRENT SYMPTOMS OF HEART FAILURE

	Preserved systolic function		Ventricular Dysfunction	Pressure overload	RV Dysfunction
	Left to right shunts	MR/AR			
Diuretics	I	I	I	IIa	I
Digoxin	IIa	IIa	I (for symptoms)	III	IIa
ACEi	IIa	I	I	III	I
Betablockers	III	III	IIa	III	IIb
Anticoag	III	III	IIa	Urgent intervention to relieve obstruction	

*ACEi: angiotensin converting enzyme inhibitor; AR: aortic regurgitation; MR: mitral regurgitation; RV: right ventricle*



**HYPERTENSION**

Systemic hypertension is an important, often underdiagnosed, condition in children. In developed countries, the estimated prevalence is 1%-2% during childhood. Small surveys in school children suggest a prevalence of 2%-5% in India(31). It is recommended that all children over 3 years of age should have their BP measured whenever seen by a doctor. Hypertension in children can be essential (primary) or secondary (often to renal or endocrine disorder). Readers are encouraged to refer to the guidelines on “Evaluation and management of hypertension” recently published in *Indian Pediatrics*(32).

**Definition of Hypertension**

*Normal BP:* systolic or diastolic BP < 90<sup>th</sup> centile for gender, age and height.

*Pre hypertension:* systolic or diastolic BP between 90<sup>th</sup> & 95<sup>th</sup> centile.

*Hypertension:* systolic or diastolic BP exceeding 95<sup>th</sup> centile on 3 separate occasions. This is further subdivided into 2 stages

Stage I: Systolic or diastolic BP >95<sup>th</sup> centile and up to 5 mm above the 99<sup>th</sup> percentile

Stage II: Systolic or diastolic BP values 5mm or more above the 99<sup>th</sup> percentile

***Anti Hypertensive agents***

Before starting drug therapy, it is important to differentiate essential or primary hypertension from secondary hypertension. In most cases of secondary hypertension, treatment of the underlying cause can cure the child of high BP and hence the need for long term antihypertensive therapy. The doses of various antihypertensive agents are given in **Table V**.

***Algorithm for treatment of Hypertension***

Life style modifications are very important; their discussion is beyond the scope of this article, but they are required for all stages of hypertension, with or without drug therapy. Drug therapy is indicated in children with hypertension and in those with pre

hypertension, when associated with co-morbid conditions. The goal of treatment is to reduce BP to below 95<sup>th</sup> centile or below 90<sup>th</sup> centile, if target organ damage or a co-morbid condition is present. Commonly used medications include ACEi, calcium channel blockers (CCB), other vasodilators, beta blockers and thiazide diuretics. Recommended algorithm for treatment of hypertension is:

- *Initial treatment with CCB or BB or ACEi*
- *If BP continues to be >95<sup>th</sup> centile: Use combination therapy - ACEi + CCB or ACEi + Thiazides or CCB + BB. (Watch for bradycardia when combining BB and CCB)*
- *If BP continues to be >95<sup>th</sup> centile: Add third agent - ACEi + CCB + Diuretic/BB. Other agents: prazosin, clonidine, hydralazine. BB: betablockers, CCB: calcium channel blockers*

***Choice of drugs according to the cause of hypertension***

For essential hypertension in children, one can start with a drug from the group of calcium channel blocker, ACEi or betablocker. If hypertension is secondary to acute glomerulonephritis, loop diuretic like furosemide along with a calcium channel blocker or ACEi should be used. ACEi can be used for hypertension secondary to renal disease as long as the GFR is >30 mL/hour. If it is <30 mL/hour, calcium channel blocker and/or betablocker should be used instead of ACEi. It is important to monitor serum potassium and creatinine levels in such cases. For renovascular hypertension, ACEi should not be used if renal artery anatomy is not clear or if there is bilateral renal artery stenosis. A combination of a calcium channel blocker and a diuretic should be used. One can use a betablocker instead of a calcium channel blocker if ventricular function is normal or mildly deranged. Same is true for hypertension secondary to coarctation of aorta.

**ANTI-THROMBOTIC, ANTIPLATELET AND THROMBOLYTIC THERAPY**

Recommendations for anti-thrombotic therapy in children have been extrapolated from experience in adult patients, perhaps due to relative infrequency of

**TABLE V** ORAL ANTIHYPERTENSIVE MEDICATIONS

Drug	Initial dose (maximum)
<i>Calcium channel blockers</i>	
Amlodipine	Children 6-17 years: 2.5-5mg once daily, od-bid
Nifedipine (extended release)	0.25-0.5mg/kg/d (3mg/kg/d up to 120mg/d), od-bid
Isradipine	0.15-0.2mg/kg/d (0.8mg/kg/d up to 20mg/d), tid-qid
<i>Angiotension converting enzyme inhibitors, angiotension receptor blockers</i>	
Captopril	0.3-0.5mg/kg/d (6mg/kg/d), tid
Enalapril	0.08mg/kg/d up to 5 mg/d (0.6mg/kg/d up to 40mg/d), od-bid
Lisinopril	0.07mg/kg/d up to 5mg/d (0.6mg/kg/d up to 40mg/d), od
Ramipril	6 mg/M <sup>2</sup> , od
Irbesartan	4-5mg/kg/d (6-12 years:150mg/d, ≥13 years: 300mg/d), od
Losartan	0.7mg/kg/d up to 50mg/d (1.4mg/kg/d up to 100mg/d), od
<i>Beta blockers</i>	
Atenolol	0.5-1mg/kg/d (2mg/kg/d up to 100mg/d), od-bid
Metoprolol	1-2mg/kg/d (6mg/kg/d up to 200mg/d), bid
Propranolol	1-2mg/kg/d (4mg/kg/d up to 640mg/d), bid-tid
Labetalol	1-3mg/kg/d (10-12mg/kg/d up to 1200mg/d), bid
<i>Central alpha agonist</i>	
Clonidine	5-25 ug/kg/d (2.4mg/d), tid-qid
<i>Peripheral alpha antagonist</i>	
Prazosin	0.05-0.1mg/kg/d (0.5mg/kg/d), bid-tid
<i>Vasodilators</i>	
Hydralazine	0.75-1mg/kg/d (8mg/kg/d), qid
Minoxidil	0.1-1mg/kg/d (50mg/d),od-bid
<i>Diuretics</i>	
Frusemide	0.5-2mg/kg/d (6mg/kg/d),od-bid
Spirolactone	1mg/kg/d (3.3mg/kg/d up to 100mg/d), od-bid
Metolazone	0.2mg/kg/d (0.4mg/kg/d), od
Hydrochlorothiazide	1mg/kg/d (3mg/kg/d), od
Amiloride	0.4-0.6mg/kg/d (20mg/d), od

od: once a day; bid: twice a day; tid: thrice a day; qid: four times a day

thromboembolic events in children. Anti-thrombotic agents are required in critically ill-neonates with umbilical catheters, children with cancer (requiring long term indwelling lines), children with pro-coagulation abnormalities, post cardiac surgery etc.

**1. Heparin**

Unfractionated heparin is the most commonly used anticoagulant. It acts by forming a complex with

antithrombin III which inhibits coagulation factors IX, X, XI, XII, plasmin and kallikrin. Heparin also binds to a glycoprotein, cofactor II that inactivates thrombin independently of antithrombin III. Neonates and infants have reduced level of antithrombin III and have faster clearance of heparin, both these facts result in increased dose requirements in pediatric group. Resistance to heparin can be overcome by increasing either the dose of heparin or

the antithrombin concentration(33). Heparin dose is titrated to achieve an activated partial thromboplastin time (aPTT) of 60-85 seconds which generally correlates with anti Xa level of 0.35-0.7 unit per mL.

*Indications:* Heparin is used as first line anticoagulant until oral agents such as warfarin are initiated. Heparin bolus is given in the catheterization lab to prevent risk of arterial thrombosis. Heparinised saline is used to flush catheters in the catheterization lab.

*Dosage:* An IV bolus dose of 75-100 units/kg of heparin results in a therapeutic aPTT in 90% of children.

Maintenance dose (as IV infusion)

< 2 months of age	28 units/kg/hour
2 mo-1yr	25 units/kg/hour
> 1 yr	20 units/kg/hour
Older children	18 units/kg/hour (same dose as for adults)

Dosage in catheterization lab: 50-100 units/kg bolus IV or through arterial sheath.

*Monitoring:* Heparin dosing monograms have been validated in children(34). Many physicians use anti Xa levels for infants or in critically ill children as aPTT may not be very predictive. In relatively stable infants and in older children, aPTT is used for monitoring as it is more easily performed and is widely available. If aPTT is <60 seconds, dose of heparin should be increased by 10% every 4-6 hours till aPTT is over 60 seconds. If aPTT exceeds 85 seconds, heparin dose should be decreased and if aPTT is >95 sec, the heparin infusion should be stopped.

*Side effects:* Bleeding occurs in 1.5%-24%, the true frequency may be somewhere in between these figures. Reports of heparin induced thrombocytopenia have been described in up to 2.3% for children in intensive care. Osteoporosis is rarely seen, it is related to long duration of use. Protamin sulfate is used to counter effect of heparin

immediately, in case bleeding occurs. The dose is 1 mg for every 100 units of heparin, if heparin infusion has been received in past 30 minutes. Reduced doses of protamin sulfate are required if the last heparin infusion given was over 30 minutes ago.

**2. Low Molecular Weight Heparin**

Low molecular weight heparin (LMWH) is increasingly used in children, primarily due to less stringent monitoring requirement. The mechanism of action is similar to that of heparin. Studies from Hospital for Sick Children in Toronto confirm the advantages of LMWH over standard heparin(35,36). These advantages are relative ease of subcutaneous administration, minimal need for monitoring, minimal interference by other concurrent medications, decrease effect on bones with long term use and decreased incidence of thrombocytopenia. Several studies have confirmed the efficacy of LMWH in children and a need for higher dose has been confirmed in these studies, when compared to adults(37-39). Therapeutic dose is extrapolated from adults and is based on anti factor Xa levels. The recommended level of Xa is 0.50-1.0 unit/mL when sample is taken after 4-6 hours of a subcutaneous injection.

*Dosage:* Majority of data in children is with enoxaprin. Dose is 1.5mg/kg 12 hourly for <2 month (<5kg) and 1 mg 12 hourly for older infants and children. For preterm babies a higher dose, up to 1.5 – 2 mg/kg 12 hourly, may be required.

Adverse reactions include major bleeding (4%).

**3. Vitamin K Antagonists**

These drugs reduce the concentration of vitamin K dependent factors, II, VII, IX and X. In newborns, concentration of these factors is physiologically reduced, resulting in a prolonged prothrombin time, the international normalized ratio (INR) being 2.0-3.0. So, the role of vitamin K antagonists is limited in newborn period. The breast milk has a low concentration of vitamin K, making breast fed infants very sensitive to these drugs. On the other hand, formula milk has high vitamin K levels and therefore, babies on formula milk are relatively resistant to vitamin K antagonists.

Warfarin and acenocoumerol are available drugs in this category. Only oral preparations are available in the market. Warfarin is the most common oral anticoagulant used; it is indicated for prophylaxis and treatment of thromboembolic disorders. The efficacy of warfarin is judged by measuring INR.

**Dosage:** Initial loading dose is 0.2 mg/kg. Infants <1 yr usually need higher maintenance dose compared to older children. The dosage schedule is as per INR value given in the **Table VI**. Average dose of warfarin in infants and young children is 0.33 mg/kg/day to achieve an INR of 2.0-3.0. For teenagers, the dose is 0.09 mg/kg/day and for adults, 0.04-0.08 mg/kg/day.

**Monitoring:** Frequent dose adjustments warrant close supervision of INR. Vitamin K antagonists have extensive cross-reactivity with several commonly used drugs and dietary agents. Certain “point-of-care” monitors are commercially available, which are considered reliable and acceptable for checking INR in home setting. These are somewhat similar to “glucometers”.

**Side effects:** Bleeding is the main complication; the risk of major bleeding is 0.5% per patient year. Risk

increases significantly when INR is >8 units. Other side effects are development of osteoporosis on prolonged use. The complication of bleeding can be treated with vitamin K administration (30 mcg/kg). In serious cases, fresh frozen plasma should be used.

**Contraindications:** These include severe renal or hepatic impairment, cerebral or dissecting aortic aneurysms, active ulceration, severe hypertension, infective endocarditis, pericardial effusion, pregnancy and hypersensitivity to warfarin.

**Interactions:** A major concern in using vitamin K antagonists is their interaction with several drugs and dietary substances, requiring dose adjustments. The dose of warfarin needs to be increased when using anticonvulsants like phenobarbital and carbamazepine. Other drugs interacting with warfarin are aspirin, steroids, nonsteroidal anti inflammatory agents, alcohol, fluconazole, metronidazole, amoxicillin, rifampicin, chloramphenicol, sulfamethoxazole-trimethoprim combination etc. As mentioned earlier, breast fed infants are more sensitive to warfarin as compared to formula fed infants.

Patients should be told not to make frequent changes in their diet. If a new drug is needed e.g. antibiotics, INR should be monitored. INR level is affected by cumulative dose of warfarin taken over the last 5-7 days, so testing INR just after a day of change in dose is not very useful.

**TABLE VI** DOSING OF WARFARIN

<i>Loading dose (Day 1)</i>
0.2mg/kg (maximum 10mg); 0.1 mg/kg in presence of hepatic dysfunction
<i>Days 2-4</i>
INR 1.1-1.3, repeat loading dose
INR 1.4-1.9, give 50% of initial loading dose
INR 2.0-3.0, give 50% of initial loading dose
INR 3.1-3.5, give 25% of initial loading dose
INR > 3.5, hold until < 3.5, restart at 50% of previous dose
<i>Maintenance dose (day 5 and beyond)</i>
INR 1.1-1.4, increase dose by 20% of previous dose
INR 1.5-1.9, increase dose by 10% of previous dose
INR 2.0-3.0, no change
INR 3.1-3.5, decrease dose by 10% of previous dose
INR >3.5, hold until <3.5, restart at 20% of previous dose

INR: international normalized ratio

#### 4. Antiplatelet Agents

##### *Aspirin*

The effect of aspirin is mediated through inhibition of prostaglandin synthetase, which results in prevention of formation of the platelet aggregating substance thromboxane A2. This antiplatelet effect is generally seen at doses of 3-5 mg/kg/day. Aspirin resistance, as seen in adults is prevalent in children also, 26% in one study(40). The main indications in children are, following palliative Blalock Taussig (BT) shunts and in patients with Kawasaki syndrome. In a nonrandomized observational study, aspirin was found to lower the risk of death and BT shunt occlusion(41). Low dose aspirin has also been used following Glenn and Fontan procedures. Aspirin clearance is slower in neonates. Aspirin

should be administered with milk or food as it may cause gastric irritation. A controlled release preparation must not be crushed or chewed as the bioavailability will change. Generally no specific monitoring is required when using low dose aspirin, however hemoglobin may be checked every 6 months to detect anemia which may occur due to blood loss from gut.

*Side effects:* Aspirin is relatively safe in anti platelet doses. Rarely it may result in bleeding, especially in those with underlying coagulation disorder. Symptoms of peptic ulcer may be precipitated. Reye syndrome is dose dependent, hence not seen with low dose aspirin. In the rare event of significant bleeding, platelets should be transfused.

### ***Clopidogrel***

It is one of the thienopyridines and selectively inhibits ADP-induced platelet aggregation via the inhibition of P2Y<sub>12</sub> receptor. Its effect is additive to anti platelet effect of aspirin.

Data in children on the use of clopidogrel is emerging. The initial report was on 15 children(42). More recently there is a prospective, multicenter, randomized, placebo controlled trial (PICOLO) that was conducted to evaluate the pharmacodynamics of clopidogrel in 116 children with risk for arterial thrombosis(43). The drug was well tolerated and a dose of 0.2 mg/kg/day was able to achieve platelet inhibition level similar to that in adults taking the standard dose of 75mg/day. 80% of children were also taking aspirin, no serious bleeding occurred.

The indications for clopidogrel are same as for aspirin. It may be considered in cases that are intolerant to aspirin. Clopidogrel can be combined with aspirin in cases where stronger antiplatelet effect is required.

*Side effects:* Frequency of side effects is low. Main side effects are gastrointestinal. Rarely rash, neutropenia and bleeding has been described in adults.

***Ticlopidin*** is another thienopyridine, given in doses of 10 mg/kg/day in two divided doses, but there is no data to support its use in children.

### ***Intravenous antiplatelet agents***

These include glycoprotein IIb-IIIa antagonists such as intravenous abciximab, eptifibatide and tirofiban. One study on use of abciximab for patients with Kawasaki disease demonstrated greater reduction in coronary aneurysm diameter at early follow up compared to patients who received standard therapy alone(44). Abciximab therapy may be considered in patients of Kawasaki disease who develop large coronary aneurysms in acute or sub acute phase.

## **5. Thrombolytic Agents**

Thrombolytic agents act by converting endogenous plasminogen to plasmin. The various agents in this group are streptokinase, urokinase and tissue plasminogen activator (tPA). Levels of plasminogen are much lower at birth (50% of adult values). Therefore the thrombolytic effect of these drugs is decreased in neonates. Streptokinase is the cheapest of all three agents but may produce allergy in some cases. In Western countries, tPA is the agent of choice. A review of 182 neonates and infants given thrombolytic agents failed to show any significant difference between the three agents(45). Fresh frozen plasma supplementation may be used to increase efficacy of tPA.

*Indications* include femoral artery occlusion (following cardiac catheterization), aortic thrombosis, intracardiac thrombi, pulmonary embolism, thrombosed prosthetic valves and thrombosed BT shunts.

*Dosage:* The optimal dose for pediatric patients is not known. **Table VII** outlines the usual dosage schedule and monitoring parameters. These drugs are generally administered intravenously; however local therapy may be better for catheter induced thrombosis, if the catheter is already in situ. It is important to start heparin therapy immediately after completion of thrombolytic therapy, a loading dose for heparin is not required.

*Side effects:* The major adverse effect is bleeding, seen in 20%-68% of cases. A higher dose and a long duration of therapy, predispose to bleeding. Intracranial bleed has been reported in 4% of pre-term babies as compared to 1% in term babies(46).

**TABLE VII** DOSAGE FOR THROMBOLYTIC AGENTS

	Loading	Maintenance	Monitoring
Urokinase	4,400u/kg	4,400 u/kg/h for 6-12h	Fibrinogen, TCT, PT, aPTT
Streptokinase	2,000 u/kg	2,000 u/kg/h for 6-12h	Fibrinogen, TCT, PT, aPTT
tPA	None	0.1-0.6mg/kg/h for 6h	Fibrinogen, TCT, PT, aPTT

*aPTT*: activated partial thromboplastin time; *INR*: international normalized ratio; *PT*: prothrombin time; *TCT*: thrombin clotting time; *tPA*: tissue plasminogen activator

Major bleeding may be treated with cryoprecipitate and other blood products.

*Contraindications* include stroke, transient ischemic attacks and severe hypertension.

**GUIDELINES FOR USE OF ANTI-THROMBOTIC AGENTS**

**1. Blalock – Taussig Shunts**

Modified BT shunt involves interposition of a Gortex tube between the subclavian artery and ipsilateral branch of pulmonary artery. The risk of thrombotic occlusion of graft varies from 1%-17% depending on various factors such as size of the graft, size of the pulmonary artery, age of the patient, hematocrit, etc.

*Recommendations*: Heparin should be used during and immediately following a BT shunt. This should be followed by aspirin in a dose of 3-5 mg/kg/day (*Class I*). Clopidogrel may be used in place of aspirin in those unable to tolerate aspirin (*Class IIa*). A combination of aspirin and clopidogrel may be used if one episode of shunt thrombosis has occurred on aspirin alone (*Class IIa*).

**2. Mechanical Valves**

Thrombosis of a prosthetic valve can be catastrophic and must be prevented. Warfarin is a very effective oral anticoagulant to prevent prosthetic valve thrombosis in adults; data in children is less robust.

*Recommendations*: Warfarin (or other vitamin K antagonists) to be used for all children with mechanical valves (*Class I*). The recommended INR is 2.5-3.5 for prosthetic mitral valve and 2.0-3.0 for prosthetic aortic valve. The dose of oral anti-coagulant should be titrated accordingly.

For those who have had a valve thrombosis while on adequate oral anticoagulation, addition of aspirin, in a dose of 3-5 mg/kg/day should be considered. (*Class IIa*).

For a bioprosthetic valve, oral anticoagulation to maintain INR between 2.0 and 3.0 is recommended for initial three months after surgery, no anticoagulation is required thereafter. Low dose aspirin may be used (*Class IIb*).

**3. Kawasaki Disease**

Coronary artery aneurysms develop in 15%-25% of patients with Kawasaki disease. Treatment with high dose intravenous gamma globulins has been shown to reduce the risk of coronary aneurysm. Antiplatelet agents are used to prevent coronary thrombosis in acute phase and myocardial infarction in chronic phase.

*Recommendations*: Aspirin, in anti inflammatory dose of 80 -100 mg/kg/day is used for initial phase, sometimes up to 14 days (*Class I*). Later, the dose is reduced to 3-5 mg/kg/day to exert antiplatelet effect. It is given for 6-8 weeks if no coronary abnormalities are present (*Class I*). If coronary aneurysms are present, aspirin in low doses is continued till the aneurysms persist, which may be life long (*Class I*). For big coronary aneurysms, (over 6-8 mm in diameter), clopidogrel may be added to aspirin therapy (*Class IIb*). For giant aneurysms (>8mm in diameter), addition of oral anticoagulation is recommended to aspirin therapy (*Class I*). The target INR should be maintained between 2.0 and 3.0. For coronary artery thrombosis, glycoprotein IIb IIIa inhibitors like abciximab may be used (*Class IIa*). Abciximab may also be indicated for giant aneurysms (*Class IIb*).

#### 4. Intracardiac Thrombi in Neonates with Normal Ventricular Function

Neonates are particularly vulnerable to intracardiac thrombi due to imbalances in their fibrinolytic systems and low levels of natural anticoagulants in their body.

*Recommendations:* Direct infusion of the thrombolytic agent as close to thrombus as possible is preferred (*Class I*). If given IV, higher doses are required, which increase the risk of cerebral hemorrhage, more so in preterm babies. The dose for urokinase is 1000 to 3000 units/kg/hour and for tPA 0.01-0.05 mg/kg/hour(47). Fibrinogen levels should remain above 100 mg/dl during treatment. The thrombolytic treatment should be followed by heparin infusion.

#### 5. Dilated Cardiomyopathy/myocarditis

Dilated cardiomyopathy or myocarditis with heart failure predisposes to stroke and pulmonary embolism.

*Recommendations:* Those with gross heart failure should receive oral anticoagulants (*Class I*). Oral anticoagulants are also preferred for other children with cardiomyopathy who have significant ventricular dysfunction (*Class IIa*). The target INR is kept between 2.0 and 3.0. If intracavitary thrombus is present, anticoagulant therapy is again warranted (*Class I*).

#### 6. Idiopathic Pulmonary Hypertension

Anticoagulants are often used for prophylaxis in this group of patients, based on the data generated in adults.

*Recommendations:* Oral anticoagulation with vitamin K antagonists to maintain INR between 2.0 and 3.0 (*Class IIa*). Antiplatelet agents have no role.

#### 7. Arterial Cardiac Catheterization (Diagnostic and Interventional)

Young children are at increased risk of femoral artery thrombosis following arterial access for cardiac catheterization. Femoral artery thrombosis should be suspected if the pulse in the corresponding limb remains absent after 2-4 hours of the procedure and it should be treated with anticoagulants.

#### *Prophylaxis for femoral artery thrombosis*

Use of heparin during cardiac catheterization is shown to reduce incidence of femoral artery thrombosis in children by 40% to 80%. In a study, 50units/kg bolus was found to be as effective as 100units/kg, given immediately after arterial puncture(48). However most recommend the higher bolus dose of 100units/kg in infants and young children (*Class I*). If procedure is prolonged, additional doses of heparin or a heparin infusion is used. Activated clotting time should be monitored if the procedure is prolonged; it is maintained between 200-250 seconds.

#### *Treatment of femoral artery thrombosis*

If pulse in the index limb does not appear after 2-4 hours of cardiac catheterization, heparin should be given in a dose of 20 units/kg/hour (*Class I*). If pulse still remains absent after 36-48 hours, thrombolytic therapy is recommended (*Class IIa*). For significantly ischemic limb (threatening to extend or limb death), thrombolytic therapy may be initiated early (*Class I*). IV streptokinase is used, the bolus dose is 1000-4000 units/kg given over 20-30 minutes. This should be followed by infusion at 1000 units/kg/hour. If thrombolytic therapy is contraindicated, surgery should be done. It is believed that in about 70% of cases, heparin resolves the thrombus.

#### 8. Peripheral and Umbilical Arterial Catheter in Neonates and Children

For prophylaxis against catheter thrombosis, heparin infusion in concentration of 5units/mL should be continued through the catheter at a rate of 1mL/hour. In case thrombosis has occurred in the arterial catheter, the catheter should be removed and heparin infusion given intravenously. In cases with significant limb ischemia, thrombolytic agents may have to be used.

### PHARMACOTHERAPY FOR ARRHYTHMIAS

#### A. SUPRAVENTRICULAR TACHYCARDIA

SVT is the most frequent form of symptomatic tachyarrhythmia in children. The heart rate is usually

more than 180-200 bpm. The commonest type is due to an accessory connection between the atrium and ventricle; it is called atrioventricular re-entrant tachycardia (AVRT). Atrioventricular nodal reentrant tachycardia (AVNRT) is less common in children. The least common type is ectopic atrial tachycardia (EAT). SVT is poorly tolerated in neonates and infants, leading to heart failure. Palpitation is the main symptom in older children and adolescents. Most SVT patients have a structurally normal heart. In rare instances, a persistent, chronic SVT may cause ventricular dysfunction and a dilated cardiomyopathy like picture. Drugs for pharmacological treatment of SVT include adenosine (for acute episode only), calcium channel blockers like verapamil and diltiazem, digoxin, betablockers, amiodarone, sotalol, flecainide and propafenone. Antiarrhythmic drugs are classified into four categories based on their mechanism of action (**Table VIII**). Digoxin and betablockers (already discussed) are the most commonly used drugs for SVT. Other drugs like amiodarone, sotalol and flecainide will be discussed in this section.

**1. Amiodarone**

Amiodarone has been used as an antiarrhythmic agent since 1970s and is useful for both SVT and VT. It is primarily a class III anti-arrhythmic drug, but has other class effects also. Oral amiodarone usually takes days to exert its antiarrhythmic effect, but IV amiodarone has immediate onset of action and can be used in acute settings. The predominant effect after IV administration is due to its betablocking and calcium channel blocking actions. Class III antiarrhythmic effect takes much longer.

*Indications:* Amiodarone is indicated for difficult to control SVT, which may be due to AVRT, AVNRT, atrial flutter or AF. Amiodarone is the drug for choice for junctional ectopic tachycardia (JET) which may occur in postoperative setting in the intensive care unit. This drug is also useful for various types of VT.

*Evidence:* Several studies have been reported on oral and intravenous amiodarone use in children(49-51). It has also been successfully used in combination with flecainide(52) and propranolol(53) for refractory tachyarrhythmias in infants and children.

*Dosage:* IV - Loading dose is 5mg/kg given over 20-30min, it is followed by 5-15 mcg/kg/min infusion. In rare cases, a higher loading dose, up to a maximum of 15 mg/kg, can be given. Oral - Loading dose is 5 mg/kg given 2-3 times a day (maximum 200 mg/dose) for 5 days followed by 5 mg/kg/day as a single dose.

Amiodarone has a long duration of action and may exert effect for weeks or months after discontinuation. Since it is metabolized in liver, its dose must be adjusted in hepatic dysfunction.

*Side effects:* Very toxic, especially on chronic usage. Side effects are seen in up to 75% of cases. IV amiodarone may result in hypotension, nausea, sweating, and hot flushes.

Side effects of oral amiodarone are:

- *Cardiac:* bradycardia, prolongation of QT interval, myocardial depression
- *Thyroid:* hypothyroidism or hyperthyroidism

**TABLE VIII VAUGHAN WILLIAMS CLASSIFICATION OF ANTIARRHYTHMIC DRUGS**

Class	Mechanism of action	Drugs
I	Sodium channel blockade	
Ia	Prolong repolarization	Quinidine, procainamide, disopyramide
Ib	Shorten repolarization	Lidocaine, mexiletine, tocainide, Phenytoin
Ic	Little effect on repolarization	Encainide, flecainide, propafenone
II	Beta adrenergic blockade	Propranolol, esmolol, acebutolol, I-sotalol
III	Prolong repolarization (potassium channel blockade)	Amiodarone, bretylium, d,l-sotalol, ibutilide
IV	Calcium channel blockade	Verapamil, diltiazem, bepridil



- *Pulmonary:* pulmonary alveolitis, pneumonitis and fibrosis
- *Nervous system:* peripheral neuropathy, vertigo, headache, insomnia
- *Skin:* rashes, photosensitivity
- *Eyes:* corneal deposits, optic neuropathy
- *Liver:* jaundice may occur due to hepatic toxicity.

*Interaction with other drugs:* Amiodarone decreases the clearance of digoxin, flecainide, procainamide and warfarin. There is increased risk of ventricular arrhythmias when given with erythromycin.

*Contraindications:* Hepatic dysfunction, restrictive lung disease, long QT interval.

*Monitoring:* BP monitoring when using IV amiodarone, especially in patients with ventricular dysfunction. Periodic ECGs must be done for QT interval. Testing for thyroid functions (before starting amiodarone, after loading dose and 6 monthly), liver functions (before, after loading and 6 monthly), pulmonary functions, chest X-ray (before and 3-6 monthly later) and slit lamp examination of the eyes should be carried out periodically.

Amiodarone, though a very effective antiarrhythmic agent, must be avoided as it results in serious side effects, especially for chronic use. Unfortunately due to difficulties in procuring other, safer antiarrhythmics, amiodarone is being widely used in India. It should be reserved for refractory arrhythmias not responding to simpler medications.

Amiodarone is available as 100mg and 200mg tablet and 50mg/mL injection.

## 2. Sotalol

Sotalol is a mixture of D-and L-isoform. It is primarily a class III antiarrhythmic agent, but has some class II (beta blockade) effect also, due to L-isoform. It prolongs action potential duration and results in lengthening of QTc interval. It exerts a negative inotropic and chronotropic effect and reduces AV nodal conduction.

*Indications:* Sotalol is indicated for refractory atrial tachyarrhythmias. It is often used for arrhythmias in

postoperative patients. For ventricular arrhythmias, sotalol has been shown to be superior to class I agents. It is preferable to amiodarone due to less serious side effects. Sotalol has also been used for fetal arrhythmias successfully.

*Evidence:* Experience with sotalol in children is limited, most studies are observational or retrospective, reporting a success in 90% for SVT(54,55). In refractory cases, it can be combined with flecainide(56).

*Dosage:* Sotalol is given orally in a dose of 2-4 mg/kg/day in two divided doses. Doses up to 8 mg/kg/day have been used. Body surface area is reported to be a better predictor for sotalol dosing; the recommended dose is 30-70 mg/m<sup>2</sup>/day(57).

*Side effects:* Sotalol is a relatively safe drug apart from its proarrhythmic effect seen in 3%-5%, due to prolongation of QTc interval. Bronchospasm may occur in predisposed patients, due to its beta blocking effect.

*Contraindications:* Long QTc interval (>450 msec) is an absolute contraindication. Dosage adjustment is required in renal failure. Hypokalemia and hypomagnesemia are other relative contraindications. It should be used with caution in patients with significant ventricular dysfunction and heart failure.

*Monitoring:* Sotalol should always be initiated in the hospital setting. A baseline QTc interval should be measured on ECG. QTc should be monitored for at least 3 days after initiation of therapy and again whenever the dose is increased. If QTc interval increases to > 500 msec, the dose should be reduced or drug stopped.

Sotalol is available as 40 mg tablet.

## 3. Flecainide

Flecainide is a class Ic antiarrhythmic and acts by inhibition of the fast Na channel, prolongation of the action potential duration and inhibition of the rapid repolarization current. Its greatest effect is on His-purkinje system and ventricular myocardium producing prolongation of QRS duration. Flecainide is a negative inotropic and may induce ventricular

arrhythmia in patients with significant myocardial dysfunction.

*Indications:* Flecainide is indicated for chronic prophylaxis of SVT in cases refractory to conventional drugs like digoxin, betablockers and calcium channel blockers. Intravenous preparation has been used for termination of acute episode of SVT. It is particularly useful for treatment of automatic atrial tachycardia and JET. It is also used for atrial flutter, postoperative intraatrial reentrant tachy-cardia and VT. Flecainide should be initiated by a cardiologist or electrophysiologist, who is familiar with its usage and side effects.

*Evidence:* Flecainide has been extensively used for chronic prophylaxis of SVT in children with no underlying heart disease or ischemia. It is effective in over 90% of cases(58,59). Flecainide has also been used successfully in combination with amiodarone(52) and sotalol(56). Flecainide is also useful for fetal SVT.

*Dosage:* IV dose for aborting an acute episode of SVT is 2 mg/kg over 30 minutes. For maintenance, 100-250 mcg/kg/hour infusion is given. The oral dose ranges from 2-8 mg/kg/day in 2-3 divided doses, usual dose is 2-4 mg/kg/day. Dose according to the body surface area is 50mg/m<sup>2</sup>/day for children under two years and 80mg/m<sup>2</sup>/day for over two years.

The drug is metabolized in liver and 30-40% is excreted unchanged in urine. Half life is about 20 hours, but it is shorter in neonates. Drug takes about 3-5 days to reach a steady state level after oral administration. Milk inhibits absorption of flecainide. It is advisable to avoid milk consumption one hour before and after flecainide administration.

*Side effects:* These include bodyache, asthenia, tremors, headache, fatigue, agitation and gastrointestinal upset. The most dreaded side effect is proarrhythmia, seen in 7-8% of cases. Proarrhythmia is more likely if there is myocardial ischemia or ventricular dysfunction.

*Drug interaction:* Digoxin increases level of flecainide. When using with amiodarone, flecainide dose should be reduced by about 50%.

*Contraindications:* These include significant valvular heart disease, ventricular dysfunction, heart failure, hypoxia, recent myocardial infarction/ ischemia, heart blocks, sinus node dysfunction and bundle branch block.

*Monitoring:* Flecainide should be started in a hospital setting. The QRS duration needs to be monitored meticulously. A 10% increase is expected. An increase of >25% in QRS width should be an indication to reduce the dose or stop the drug. QRS width is best judged when ECG is taken at a faster paper speed (50mm/sec or 100mm/sec). Plasma levels of flecainide should be monitored ideally, especially in hepatic or renal impairment, but this facility is not yet available in India. Flecainide is available with difficulty in India.

The tablet strength is 50 mg and 100mg.

#### B. ALGORITHM FOR TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA IN CHILDREN

Natural history of SVT is different in infants and children as compared to adults and it influences the long term pharmacotherapy for these patients. 40%-70% of infants do not need drug therapy for SVT beyond infancy, although many of these still have an inducible SVT on electrophysiologic study. About one third of SVT patients lose accessory pathway but 30% of these may develop recurrence of SVT at 8-10 years of age. Therefore, infants with SVT due to an accessory pathway (AVRT), such as Wolff Parkinson White (WPW) syndrome, can wait for spontaneous resolution of the pathway.

The treatment of SVT is described under two subheadings, abolition of the acute attack and chronic prophylaxis.

#### *Acute Management of SVT*

- (i) *Vagal maneuvers:* In a hemodynamically stable child, vagal maneuvers should be tried before pharmacologic therapy. Such maneuvers include ice bag application on the face of infants, pressure on infant's abdomen and gagging. Ice bag application is most commonly used and it has an efficacy of up to 90%. A plastic bag with

ice cubes and water should be applied on child's face for 10 seconds at a time. Vagal stimulation by applying ocular pressure is contraindicated in infants and young children (*Class III*).

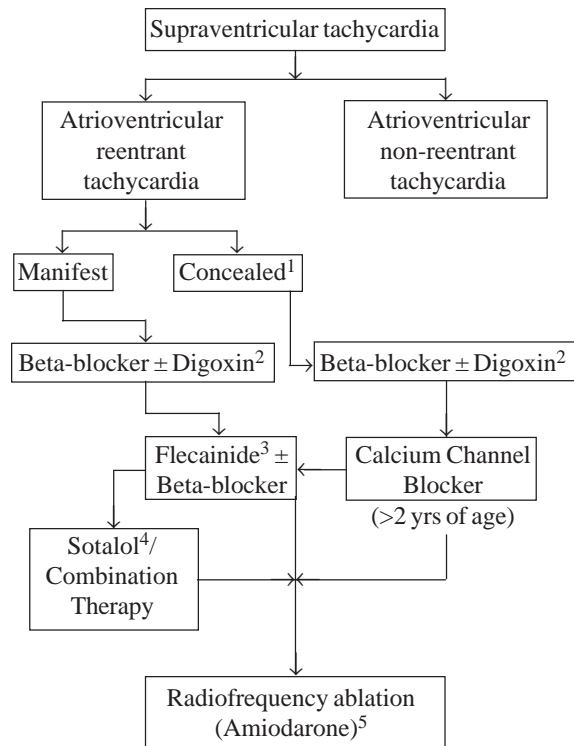
- (ii) *Adenosine*: Intravenous adenosine is considered the drug of choice for acute termination of SVT. It is effective in 95% of cases of re-entrant tachycardia, although success rate in neonates may be lower. Adenosine has a very short duration of action and therefore recurrence of SVT is common. The dose is 0.1-0.2 mg/kg, given as a rapid IV bolus. A 5 to 10ml of saline should be pushed immediately after giving adenosine bolus. Adenosine breaks SVT by producing block at the AV node level.
- (iii) *Intravenous Verapamil/ Diltiazem*: These drugs have >90% efficacy for terminating reentrant SVT i.e. AVRT and AVNRT. Verapamil or diltiazem should not be used in small children (< 4 years) and in the presence of heart failure or pre-excitation on the ECG. Verapamil or diltiazem is rarely used now, since adenosine is available. These drugs still have place in older children who show recurrence of SVT after adenosine administration.
- (iv) *Esmolol*: Intravenous esmolol (a betablocker) has been used to terminate SVT in some cases with moderate success.
- (v) *Intravenous Amiodarone*: IV amiodarone reverts most of reentrant tachycardia which use AV node for their sustenance i.e. AVRT and AVNRT. This drug should be reserved for resistant and recurrent SVT.
- (vi) *Others*: Intravenous/oral Flecainide has also been used to terminate SVT.

**Chronic Prophylaxis for SVT**

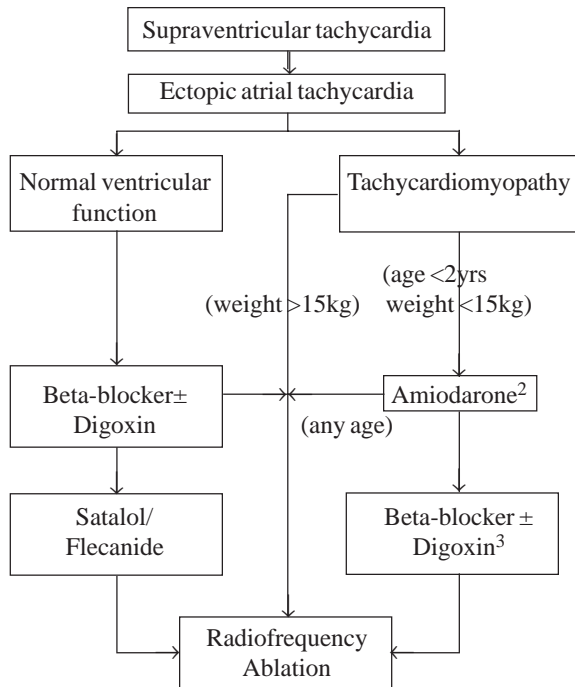
Chronic prophylaxis with drugs may be required for short periods, as spontaneous resolution occurs in a significant number of cases who present in infancy. Choice of the drug depends on the tachycardia mechanisms, age of the child, associated structural heart disease, ventricular function and familiarity of the physician with the drug. The algorithm based on

above factors is given in **Fig.1 and 2**. As can be seen in figures, initial treatment must start with one of the safe drugs like a betablocker or digoxin.

AVRT is the commonest cause of SVT in infants. The accessory pathway in such cases may be concealed or manifest. If the accessory pathway is concealed, it is not capable of antegrade conduction. ECG in such cases shows normal PR interval and no delta waves. Manifest pathway is seen in 70% of cases, i.e. the pathway is capable of antegrade conduction and the ECG shows short PR interval and delta waves.



**FIG.1** Management algorithm for children with regular narrow QRS, reentrant SVT.<sup>1</sup> Rarely fatal, hence does not warrant drugs like amiodarone / sotalol on long term basis (>6 months);<sup>2</sup> Use of Digoxin in manifest pathways remains debatable; probably safe for infants (<2yrs);<sup>3</sup> Interchangeable with propafenone;<sup>4</sup> Always initiate in hospital; 3-5% risk of Torsades de Pointes even in normal hearts;<sup>5</sup> Amiodarone may be used in special situations like uncontrolled recurrent episodes in infants, severe LV dysfunction (tachycardiomyopathy), or when it is difficult to monitor drugs like flecainide/sotalol etc.



**FIG. 2** Treatment algorithm for management of Ectopic atrial tachycardia (EAT).<sup>1</sup> In small children with severe LV dysfunction (EF <20%) short term amiodarone (<1 yr) can be used to control the tachycardia. RF ablation can be performed for these children if the tachycardia continues to occur at a later age. Older children (>15 kg) can have a RF ablation at the first instance or treated with amiodarone as in small children.<sup>2</sup> Amiodarone is highly successful in managing EAT and thus improving LV dysfunction. If the tachycardia does not get controlled with amiodarone, RF ablation can be performed even in small infants.<sup>3</sup> Once LV function normalizes, a trial of  $\beta$ -blocker  $\pm$  Digoxin, or Flecainide/Sotalol can be given till either the tachycardia spontaneously disappears (upto 30%), or RF ablation can be performed safely.

Some of the key concepts regarding antiarrhythmic drugs are given in **Box 2**.

**DRUGS IN INTENSIVE CARE SETTING**

**1. Dopamine**

Dopamine causes  $\beta$  adrenergic stimulation resulting in positive chronotropy, inotropy and dromotropy.

*Indications:* Infusion is indicated in acute decompensated heart failure, cardiogenic shock, septic shock and to improve renal perfusion. Dopamine is used routinely for low cardiac output

syndrome after open heart surgery for congenital and acquired heart defects. It is also useful for birth asphyxia and myocardial ischemia, as seen in newborns(60,61).

*Dose:* Dopamine is given as a continuous IV infusion. In the dose of 2-5 mcg/kg/min, it exerts effect on dopaminergic receptors which are present in renal, splanchnic, and coronary vascular beds producing vasodilatation. These effects are not antagonized by beta blockers. The increased renal blood flow results in diuresis and natriuresis(62). At higher doses, 5-10 mcg/kg/min, it is a pure  $\beta$  agonist, producing positive inotropic effect on the heart. At doses of >10 mcg/kg/min, it exerts alpha agonistic action, resulting in vasoconstriction. The usual starting dose is 5 mcg/kg/min; increased gradually, if required, up to a maximum of 20 mcg/kg/min.

*Side effects:* May produce tissue necrosis with subcutaneous infiltration; a large vein should be used

**BOX 2** KEY CONCEPTS IN MANAGEMENT OF ARRHYTHMIAS

- Verapamil
  - (a) Not to be used in neonates with SVT; it could lead to cardiogenic shock.
  - (b) Not to be combined with beta blockers at any age.
  - (c) Not to be used in broad QRS tachycardia, due to the risk of electromechanical dissociation.
- In a hemodynamically unstable child with tachyarrhythmia, cardiovert with direct current irrespective of underlying mechanism of arrhythmia.
- Therapy with drugs like amiodarone, flecainide, sotalol or propafenone should always be initiated in the hospital setting, preferably initiated by a cardiologist/ electrophysiologist well acquainted with these drugs.
- It is advisable to refer resistant cases to experts or to a centre with expertise in arrhythmias.
- Amiodarone is very effective for treatment of tachyarrhythmias, but produces frequent, serious side effects and is best avoided for long term use.
- Flecainide is also very effective, its use should be encouraged in those with no or minor underlying structural heart disease and normal myocardial function.

for infusion. Tachycardia and ectopic beats occur at high doses. Dopamine may worsen pulmonary hypertension and ventilation perfusion mismatch in the lung.

*Contraindications:* Avoid in tachyarrhythmias unless these can be corrected rapidly. Pheochromocytoma and hyperthyroidism are other contraindications.

*Monitor:* The heart rate and BP should be closely monitored and dose of dopamine titrated accordingly. Urine output is an excellent marker of cardiac output and must be measured in all critical cases on dopamine infusion.

## 2. Dobutamine

Unlike dopamine, dobutamine is a synthetic sympathotometic agent and has a pure positive inotropic effect on myocardium by stimulation of alpha and beta receptors directly. Dobutamine produces a reduction in systemic vascular resistance with only a modest increase in heart rate, its main advantage over dopamine. The BP is also not much affected.

*Indications:* Indicated in acute heart failure, low cardiac output state after open heart surgery, neonates with asphyxia, myocarditis and after open heart surgery.

*Dosage:* Given as continuous IV infusion in dose of 5-15 mcg/kg/min. The maximum dose is 20 mcg/kg/min. The drug must be diluted adequately (not less than 5mg/mL concentration). Infusion should be gradually tapered after 48-72 hours of administration. In cases with low BP, dopamine or noradrenaline infusion may be used concomitantly with dobutamine.

*Side effects:* Like dopamine, dobutamine also produces increase in heart rate and ectopic beats, albeit to a lesser extent. High dose infusion may result in hypotension due to vasodilatation.

*Contraindications:* Contraindicated in obstructive lesions of heart, cardiac arrhythmias. Hypovolemia must be corrected prior to dobutamine administration.

*Monitoring:* BP, heart rate and ECG

## 3. Milrinone

Milrinone is a selective inhibitor of phosphodiesterase III, thereby increasing levels of cyclic AMP. It produces a positive inotropic effect on myocardium and a vasodilatory effect on systemic and pulmonary vasculature. These favorable changes occur without a concomitant increase in myocardial oxygen consumption. Additional effects include augmentation of ventricular relaxation (lusitropic effect), anti-ischemic effect on myocardium and inhibition of proinflammatory cytokines.

*Indications:* Indicated for heart failure, especially in post operative setting following cardiac surgery(63-65). Milrinone infusion is also indicated in acute heart failure due to other etiologies, like dilated cardiomyopathy.

*Dosage:* Milrinone is given IV, as 25-50 mcg/kg bolus over 10 minutes, followed by infusion at 0.25-0.75 mcg/kg/min.

*Side effects:* Arrhythmias including ventricular ectopics, non sustained VT. Other side effects include hypotension, hypokalemia, angina (in older patients) and tremor. The incidence of thrombocytopenia is much less compared to that with amrinone infusion.

*Contraindications:* Milrinone should be used with caution in presence of hypotension. It is contraindicated in severe obstructive lesions like aortic or pulmonic stenosis.

*Monitor:* Heart rate, BP and ECG.

## 4. Adrenaline/Epinephrine

Adrenaline increases BP, heart rate and cardiac output in a dose dependent manner. It is also a potent bronchodilator.

*Indications:* Post cardiac surgery, in the management of low cardiac output syndrome, during cardiac resuscitation. Life saving for acute exacerbation of bronchial asthma and in anaphylactic shock.

*Dose:* Adrenaline is given as an IV infusion. At a

dose of 0.05-0.3 mcg/kg/min, adrenaline exerts only beta 1 and 2 effect, thereby increasing cardiac output and heart rate without vasoconstriction. It may produce vasodilation due to its effect on B<sub>2</sub> receptors. At a higher dose, 0.3-1.0 mcg/kg/min, both alpha and beta effects are seen. At further higher dose (>1.0 mcg/kg/min) the alpha effect predominates resulting in vasoconstriction. Bolus dose is used for anaphylactic reaction and for acute bronchial asthma.

*Side effects:* Ventricular arrhythmias. Extravasation of infusion can produce skin necrosis; it should be infused through a large peripheral vein or through a central vein.

*Contraindications:* There are no absolute contraindications.

*Monitor:* Heart rate, BP, ECG and urine output.

### 5. Noradrenaline

Unlike adrenaline, it has predominant alpha adrenergic action, producing vasoconstriction.

*Indications:* Noradrenaline is indicated in septic and other types of shock, where systemic vascular resistance is low(66). Noradrenaline is sometimes used to raise BP after a BT shunt to facilitate flow through the shunt.

*Dosage:* 0.3-2mcg/kg/min infusion IV.

*Side effects:* These include increased myocardial oxygen demand and increased pulmonary vascular resistance. Skin necrosis occurs if drug extravasates.

### 6. Isoproterenol

Isoproterenol is a synthetic catecholamine and has selective effect on beta 1 and 2 adrenergic receptors. Tachyphylaxis develops on prolonged usage.

*Indications:* To increase heart rate in atrioventricular blocks, bradycardia, while waiting for pacing electrode to be inserted. It is also useful in post-operative pulmonary hypertension with or without right heart failure, as it is a pulmonary vasodilator.

### 7. Sodium Nitroprusside

Sodium nitroprusside is a nitric oxide donor and has a potent, short acting vasodilator effect on venous

and arterial beds. It has a very fast onset and a very short duration of action, enabling its use in critical care setting.

*Indications:* Systemic hypertension e.g. after repair of coarctation of aorta, malignant hypertension of renal vascular origin; acute, severe valvular regurgitation(67,68); low cardiac output state following cardiac surgery, especially after valvular surgery; and, acute heart failure.

*Dosage:* It is advisable to start with a low dose, 0.5mcg/kg/min IV infusion. The dose can be gradually titrated according to improvement in symptoms, status of BP, filling pressures, to a maximum of 10mcg/kg/min.

*Side effects:* Main side effect is hypotension. Other side effects include acute increase in intracranial pressure, headache, dizziness, palpitations and sweating. Cyanide poisoning can occur on prolonged use. It should not be combined with ACEi, other vasodilators and betablockers, as precipitous fall in BP may occur.

*Contraindications:* Contraindicated in severe hepatic and renal impairment, cyanide toxicity may develop earlier in these patients.

### 8. Nitroglycerine

Nitroglycerine is a powerful venodilator and a mild arteriolar and coronary vasodilator.

*Indications:* Post cardiac surgery for valvular regurgitation; cardiac surgeries where coronaries are involved, e.g. arterial switch operation, Ross operation and repair for anomalous left coronary artery from pulmonary artery; and, systemic hypertension.

*Dosage:* The initial dose is 0.5mcg/kg/min IV, it is up titrated depending on the response, to a maximum of 10mcg/kg/min.

*Side effects:* Hypotension, tachycardia, methemoglobinemia leading to cyanosis, acidosis, convulsions and coma.

*Contraindications:* Hypotension, hypoxia, hypertrophic cardiomyopathy, hypersensitivity to nitrates.

Nitroglycerine should not be combined with ACEi and betablockers, as severe hypotension may occur.

**9. Phenoxybenzamine**

It is a long acting alpha receptor blocker producing vasodilatation. It also reduces pulmonary artery pressure, even in neonates(69). Phenoxybenzamine has a long half life and may result in severe hypotension.

*Indications:* For postoperative pulmonary artery hypertension. It is also used in pheochromocytoma.

*Dosage:* 1mg/kg bolus given IV over 30 min, followed by 0.5-1mg/kg/day infusion

*Side effects:* Hypotension, reflex tachycardia, dryness of mouth.

**10. Vasopressin**

Arginine vasopressin is a vasoconstrictor. It is used in cases with refractory hypotension after conventional drugs have failed. It has also been used for heart failure. Vasopressin is particularly useful in vasodilatory shock; the classical example is septic shock.

*Dosage:* It is given as IV infusion at a dose of 0.0003-0.006 units/kg/min.

*Side effects:* Splanchnic ischemia due to its vasoconstrictor action.

**11. Nitric Oxide**

Inhaled nitric oxide is a potent pulmonary vasodilator with no effect on systemic vasculature. Therefore, its main role is in treatment of pulmonary arterial hypertension. The effect is usually dose dependent.

*Indications:* Pulmonary hypertension of the newborn;

Persistent pulmonary hypertension after correction for congenital heart disease, especially when there is difficulty in coming off bypass or wean off ventilator: It is also used to test for operability in shunt lesions with high pulmonary vascular resistance.

*Dosage:* Delivered along with oxygen, through the ventilator circuit, in a dose of 5-80 ppm. The starting dose is 5-20 ppm and it is gradually increased depending on the response. Nitric oxide should not be used for long term, as it results in methemoglobinemia.

BP, pulmonary artery pressure, and arterial oxygen saturation should be monitored during therapy with nitric oxide.

**Box 3** Summarizes the drugs used in common cardiac conditions encountered in intensive care settings.

**BOX 3** MANAGEMENT ALGORITHM FOR VARIOUS SETTINGS IN INTENSIVE CARE UNIT

*Acute myocarditis/cardiomyopathy with cardiogenic shock*

- Dopamine infusion, increase dose if necessary
- Add adrenaline if hypotension persists
- If BP acceptable, add milrinone (avoid loading dose) or dobutamine

*Acute mitral or aortic regurgitation (infective or traumatic)*

- Use sodium nitroprusside infusion, invasive BP monitoring is preferable

*Pulmonary hypertension of the newborn*

- Raise BP by using dopamine/dopamine plus dobutamine infusion
- Add milrinone in place of dobutamine if BP is in acceptable range, as milrinone is a pulmonary vasodilator.
- Add inhaled nitric oxide if available
- Continue with other measures like high frequency respiration and surfactant therapy.

*Septic shock*

- IV infusion of isotonic saline or colloid boluses
- Correct hypoglycemia, hypocalcemia
- If still hypotensive, start dopamine infusion, gradually increase the dose
- If still hypotensive, add adrenaline or noradrenaline infusion
- Vasopressin infusion in refractory cases.

**OTHER DRUGS**

**1. Intravenous Immunoglobulins (IVIg)**

IVIg is an immunomodulator, affecting function of B and T lymphocytes. It is known to neutralize pathogenic antibodies and suppress the synthesis of antibodies.

**Kawasaki disease (Class I) Myocarditis/ cardiomyopathy:** No randomized controlled trials are available. In adults with myocarditis, no significant improvement with seen with IVIg(70). Drucker et al reported a better, albeit non significant, survival with IVIg in suspected myocarditis in children(71). IVIg may be useful in initial stage of viral replication. IVIg may be considered in cases where onset of symptoms is preceded by a viral illness, or history is short (<3 months duration) or cardiac enzymes are elevated (*Class IIa*). Some physicians use IVIg in all infants <1 year of age with idiopathic left ventricular dysfunction (*Class IIb*).

**Acute rheumatic fever:** IVIg has been used to counter inflammation in acute rheumatic fever(72). However no clear benefit has been shown and it is not indicated for rheumatic fever (*Class III*).

**Dosage:** For Kawasaki disease, the dose is 2gm/kg given over 8-12 hours period. The treatment should be given within 10 days of onset of illness, preferably within 7 days (*Class I*). If active inflammation persists beyond 10 days in the form of persistent fever, raised ESR and C-reactive protein, or presence of coronary aneurysms, IVIg can be given (*Class IIa*). IVIg is not indicated in Kawasaki after 10 days if there are no signs of ongoing inflammation or coronary aneurysms (*Class III*). IVIg is also indicated in incomplete Kawasaki disease with echocardiographic demonstration of coronary aneurysms (*Class I*) or with normal echocardiography (*Class IIb*). In non responders or partial responders, a second course of IVIg may be given after 48 hours. For myocarditis, the dose is same i.e. 2gm/kg, however it is generally given over 2 days as the volume of fluid is too much in the presence of ventricular dysfunction.

**Side effects:** IVIg is a relatively safe drug. The side effects are primarily related to hypersensitivity

reactions and include fever, chills, nausea, vomiting, headache, malaise.

**Contraindications:** IVIg is contraindicated in patients with hypersensitivity to blood products, and in those with IgA deficiency. Relative contraindications include previous thrombotic episodes and sepsis.

**Interactions:** Live vaccines like measles, MMR and chicken pox should be postponed for at least 3 months after IVIg has been administered, recommended interval is 11 months. Similarly IVIg should be avoided for 3 weeks after a live vaccine has been given.

IVIg is available as 0.5, 2.5, 3, 5, 6 and 10 gm preparation. Its availability has been a problem recently and it is quite expensive.

**2. Sildenafil**

Sildenafil is a phosphodiesterase inhibitor. It potentiates the vasodilatory effect of nitric oxide and prostacyclines.

**Indications:** Idiopathic pulmonary artery hypertension (*Class I*); pulmonary hypertension secondary to connective tissue disorders (*Class I*); Eisenmenger’s syndrome, if arterial saturation is < 85% or right ventricular dysfunction is present or patient is in NYHA class III or IV (*Class IIa*); and, postoperative pulmonary hypertension with no residual defect (*Class IIa*); Pulmonary hypertension of the newborn (*Class IIa*).

Sildenafil should not be used in large left to right shunts with hyperkinetic pulmonary hypertension, obstructive total anomalous pulmonary venous connection, parenchymal lung lesion leading to pulmonary hypertension (*Class III*). Children with Down’s syndrome may have severe pulmonary hypertension due to upper air way obstruction and chronic hypercapnia, sildenafil should not be used in them (*Class III*).

**Evidence:** Several randomized trials on use of sildenafil in pulmonary hypertension have been reported; almost all have shown improvement in NYHA class, quality of life, six minute walk distance and cardiac output(73-76). Its benefit has also been



reported in Eisenmenger syndrome(77). A recent meta analysis(78) concluded that sildenafil may be useful in treatment of postoperative pulmonary hypertension after pediatric heart surgery.

**Dosage:** 0.5-5mg/kg/day in 3 or 4 divided doses; dose reduction is required in renal and hepatic disease.

**Side effects:** Most important side effects are due to vasodilation and include flushing headache, nasal congestion, dizziness and hypotension, painful erection. Ocular side effects include blurred vision, increased light perception. There are reports of seizures, myalgia, transient ischemic attacks, amnesia and stroke.

**Contraindications:** Sildenafil should not be combined with nitric oxide or nitrates due to risk of severe hypotension. Relative contraindications include thrombocytopenia. Due to increased risk of bleeding, antiplatelet agents should not be used with sildenafil.

**Alert:** Parents and patients must be told not to discontinue drug abruptly. The dose should be gradually increased, initiating with a small dose.

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**Disclaimer:** These recommendations are for use by the physicians only and are not to be used for medico-legal purposes.

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