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RECENT TRENDS IN MANAGEMENT OF HEART FAILURE

* Neeraj Awasthy
** Savitri Shrivastava

Abstract: Heart failure (HF) refers to a clinical state of systemic and pulmonary congestion resulting from inability of the heart to pump as much blood as required for the adequate metabolism of the body. Identification of the etiology of the heart failure and selective and optimal therapeutic approach, with care of precipitating factors forms ideal approach to a heart failure. With the rapid pace of development of human medicine, one should be well aware of new drug development and optimize the use of classical medicines. This article aims to review recent developments in the management of heart failure in children.

Keywords: Heart failure, Children, Newer drugs

Heart failure (HF) 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 case of children, this requirement includes “growth and development”. To optimize the outcome one should have a sound knowledge of common cardiovascular drugs and formulate protocols to optimize the clinical management of these patients. At the same time one should be alert to new drug developments and be willing to modify one’s approach to drug therapy as new information is available. This article attempts to fulfill the latter objective.

Pathophysiology and diagnostics of CHF: Target for therapeutics

Diagnostics: Search for the anatomical cause forms the most important aspect of evaluation of a child with HF. Precipitating causes like rheumatic activity, infective endocarditis, intercurrent infections, anemia, electrolyte imbalances, arrhythmia, drug interactions, drug toxicity or non-compliance and other systemic disturbances etc should also be carefully looked for.

Therapeutics: The basic requirements for rational drug therapy are: 1) Complete correct diagnosis (anatomical and pathophysiological cause of CHF) - This forms the most important aspect particularly in pediatric population. With timely diagnosis and intervention of various conditions viz critical stenotic lesions, shunt lesions, anomalous left coronary artery from pulmonary artery (ALCAPA), hypocalcemia, dramatic improvement is achieved 2) Clear understanding of pharmacology of various drugs available (includes pharmacokinetics, drug dosages, potential efficacy and side effects), 3) Meticulous monitoring of patient for therapeutic end points and side effects 4) Readiness to modify or change the drug therapy if ongoing treatment is not effective or unacceptably toxic.
Supportive care measures are extremely important

1) Airway and oxygen therapy, proper position and airway management is essential to keep it patent and to clear the secretions. Assisted mechanical ventilation may be needed in some patients to help in stabilizing hemodynamics by decreasing the work of breathing, 2) Maintenance of homeostasis: warm environment, care of metabolic derangements, 3) Nutritional care, 4) Treatment of precipitating factors: intercurrent infections, infective endocarditis, anemia, electrolyte imbalances, hypo/hyperthyroidism, arrhythmias, rheumatic activity and drug toxicity.

Hemodynamic monitoring

Invasive hemodynamic monitoring may be needed in the following patients with acute decompensated HF (Class IIa)

1)patients with uncertain fluid status, perfusion, systemic or pulmonary vascular resistance 2)persistent symptomatic hypotension 3)worsening renal function 4)patients who require parenteral vasoactive agents.

Pharmacological intervention

Drug therapy has to be individualized as per clinical setting A-D which have been adapted from consensus guidelines. Commonly used drugs are given in Table I.

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 rhythm. There is no role for 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. ACE inhibitors, beta blockers (Class I indication) are to be used particularly when dysfunction sets in these cases.

Clinical setting C: Patients with past or current symptoms of heart failure (commonest group). Diuretics, ACE inhibitors and digoxin main line of therapy in this subgroup.

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 ACE inhibitors should not be used (Class III).

Conventional drugs

Whatever new is new, we still stand by our old friend.

1. Digoxin: This glycoside has been shown to improve symptoms and signs of HF even if the ventricular function is not very much affected or disturbed, as it has actions other than inotropic effect in the form of neurohormonal activation, improvement in baroreceptor function, increased vagal tone, sympathoinhibitory effect, decreased circulating norepinephrine levels, and possibly aldosterone antagonistic effects. However, it has not been shown to provide survival benefit in adults or in children. Lower dose may reduce the incidence of side effects and toxicity. Higher digitalis levels can cause increased mortality.
Table I. Dose and available formulation of commonly used drugs for heart failure

Mg = milligram, gm = gram, μg = microgram, amp = ampoules
2. **Diuretics:** Diuretics are currently recommended for all patients with HF who have volume overload of the ventricle. Diuretics from different groups (a-c) can be combined for greater efficacy: (a) Loop diuretics: eg. furosemide, torsemide. (b) Thiazides: viz hydrochlorothiazide and metolazone. (c) Aldosterone antagonists: eg spironolactone and eplerenone.

**Furosemide** is beneficial for symptomatic relief.

**Torsemide** is a loop diuretic more potent than furosemide, (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 HF.4

**Thiazides:** These are relatively milder diuretics (except for metolazone) primarily used in mild hypertension and edema. Metolazone is ten times more potent than hydrochlorothiazide, useful in resistant cases of hypertension and HF. Intermittent doses of metalozone may help to overcome diuretic resistance which may occur due to fluid overload, mesenteric congestion (inadequate absorption) and low renal blood flow.

**Spironolactone:** This aldosterone blocking agent has been shown to improve survival in adult patients with HF. Usually it is given in conjunction with furosemide as it is potassium sparing and has additive action as diuretic. Small observational studies using spironolactone5 in children have shown benefit in controlling HF.

3. **Vasodilators: angiotensin converting enzyme inhibitors (ACEi)**

ACEi decrease the adrenergic drive and blocks activation of renin angiotensin aldosterone system (RAAS). ACEi therapy can be used as the first line treatment for HF, when it is not secondary to an obstructive lesion. Improvement in symptoms and survival has been shown in adults with symptomatic HF on ACEi.6 Enalapril is commonly started with 0.1 mg/kg/dose and increased gradually to a maximum of 0.5 mg/kg dose. Lisinopril is another useful drug. High dose of lisinopril was more beneficial than a low dose (ATLAS trial).7 One must up titrate the dose to the maximum tolerable permissible dose. Several small observational studies have proven the efficacy of these drugs in children and survival benefit with ACEi has been shown in children with idiopathic dilated cardiomyopathy. ACEi have been found to be useful in valvular regurgitation, large left to right shunts, if the systemic vascular resistance is elevated at the baseline and myocardial dysfunction (without obstruction). As it can cause hyperkalemia, it should not be given along with spironolactone.

**Hydralazine:** It is a non ACEi peripheral vasodilator that does not produce hyperkalemia, and is safe in patients with renal impairment. It should be used in patients in whom ACEi are not tolerated or contraindicated with a starting dose of 0.75 mg/kg/ day which may be increased gradually up to maximum of 5mg/kg/day in four divided doses.

4. **Angiotension receptor blockers (ARB)**

ARB are competitive antagonists for the angiotension II receptors. A meta analysis of randomized trials in adults did not show any advantage of ARB over ACEi. Studies in children are in progress. A combination of ACEi and ARB is currently not recommended in pediatric patients.8

5. **β blockers**

Several studies have shown the benefits of beta blocker therapy in adult patients with HF. Carvedilol has been shown to decrease mortality and risk of clinical progression of HF. It improves functional class and fractional shortening in
children with ventricular dysfunction. In the first multi centre, randomized, double blind, placebo controlled trial for carvedilol in children there was no statistically significant difference due to unexpectedly low rate of events for patients in worsened category and trial may have been underpowered.9

Various new drugs are in various stages of clinical application (Table II). Other new drugs which are still experimental include adenosine antagonists, nitric oxide modulators, natriuretic peptides, xanthine oxidase inhibitors.

**Inotropic agents (acute decompensated HF)**

Current generation inotropes include catecholamines, either endogenous (epinephrine, norepinephrine and dopamine) or synthetic (dobutamine, isoproterenol) and afterload reducing agents milrinone, nitroglycerine. All these drugs increase metabolic demands, induce maladaptive remodeling and also are proarrhythmic secondary to accumulation of calcium. Newer agents aim to prevent the same, which includes calcium channel sensitizers, nestritide, cardiac myosin activators, Na/K ATPase inhibitor- Istaroxime, (Table II). Despite the standard pharmacotherapy, some children and young adults with HF remain in a chronic decompensated state requiring intravenous inotropes and vasodilator medications. Some of these patients with end-stage HF become inotrope-dependent, and are candidates for newer therapies like ventricular assist device and also cardiac transplantation.

**Other drugs**

**Intravenous immunoglobulins (IVIg)**

IVIg is an immunomodulator, affecting function of B and T lymphocytes and is known to neutralize pathogenic antibodies and suppress their synthesis.2 Drucker, et al reported a better, albeit non significant,survival with IVIg in suspected myocarditis in children. IVIg may be useful in the initial stage of viral replication especially 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) however its use in idiopathic left ventricular dysfunction remains controversial. IVIg is contraindicated in patients with hypersensitivity to blood products and in those with IgA deficiency. Relative contraindications include previous thrombotic episodes and sepsis. Live vaccines should be postponed for at least 3 months after IVIg has been administered and the recommended interval is 11 months. Similarly IVIg should be avoided for 3 weeks after a live vaccine has been given.2

**Anticoagulation**

Dilated cardiomyopathy or myocarditis with HF predisposes to stroke and pulmonary embolism. Those with gross HF should receive oral anticoagulants (Class I). Oral anticoagulants are also preferred for other children with cardiomyopathy who have significant ventricular dysfunction (LVEF < 20 %) (Class IIa). The target INR is kept between 2.0 and 3.0. If intracavitary thrombus or marked dilatation of atrial with spontaneous contract is present, anticoagulant therapy is again warranted (Class I).2

**Non pharmacological intervention:**

**Mechanical interventions and devices**

**Ultrafiltration:** UNLOAD trial (ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated congestive HF) showed ultrafiltration (UF) caused more weight loss than conventional medical therapy but dyspnea assessment indicated similar scores in both the groups. UF was associated with 50% reduction in number and length of
Table II. Newer drugs for heart failure*

<table>
<thead>
<tr>
<th>New Drugs</th>
<th>Mechanism of action</th>
<th>Advantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Calcium Sensitizing drugs</td>
<td>Binding to calcium saturated N-terminal domain of calcium troponin C-stabilizing &amp; prolonging the lifespan of cardiac Troponin C without impairment in filament relaxation. Anti ischemic effects - opening ATP dependent potassium channels.</td>
<td>No inc. myocardial O$_2$ consumption, not arrhythmogenic, dec. the levels of endothelin - peripheral and coronary vasodilatation.</td>
<td>European trials have shown benefit in acute state in children in DCM and after cardiac surgery. prospective studies needed RUSSLAN trial – showed benefit</td>
</tr>
<tr>
<td>Levosimindan</td>
<td></td>
<td></td>
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<tr>
<td>Pimobendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Nesiritide (human type B naturitic peptide)</td>
<td>Systemic vasodilator, modest naturitic properties &amp; exerts its effects by binding to the guanylate cyclase receptor on endothelial and smooth muscle cells</td>
<td>Can increase cardiac output and dec LV filling pressures.</td>
<td>Limited data in pediatric patients. Dose: 2 ìg/kg stat; then 0.01ìg/kg/min( 0.005 - 0.03) has been used</td>
</tr>
<tr>
<td>Cardiac myosin activators</td>
<td>Accelerate myocardial myosin ATP ase and does not alter intracellular calcium.</td>
<td>Betablockade does not alter inotropic effect</td>
<td>Uncouples contractility and chronotropy.19</td>
</tr>
<tr>
<td>3 Istaroxime</td>
<td>Nonglycoside Na/K ATP ase inhibitor</td>
<td>Lesser tachycardia than dobutamine</td>
<td>Uncouples inotropy and arrhythmogenecity. It has rapid onset and decay of effect</td>
</tr>
<tr>
<td>4 Ibopamine</td>
<td>Oral drug stimulating dopaminergic type 1 and 2 receptors Primary effects on peripheral and renal dilatation</td>
<td>Little inotropic or proarrhythmic effects.</td>
<td>PRIME 2 trial comparing its efficacy with a placebo stopped prematurely because of the adverse effect.</td>
</tr>
<tr>
<td>5 Vasopressin receptor antagonists</td>
<td>Excess circulating plasma vasopressin is one of the maladaptive responses to HF. V2 receptor antagonism facilitates aquarexis of mainly electrolyte free water, produces sustained diuresis</td>
<td>No activation of RAAS compared to frusemide less reduction in sodium and increase in serum creatinine than equipotent</td>
<td>Significantly increases in 24 hour urine volume and decreases body wt compared to placebo Dual (V1a&amp;V2): Conivaptan, SelectiveV1: Relcovaptan Selective V2: Tolvaptan, Lixivaptan, Mozavaptan, Satavaptan, Tolvaptan</td>
</tr>
<tr>
<td>Urodilatin</td>
<td>Renally synthesized(DCT) isoform of ANP, which is resistant to biological inactivation by neural endopeptidase</td>
<td>Significant diuresis</td>
<td>Produced hypotension(16%) It did not alter 30 day survival or improve renal function</td>
</tr>
<tr>
<td>7 NEP inhibitors</td>
<td>Prevents break down of endogenous ANP. Oral forms of NEP are available</td>
<td>NEP inhibitor that inhibits ACE also.</td>
<td>Drugs currently under evaluation are candoxatril, ecadotril, omapatrilat</td>
</tr>
<tr>
<td>Metabolic modulator-Perhexiline</td>
<td>Promotes glucose utilization through inhibition of carnitine palmitoyl transferase 1, an enzyme critical to mitochondrial uptake of free fatty acids (FFAs)</td>
<td>Developed as antianginal, Glycolysis requires 15% less oxygen than FFA oxidation.</td>
<td>Significant benefits in the form of increase in ejection fraction and peak exercise oxygen consumption, Improved quality of life and but it requires monitoring of serum levels</td>
</tr>
<tr>
<td>New Drugs</td>
<td>Mechanism of action</td>
<td>Advantages</td>
<td>Comments</td>
</tr>
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<td>---------------------------</td>
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</tr>
<tr>
<td>10 Endothelin antagonist*</td>
<td>There are no safety or efficacy data in children and use in children should elicit concern in view of hepato toxicity.</td>
<td>Progressive LV dysfunction, pulmonary edema, LV remodeling, fetal gene expression, &amp; cardiomyopathy.</td>
<td>Trials with etanercept, a soluble recombinantly produced chimeric TNFα antagonist &amp; Infliximab, a monoclonal antibody against TNFα are underway for treatment of heart failure in adults</td>
</tr>
<tr>
<td>11 Anti cytokine drugs (eg anti TNF α)*</td>
<td>Elevated levels of inflammatory cytokines have been associated with HF in children. Many aspects of HF can be explained by the known biologic effects of this cytokine</td>
<td>Role of MMPs in cardiac fibrosis and the progression of HF, along with the possibility of halting the progression of HF by modulating extracellular matrix remodelling are important issues under intense experimental study.</td>
<td>Upregulation of GRKs may be connected to the desensitization &amp; down-regulation of the beta-adrenoceptors in the failing heart, thus the antagonism is being studied as a potential target for HF.</td>
</tr>
<tr>
<td>12 MMP inhibitors</td>
<td>Members of the zinc-dependent MMPs play a role not only in degradation of the extracellular matrix, but also in acute regulatory processes</td>
<td>Effective in preventing the upregulation of renal AQP2 gene and protein expressions in HF</td>
<td>Treatment with Fosinopril (Fos), Valsartan (Val), and combination caused cardiac &amp; renal expression of AQP1 &amp; AQP2 in HF on rat model.</td>
</tr>
<tr>
<td>13 GRK antagonists</td>
<td>Phosphorylate only agonist-occupied receptors &amp; facilitate their binding to h-arrestins. h-Arrestins, prevent further receptor-G-protein activation, &amp; control of receptor endocytosis.</td>
<td>Involved in cardiomyocyte proliferation &amp; angiogenesis during cardiac development,</td>
<td>MAP kinase proteins may be redeployed therapeutically to enhance cardiac regeneration after myocardial infarction</td>
</tr>
<tr>
<td>14 Aquaporin protein (AQP) therapies</td>
<td>Effective in preventing the upregulation of renal AQP2 gene and protein expressions in HF</td>
<td>MAP kinase proteins may be redeployed therapeutically to enhance cardiac regeneration after myocardial infarction</td>
<td>No beneficial effects of Coenzyme Q 10 supplementation on the left ventricular ejection fraction, peak oxygen consumption, or exercise duration; drug is still experimental</td>
</tr>
<tr>
<td>15 Coenzyme Q 10</td>
<td>Improve energetics in myocardium by helping as an electron carrier in production of adenosine tri-phosphate, an antioxidant &amp; free radical scavenger with membrane stabilizing properties</td>
<td>MAP kinase proteins may be redeployed therapeutically to enhance cardiac regeneration after myocardial infarction</td>
<td>No beneficial effects of Coenzyme Q 10 supplementation on the left ventricular ejection fraction, peak oxygen consumption, or exercise duration; drug is still experimental</td>
</tr>
</tbody>
</table>

(inc=increase, dec=decrease, ANP=atrial natriuretic peptide, NEP= Neutral endopeptidase inhibitors, MMP= Matrix metalloproteinases, GRK= G protein coupled receptor kinase, AQP=aquaporin, Coenzyme Q 10 (2, 3-dimethoxy-5-methyl-6-decaprenyl-1, 4-benzoquinone)

*not available in India
rehospitalization, and unscheduled medical visits for HF in adults. But there is paucity of data in children.\textsuperscript{10}

**Cardiac resynchronization therapy (CRT):** Dyssynchrony in myocardial contraction commonly occurs in patients with HF and left bundle branch block, leading to impaired LV function and worsening mitral regurgitation. CRT restores normal contraction to the LV wall while improving overall heart function. This should be considered after optimizing conventional pharmacological treatment. Indications for CRT for adults (are given in ACC guidelines 2009):\textsuperscript{11} In pediatric patients CRT has been successfully tried in post operative tetrology of Fallot patients with dysynchrony. Its long term benefit is yet to be established.\textsuperscript{12}

**Implantable defibrillator:** Antiarrhythmic medications have not been shown to decrease mortality in adults with HF and in some instances have actually had harmful effect. Many studies have shown that implantable defibrillator reduces the mortality in adults with HF. However, in patients who are thought to be at risk for life-threatening arrhythmias, one should consider placement of intra cardiac defibrillator in children e.g. long QT Syndrome.

**Continued positive airway pressure (CPAP):** In adult population CPAP is an effective treatment for sleep apnea seen with advanced HF. It improves LVEF, reduces urinary epinephrine levels and improves cardiac output.

**Assist device therapy:** Assist devices improve survival and quality of life of patients ineligible for a heart transplant. These also serve as a bridge to transplant and ventricular recovery. Since the early report of pneumatic paracorporeal ventricular assist devices in children, there has been increasing use of many devices such as the Berlin Heart VAD (Berlin Heart AG, Berlin, Germany), MEDOS-HIA-VAD (Helmholtz Institute, Aachen, Germany), Thoratec Ventricular Assist System (Thoratec Crop, Berkeley, California, USA), and Abiomed BVS-5000 (ABIOMED, Inc, Danvers, Massachusetts, USA) in children. Reports specifically addressing the outcomes for the longer term ventricular assist device implantation in children do not exit and what is known must be extrapolated from scattered experiences. As the number of pediatric patients requiring ventricular assist device support increases, the science of long-term mechanical circulatory support, cellular changes in cardiac remodeling and recovery and end-organ perfusion of pulsatile flow in pediatric patients will likely to be refined in the coming decade.

**Surgery:** Various surgical modalities have been proposed including mitral valve repair, left ventricular reduction, endovascular patch plasty, dynamic cardiomyoplasty, prosthetic restraint devices, but they still remain experimental.

Heart transplant in children of all ages is now accepted as a therapy for end-stage HF secondary to cardiomyopathy, hypoplastic left heart syndrome, failure of Fontan and palliated congenital heart disease when these diseases are life-threatening or are associated with a poor quality of life.\textsuperscript{13} However, the facility is not well established in India. The approach and the criteria of listing for heart transplantation in pediatric age are different from adults. Role of cardiopulmonary exercise testing is limited by lack of consensus and limited data, the adult value of peak oxygen consumption of 14 milliliter/kilogram/minute guideline does not hold true for children. The most important limitation is availability of donor heart for our growing population of HF in pediatric age group and the need for continued medication and its cost. Keeping these rare limitations in mind it is possible to use this rare resource to benefit as many children and their families as possible\textsuperscript{12}.
Genetic approach: Promising approach is still awaited

Gene transfer: These target at least 3 different biological pathways that play a crucial role in the pathophysiology of CHF and form the target for gene therapy. These include intracellular calcium signaling, $\beta_1$-adrenergic receptor ($\beta_1$-AR) signaling, and antiapoptotic signaling. Invivo over expression of SERCA2a, achieved by catheter injection of an adenovirus carrying the SERCA2a gene into the aortic root, restored systolic and diastolic function to normal levels. Intracoronary delivery of a recombinant adenovirus encoding ACVI $(1.4 \times 10^{12} \text{vp})$ improves global left ventricular function associated with reduction in LV remodeling in a large animal model of HF. Stem cell forms another promising future modality.

Many cell types have been successfully transplanted into damaged myocardium, including fetal cardiomyocytes, skeletal myoblasts, embryonic stem cells and bone marrow-derived stem cells. The best characterized of these is skeletal myoblast, an immature muscle cell that retains the ability to proliferate. Several studies have used human autologous skeletal myoblasts transplantation to determine if engraftment of these cells leads to long-term improvements in left ventricle function. However, these exciting progresses have many unanswered questions including potential arrhythmic and oncogenic potential of these cells, which can only be resolved by larger clinical trials with long-term follow-up which are not yet available.

In summary, standard therapy of vasodilators, diuretics, digitalis, ACE inhibitors and beta blockers form the backbone of HF therapy. Innovative interventions directed at the failing heart are being explored. Newer drugs and assist devices still are on the horizon particularly in children and these need more research and evaluation.

Points to Remember

- Etiology of heart failure (HF) in children and its management remains central to the management of HF in children.
- Management of precipitating cause is the most important adjunct in HF management.
- Newer drugs serve as an important upcoming modality but their usage and availability in children remain elusive.
- Optimization of the classical drug therapy is warranted in HF.

References


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**Clippings**


Infant regulatory problems, that is, excessive crying, feeding and/or sleeping difficulties, are precursors of adverse development. However, the etiology of regulatory problems is still unclear. The aim of this study was to investigate pre-, peri- and post-natal neurophysiological and psychosocial predictors of single and multiple regulatory problems at 5 months of age. This prospective longitudinal study included all children born at neonatal risk in a geographically defined area in southern Germany. The outcome measures used were single and multiple regulatory problems, that is, crying, feeding and/or sleeping difficulties at 5 months of age, which were assessed via a standardized interview with the parents by study pediatricians as part of a neurodevelopmental examination.

Very preterm birth was predictive of single feeding (OR 1.79; 95% CI 1.25–2.55) and multiple regulatory problems (OR 2.03; 95% CI 1.19–3.46), and foetal abnormalities increased the odds of single feeding and multiple regulatory problems from 1.53- to 1.64-fold. Family adversity and psychosocial stress factors were associated with single crying and multiple regulatory problems. Pre-, peri- and post-natal neurophysiological and psychosocial factors are predictive of single and multiple regulatory problems. The results may be useful in terms of early recognition of at risk groups for regulatory problems.
MANAGEMENT OF COMMON ARRHYTHMIAS IN CHILDREN

* Prem Sekar R

Abstract: The common arrhythmias that a paediatrician is likely to encounter in his clinical practice are the paroxysmal supraventricular tachycardias (PSVT). Of these, AV reciprocating tachycardia (AVRT) is predominantly seen in infancy while AV nodal re-entrant tachycardia (AVNRT) and paroxysmal junctional reciprocating tachycardias (PJRT) occur in the school going age group. The non-paroxysmal supraventricular tachycardias, ventricular arrhythmias and complete heart block are infrequent in children. A clear understanding of the mechanisms that initiate rhythm disturbances namely re-entry, automaticity and block as well as knowledge of the characteristics of myocardial and accessory tissues would enable optimal management of any arrhythmias.

Keywords: Re-entry, Arrhythmias, Radio frequency ablation, Pacemaker.

In children, symptomatic arrhythmias commonly tend to be paroxysmal supraventricular tachyarrhythmias (PSVT) while ventricular tachyarrhythmias (VT) are rare. The common PSVT are AV reciprocating tachycardia (AVRT), Atroventricular nodal re-entrant tachycardia (AVNRT) and Permanent junctional reciprocating tachycardia (PJRT). Of these AVRT is the most frequent PSVT in early life, accounting for 85% of arrhythmias in fetal life and 82% in infancy. Up to 60% of AVRT resolve spontaneously by the end of infancy and the subsequent incidence decreases by 65% in the 1-5 age group, 56% in the 6-10 age group and 68% in the above 10 years age group.1 Wolf-Parkinson White (WPW) syndrome is a typical example of AVRT. AVNRT is commoner in the school going age group with an incidence of about 23% in the 1-5 age group, 34% in the 6-10 age group and 20% in those over 10 years of age. PJRT is usually seen in the 3-4 year age group. All these tachyarrhythmias are paroxysmal (sudden onset) as they are mediated by accessory tissue and the underlying mechanism is re-entry. Accessory pathways are a result of embryological developmental anomalies that allows some atrial fibers to penetrate the ventricular myocardium across the atrio-ventricular (AV) fibrous barrier, other than at the AV node. As these fibers conduct electrical impulses faster than the AV node, they form an alternate pathway through which earlier excitation (pre-excitation) of the ventricles occur. The presence of two pathways with differing electrical characteristics facilitates re-entry. The non-accessory pathway mediated (non-paroxysmal) SVT commonly observed in children are Junctional ectopic tachycardia (JET) and Ectopic atrial tachycardia (EAT). Automaticity is the underlying mechanism of these arrhythmias and is commonly seen in patients after surgical repair for congenital heart disease. These are characterized by a slow onset and slow termination, unlike the paroxysmal tachycardias. Ventricular tachyarrhythmias (VT) in children are seen in association with Long QT
syndrome (LQTS), Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM), Brugada syndrome and post cardiac surgery.

Complete heart block (CHB) and Sick sinus syndrome are the bradyarrhythmias of note in children. CHB is usually congenital with an incidence of 1 in 25,000 live births\(^1\) and infrequently sequelae to cardiac surgery. The underlying mechanism is block to conduction of electrical impulse. Sick sinus syndrome results from an abnormality in impulse formation and conduction. This may occur after surgery for closure of atrial septal defects, Senning/ Mustard procedures, Fontan surgery and rarely be congenital.

To understand management of arrhythmia, it is required to be familiar with

- Basic electrophysiology of myocardial cell and conducting system in the heart,
- Mechanism and location of the arrhythmias
- Characteristics of the anti-arrhythmic drugs, and
- Non pharmacological modalities of arrhythmia management.

Cardiac tissue characteristics

The heart has two types of cells. Those responsible for contraction and those for impulse formation & conduction. The conduction system is formed of the Sino-Atrial (SA) node, the atrial internodal tracts, the Atrio-Ventricular (AV) node, the His bundle and the purkinje system. The contractile cells are the myocardial cells and are activated by electrical impulses from the purkinje fibers. There are important differences between the conducting and contractile cells. Histologically, the conducting system is modified cardiac tissue with no contractile elements. It can conduct and also initiate electrical impulses. Initiating an electrical impulse is owing to a special ability of all cardiac cells to undergo spontaneous depolarization, the rate of which is higher, the higher the tissue is positioned in the conducting system. As the threshold for automaticity is highest in the sino-atrial (SA) node, it acts as the dominant pacemaker in a normal heart, with the AV node, the specialized fibers of the atria and the HIS-Purkinje fibers following in that order.

Cardiac cell electrical activity

The electrical activity from a single cell during depolarization and repolarisation is termed the action potential. The surface ECG represents the sum of the electrical activity of all cardiac cells. In the resting state of the cardiac cell, the Na\(^+\) K\(^+\) ATPase transmembrane ion exchange pump, located in the cell membrane, actively pumps Na\(^+\) out and K\(^+\) in to the cells. This maintains a resting membrane potential (RMP) of -90mv in HIS-Purkinje and working myocardial cells and a lower RMP of -60mv in the SA and AV node. Spontaneous depolarisation in the SA and AV node is facilitated by the lower RMP and the enhanced selective permeability of the cell membrane of these tissues to K\(^+\). This threshold being lowest in SA node tissue, it acts as the dominant pacemaker in a normal heart. Depolarisation in the non-conducting myocardial cells is initiated and governed by the wave of electrical impulses from the conducting system. The HIS-Purkinje cells and working myocardial cells use fast-sodium influx channels for depolarisation and are termed fast response cells whereas the SA & AV nodal cells undergo depolarisation due to a slow influx of calcium ions through calcium channels and are called slow response cells. Repolarisation restores the RMP of the cardiac cell by allowing K\(^+\) and Ca\(^{++}\) influx in to the cells and Na\(^+\) efflux with the help of Na\(^+\) K\(^+\) ATPase transmembrane ion exchange pump. Pharmacological control of arrhythmias is mainly dependant on alterations of these ion exchanges across the cardiac cell membrane.
Mechanism of arrhythmias

Re-entry phenomenon: In re-entry, the electrical impulse enters a tissue, depolarizes it and is able to re-enter the tissue again to depolarize it a second time. This is possible only when an accessory pathway combines with the existing normal conducting pathway to form an anatomical circuit where there is slow conduction in one limb of the circuit and a transient or permanent one-way block to electrical impulse in the other. The normal conducting pathway A has a slow conduction velocity with short recovery time while the accessory pathway B has a fast conduction velocity with long recovery period (Fig.1). This facilitates antegrade conduction across one limb of the circuit and retrograde conduction back to the atria along the other limb, thus setting up a fast, repetitive circuitous electrical movement. Re-entry can occur in the atrial tissue, the AV node or the ventricular tissue. It could be macro re-entry (circus type) as in AV reciprocating tachycardia, when the accessory pathway B is remote from the normal conducting pathway A or Micro re-entry (focal) when the two limbs of the circuit are formed by functionally dissociated pathways within the same tissue as in AV nodal re-entrant tachycardia.

In AVRT, as the conduction velocity through the accessory pathway B is faster than the nodal pathway A, a normal sinus impulse that encounters these two pathways would travel faster through the accessory pathway and activate the ventricle earlier. As the nodal pathway A also gets partially activated, no re-entry occurs and the surface ECG demonstrates pre-excitation (delta wave) with a short PR interval due to earlier excitation of the ventricular mass through the accessory pathway. If an ectopic beat were to occur in this setting, it would find the accessory pathway B non receptive because the refractory period of the accessory pathway B is longer than that of the nodal pathway A. Therefore, the ectopic beat would travel antegrade down the slower nodal pathway A. If after traversing the nodal pathway, this impulse finds the accessory pathway to have recovered and receptive, it would travel retrograde through the accessory pathway B to the atria thus initiating re-entry. This circus type, reciprocating movement similar to a dog chasing its tail, could go on repetitively as long as the electrical impulse encounters cells which have repolarised. A tachycardia using the slow A pathway for anterograde and fast B pathway for retrograde conduction is termed “Orthodromic”. The impulse, when it reaches the HIS bundle, spreads in an antegrade direction through the ventricles and again when it reaches atrial muscle spreads in a retrograde direction through the atria resulting in a retrograde P wave appearing after each antegrade QRS complex. In Orthodromic AVRT, the P wave is seen in the ST segment (Fig.2) whereas with AVNRT the P wave may not be seen as it may be buried in the QRS complex (Fig.3) since the retrograde activation of the atria is earlier. Up to 30% of AVRT tend to have a concealed pathway and the surface ECG does not exhibit delta wave or a short PR interval.

Automaticity is enhanced excitability causing the affected tissue to spontaneously depolarize at a rate higher than the SA node, rendering it the new dominant ectopic pacemaker.

Block is a mechanism by which the electrical impulses are not able to propagate due to block in transmission.

Anti arrhythmic drugs

The Vaughan Williams classification groups antiarrhythmic drugs in to

Class I- fast sodium channel blockers (Iₐ-quinidine, procainamide, disopyramide, Iₖ-lidocaine and Iₑ-flecainide, propafenone).
Fig. 1. Mechanism of re-entry.

Fig. 2. AVRT. Note the distinct P wave in the T wave following each QRS complex.

Fig. 3. AVNRT. P waves not easily identifiable. May be buried in the QRS complex.
Fig. 4. Junctional ectopic tachycardia. Rate about 180 bpm. Dots mark p waves. Ventricular contractions greater in number than atrial contractions.

Fig. 5. Complete heart block. Note the dissociation between p waves and QRS complexes.

Fig. 6. Regular pacing spike in a patient with complete heart block.
Class II- beta-blockers (propranolol)

Class III- Potassium channel blocker (amiodarone, sotalol, dofetilide, ibutilide)

Class IV – slow calcium channel blockers. (verapamil, diltiazem)

Class I drugs exert a membrane stabilising effect by impairing the entry of sodium in to the cell. This slows the rate of depolarization and reduces the excitability of atrial and ventricular tissue, allowing the SA node to regain dominance of the cardiac rhythm. Also, prolongation of the effective refractory period abolishes impulse re-entry. QT prolongation associated with this class of drugs can be proarrhythmic. The negative inotropic effects make it unsafe for use in patients with structural heart disease.

Class II drugs reduces sympathetic activity which are known to be pro-arrhythmic and also propagate re-entry mechanisms. Hence beta blockers are useful in treating arrhythmias associated with long QT syndrome, Mitral valve prolapse syndrome, anaesthetic agent and exercise induced arrhythmias. Beta blockade reduces the spontaneous firing rate of the SA node and ectopic pacemakers, prolongs intranodal conduction and also prolongs the refractory period of the AV node. This results in a negative chronotropic effect, reducing cardiac work. Beta blockers are effective in prophylaxis of SVT by inhibiting the initiating atrial ectopic beat.

Class III drugs reduce K+ efflux out of the cells thereby prolonging the repolarisation phase. This results in prolongation of the duration of action potential and refractoriness of the cardiac tissues. The time interval required for re-excitation is prolonged and hence arrhythmias are suppressed. The predominant advantage of this class of drugs is the indication to use them in the presence of left ventricular dysfunction. Significant QT prolongation and attendant risk of torsades is an adverse effect to be watched for.

Class IV drugs act by blocking slow inward calcium flow channels, especially affecting cells whose depolarization depends on this such as the SA and AV nodes. They have no effect on infranodal conduction and are negatively inotropic. This prevents their use in infants as the myocardium is particularly sensitive to the negative inotropy of calcium channel blockers. Class IV drugs are contraindicated when pre-excitation is manifest, as they can facilitate antegrade conduction during atrial fibrillation leading to ventricular fibrillation and arrest.

Digoxin has a dual mode of action on the myocardium. It acts directly on the heart by inhibiting the Na+ K+ ATPase transmembrane ion exchange pump. This prevents active pumping out of intracellular Na+ during repolarisation causing increased intracellular Na+ and Ca++ concentration and enhanced cardiac contractility. The indirect effect is through stimulation of vagal efferents which reduces SA nodal rate and thereby heart rate. Digoxin also has a dose related AV nodal conduction block that predominantly helps in reducing ventricular response to atrial flutter/fibrillation.

Adenosine depresses the AV node conduction and produces transient AV block. Since the AV node is part of the circuit in all PSVT, adenosine is the drug of choice for acutely terminating such arrhythmias. Atrial arrhythmias, although not terminated by adenosine, may allow for identification of the underlying mechanism during the transient AV block. Ventricular arrhythmias are not affected whatsoever by this drug. The drug should be given as a fast intravenous bolus as the half life is only 6 seconds.

Radiofrequency catheter ablation (RFA) is carried out in the catheterisation laboratory under
general anaesthesia. Percutaneous access is achieved through femoral artery and vein and catheters with electrode sensors are advanced to various locations in the heart like the right atrium, right ventricle, coronary sinus and the crux of the heart near the AV node. The abnormal electrical connection causing the tachycardia is identified by the alterations that it causes of the normal electrical signals. Once the pathway is located, extremely precise mapping of the same is done using a special ablation catheter and the tissue under the exact location ablated using alternating current of a frequency between 100 kHz and 1.5 MHz. This results in controlled tissue desiccation through resistive tissue heating. The scarring results in replacement of myocytes by fibrous and elastic tissue which in later life can potentially act as a substrate for arrhythmias. As these scars have a tendency to increase in size with somatic growth of the child, RFA is undertaken in very young children only when the arrhythmia is unlikely to resolve spontaneously, or is refractory to medical management or associated with tachycardia induced cardiomyopathy. However, reports of RFA in the paediatric population continues to be encouraging with adverse events less than 1%, and long term freedom from the arrhythmias.

Management of commonly encountered tachyarrhythmias in children

Tachyarrhythmias for a re-entrant tachycardia to be sustained, the arrhythmia cycle length must be longer than the refractory period. Increasing the refractory period of one limb of the circuit blocks conduction in that limb and terminates the re-entrant arrhythmia. In AVRT, the AV nodal limb of the tachycardia circuit is the focus of attack, whereas in AVNRT, the antegrade A pathway is the one most sensitive to intervention.

A baby with PSVT typically exhibits a heart rate >200 bpm. An alert mother would notice the baby to be irritable with incessant weak cry, refusing feeds and may appreciate the ‘fast heart beat’ while trying to calm the baby down on her shoulder. Very fast heart rate close to 300 beats per minute compromises the cardiac output and the baby may present with features similar to shock. When the PSVT is sustained for a long period then tachycardiomyopathy and congestive heart failure is the mode of presentation. In a haemodynamically stable child, vagal maneuvers should be attempted first. These maneuvers terminate PSVT by acutely increasing the refractory period of the AV nodal limb / A pathway of the re-entry circuit. Recommended vagal maneuvers are application of a plastic bag with ice cubes on the infant’s face for 10 seconds at a time or applying pressure on the infant’s abdomen. Ocular pressure is no longer recommended. If these measures fail, adenosine is administered at a dosage of 100 – 200 mcg/kg. This is given as a rapid intravenous bolus injection through a large bore IV cannula with a three-way port to allow follow up of the drug with a saline push. Rapidly escalating dose of adenosine can be administered at very frequent intervals because of the short half life of the drug. If no satisfactory response is achieved, intravenous infusion of esmolol or amiodarone is initiated. Amiodarone is the preferred drug and is administered at a loading dose of 5mg/kg given over 20-30 minutes followed by maintenance infusion at 5-15 mcg/kg/minute until the tachycardia terminates. When the child is haemodynamically unstable with the tachycardia, electrical cardioversion with DC shock at 0.5 to 2 J/Kg is the recommended mode of management irrespective of the mechanism of the underlying arrhythmia. Long term management of paroxysmal SVT depends on the age of presentation and frequency. Considering the high incidence of spontaneous resolution of AVRT and because they are not life threatening, a single episode of SVT in infancy does not
warrant treatment with drugs. Treatment of recurrent supra ventricular tachycardia is ideally initiated with oral digoxin, propranolol or a combination of both. Digoxin is considered safe for treating WPW syndrome (with pre-excitation) up to the age of two years, beyond which propranolol would be the preferred drug. The loading dose of digoxin is 8-10 mcg/kg/24 hrs followed by maintenance dosage of 6-8 mcg/kg in two divided doses. Propranolol is prescribed at a dose of 0.2-0.5 mg/kg/dose 6-12 hourly up to a maximum of 1.5 mg/kg/dose 6-12 hourly. Arrhythmias resistant to above measures could be managed with flecainide at a dose of 2-8 mg/kg/day in 2-3 divided doses. Milk inhibits absorption of flecainide and therefore should not be given together. It is best avoided when there is underlying structural heart disease or ventricular dysfunction. QRS prolongation more than 25% is an indication to withhold the drug. Verapamil (1-3 mg/kg/dose 8-12 hourly), a calcium channel blocker, though available for use in SVT in children is generally not the preferred drug of choice. Amiodarone at a dosage of 4 mg/kg/dose at 8 hourly intervals for the first week followed by 12 hourly dosages for the subsequent week and then once daily administration provide excellent relief from recurrence of PSVT in infants and children, however the long term use is prevented by the wide range of adverse effects. Therefore, children whose arrhythmias are non responsive to drugs other than amiodarone are best referred for radiofrequency ablation. The dose of digoxin is halved when on concomitant amiodarone as the latter increases the serum levels of digoxin.

**PJRT** is a re-entrant supraventricular tachycardia in children where the antegrade propagation of the tachycardia circuit is down the AV nodal pathway and the retrograde activation of atrium is through remotely located accessory pathway, usually in the postero-septal region. The ECG exhibits an inverted “p” wave in leads II, III, aVf and left lateral leads with PR interval shorter than RP interval during the tachycardia. PJRT is usually incessant in character and when long standing causes tachycardia induced cardiomyopathy. It commonly occurs around 3-4 years of age. More than 20% of patients with PJRT exhibit spontaneous resolution of the tachycardia as well as a good response to pharmacological therapy with amiodarone, verapamil or either drug in combination with digoxin. This is in stark contrast to earlier held belief that PJRT does not exhibit spontaneous resolution and is refractory to medical management. RFA is therefore, reserved for children who have recurrences of the PJRT with or without tachycardia induced cardiomyopathy despite drug therapy.

**JET** is the commonest (22%) arrhythmia seen in the immediate post-operative period following intracardiac repair mostly following Tetralogy of Fallot correction. The underlying mechanism is enhanced automaticity of the HIS bundle. ECG typically reveals a narrow QRS tachycardia with a rate between 170-230 beats per minute, atrioventricular dissociation with the ventricular rate faster than the atrial rate (Fig.4). JET usually responds to surface cooling to 34°C, atrial pacing to avoid stress and intravenous amiodarone.

**Atrial tachycardias** commonly seen in children are intra atrial re-entry tachycardia (IART) due to re-entry mechanism around atriotomy scars or Ectopic atrial tachycardia due to enhanced automaticity of diseased or stretched atrial tissue. Multifocal atrial tachycardia is an ectopic atrial tachycardia with multiple foci firing independently. Digoxin toxicity is an important cause of multifocal EAT. The ECG shows multiple “p” waves of differing morphology with an isoelectric baseline between the p waves differentiating it from atrial fibrillation. Drugs which are fast sodium channel blockers
and those that prolong the refractory period are more useful in controlling arrhythmias arising in the atrial and ventricular tissues as they are the fast response cells. RFA provides long term relief. EAT is more easily amenable to RFA than IART where multiple circuits may be present.

**Ventricular tachyarrhythmias** results from either increased automaticity or re-entry in the ventricular tissue. Ventricular arrhythmias are not affected by vagal maneuvers, as parasympathetic innervations of the ventricles are minimal. Therefore, if vagal maneuvers result in slowing of a broad complex tachycardia, VT is excluded. When the patient is unstable with VT, cardioversion should be performed after adequately sedating the patient. Some may be refractory to drug therapy while some respond to radiofrequency ablation. Beta blockers have a role to play in VT associated with dilated and hypertrophic cardiomyopathies as well as in LQTS. RV outflow tract VT is benign with a left bundle branch block pattern and inferior axis on ECG. It responds to treatment with beta blockers and verapamil and is permanently relieved with RFA. Idiopathic left ventricular VT is another benign tachycardia with a right bundle branch block pattern with superior axis on ECG. This responds well to verapamil and is again cured by RFA. Incessant VT occurs in the first two years of life and can induce tachycardia induced cardiomyopathy and hence requires aggressive management with flecainide, amiodarone and when resistant, RFA.

Automatic implantable cardioverter defibrillators (AICD) are indicated in children who are susceptible to life threatening ventricular arrhythmia refractory to pharmacologic treatment and those with syncope and family history of sudden cardiac death (SCD). This usually comprises children with an underlying diagnosis of dilated and hypertrophic cardiomyopathies, LQTS with QTc > 0.55 seconds, primary ventricular fibrillation, post surgical correction for Tetralogy of Fallot and those who have undergone Mustard/Senning procedure for Transposition of the Great Arteries. The challenge currently is to identify those at higher of SCD from ventricular tachyarrhythmias to enable earlier intervention with AICD implantation.

**Bradyarrhythmias**

The American Heart Association/American College of cardiology task force in 1991 recommend cardiac pacing for symptomatic second and third degree AV block, third degree AV block greater than 14 days following cardiac surgery, complete heart block (Fig.4) with a wide QRS complex and in those with low escape rhythm variability and junctional instability. A ventricular escape rate below 55 in neonates with structurally normal heart and below 70 when associated with structural heart anomalies is an indication for permanent pacemaker implantation (Fig.5&6). In the presence of CCF or cardiac defects, pacing is frequently necessary at a higher underlying heart rate. Neonates with congenital complete heart block presenting with a very low escape rate can be managed with intravenous infusion of isoprenaline (0.1mcg/kg/min) while waiting for permanent pacemaker implantation. Inadequate response to isoprenaline and haemodynamic instability with the bradycardia may infrequently warrant an emergency percutaneous temporary cardiac pacing. The risk of sudden death in congenital AV block is highest in early infancy but continues throughout adult life. Small single chamber pacemakers weighing less than 20 gms are available nowadays and our practice is to implant these in extra pleural, intrathoracic location in the left lateral chest wall with the lead secured to the epicardial surface of the heart. This technique offers a secure position for the pacemaker in close proximity to the cardiac mass without the risks associated with
abdominal implantation. Once the child grows to 5 years of age or weighs >10 kg, an endocardial pacemaker with subclavian transvenous lead can replace the epicardial pacemaker which is then explanted.

**Points to Remember**

- **Re-entry, automaticity and block are the three mechanisms by which arrhythmias are initiated.**
- **The three sites that arrhythmias can originate from in the heart are the atria, AV node and the ventricle.**
- **Re-entrant arrhythmias have sudden onset and sudden termination while automatic tachycardias have a gradual onset of tachycardia and slow cool-down period**
- **Most AV reciprocating tachycardias resolve spontaneously by one year of age and hence do not require pharmacological management.**
- **AVRT is commonest in infancy and AVNRT in school going children.**
- **Radiofrequency ablation is a safe option in children when indicated.**

**References**

Vasoactive Agents in Cardiogenic Shock

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Abstract: Vasoactive amines play a crucial role in the management of pediatric acute decompensated heart failure, the etiology of which is multifactorial. This review aims to provide pediatricians a clinical approach to optimally diagnosing shock and appropriately using these medications. An algorithm is presented using the paradigm of post-operative low cardiac output syndrome (LCOS). The sites of action of select vaso-active amines as well as the sites of endogenous catecholamine receptors and effects of their action are tabulated with explanatory text examining their clinical relevance. Other inotropic agents used in pediatric shock are also discussed.

Keywords: Vasoactive amines, Inotropes, Wet and Dry shock, Hot and Cold shock.

Shock is defined physiologically as inadequate delivery of oxygen and substrates to meet the metabolic needs of the tissues. In essence, the perturbation of the primary equation that oxygen delivery \((DO_2)\) is the product of oxygen content \((CaO_2)\) and cardiac output \((CO)\) results in shock. The \(CaO_2\) depends on how much oxygen-carrying capacity is available in terms of hemoglobin (Hb) content and depends on how much oxygen the patient’s Hb contains, defined as the arterial oxygen saturation \((SaO_2)\). Cardiac output is the product of heart rate \((HR)\) and stroke volume \((SV)\) where stroke volume is determined by ventricular filling \((preload)\), impedance to ventricular ejection \((afterload)\) and myocardial contractility.

A state of hypoxic shock may occur when \(CaO_2\) is impaired, or by acute profound anemia, which reduces the amount of Hb and hence, reduces the body’s total oxygen-carrying capacity. As cells are starved of oxygen and substrate, they can no longer sustain efficient aerobic oxygen production and they switch to anaerobic metabolism with resulting production and accumulation of metabolites that ultimately lead to multisystem organ failure and if irreversible, cell death.

To summarize the equation:

\[
DO_2 = CaO_2 \times CO
\]

\[
CaO_2 = (Hb \times SaO_2 \times 1.34 \text{mL O}_2/\text{g}) + 0.003 \times (PaO_2)
\]

\[
CO = SV \times HR
\]

The clinical staging of shock includes compensated shock where the body responds to hypoperfusion by vasoconstriction, tachycardia and redistribution of blood to vital organs, resulting in falsely reassuring blood pressures. If untreated, this progresses to hypotensive shock with multi-organ failure.
The etiologic types of shock may be physiologically compartmentalized into “hypovolemic, cardiogenic, septic and distributive”.

Hemodynamic profiling of patients into sectors of “wet” or “dry” based on presence or absence of congestion and “warm” or “cold” based on systemic perfusion can help determine therapy.

Acknowledging the subtleties of how the age spectrum from neonate to early adult can result in differing presentation and management is crucial as well. Understanding the interplay of pathophysiology, staging, etiology, hemodynamic profile and age of the patient will facilitate an intelligent use of vasoactive amines in managing pediatric shock.

The shock continuum

Early in the evolution of compensated shock, hypoperfusion results in activation of the sympathetic nervous system which stimulates the adrenals to produce catecholamines. This increases the heart rate and systemic resistance via vasoconstriction. The renin angiotensin system is also activated, leading to fluid retention by concentrating the urine and further increasing vasoconstriction. This early compensatory phase also involves the redistribution of blood from the skin, splanchnic and skeletal muscle systems to the vital organs—the brain, heart and lungs. Clinically the primary equation manifests initially by an elevation in heart rate in children, as the stroke volume component involving preload, contractility and afterload is compromised. Vasoconstriction results in increased afterload, overall affecting stroke volume and cardiac output. At this point, the role of maintaining an adequate preload becomes critical. In summation, this phase clinically manifests as tachycardia with prolonged capillary refill, poor peripheral pulses and most importantly preserved blood pressure.

Later hypotensive shock occurs when these mechanisms fail and hypotension develops, compromising tissue perfusion and spiralling into vasomotor and microcirculatory multiorgan failure. This phase clinically manifests as hypotension, lethargy with altered mental status, decreased urine output, tachypnea, mottled extremities and multisystem abnormalities, which are confirmed by laboratory testing.

The immature myocardium in infants has limited contractile reserve. The diastolic function also gets easily compromised, leading to reduced compliance and rapid development of hypotensive shock and death if not recognized and intervened on time.

Etiology

Hypovolemic shock is the commonest type of shock in children. It is multifactorial and may occur secondary to hemorrhagic causes like surgery, trauma, hepatic or splenic rupture and from non-hemorrhagic causes like gastrointestinal losses, burns, water deprivation and diabetes insipidus or mellitus among other etiologies. It must be noted that hypotension may not occur till about 25-40% of intravascular volume is depleted. Using the primary equation, the decreased intravascular volume leads to decreased preload from inadequate systemic vascular return, resulting in decreased cardiac output.

Cardiogenic shock can occur from a myriad of congenital and acquired heart diseases affecting preload, contractility and afterload with the final outcome being pump failure. These include obstructive lesions, arrhythmias, large shunts, myocarditis, cardiomyopathies, ischemic injury and post-operative low cardiac output syndromes.

Septic shock is defined as “severe sepsis leading to circulatory failure, manifesting as tachycardia and tachypnea with fever or high leucocyte count and end organ dysfunction”, according to the
international consensus conference of the society of critical care medicine and the American College of chest physicians. Up to 60% of children with septic shock display cold shock with decreased CO and elevated SVR. Clinically, these patients will have tachycardia with initial preservation of blood pressure, with decreased capillary refill and decreased pulses. About 20% of children have warm shock with low SVR and vasodilation, which will manifest as tachycardia, decreased blood pressures, bounding pulses and delayed capillary refill. A smaller percentage will demonstrate a decrease in both CO and SVR.

**Distributive or vasodilatory shock:** One of the scenarios where this can occur is when anaphylaxis results in activation of the cytokine cascade leading to an overwhelming loss of systemic vascular tone and third spacing, culminating in shock. A neurological injury could result in catastrophic hypotension from acute loss of sympathetic tone. The skin may appear falsely reassuring being briskly perfused, with warm extremities, bounding pulses and brisk or flash capillary refill (<1-2 s). The presence of hypotension and tachycardia or other evidence of metabolic disturbances, such as persistent lactic acidosis may point to the diagnosis of distributive shock.

**Hemodynamic profiling of cardiogenic shock**

An evolving framework translated from the adult literature is a useful paradigm in managing pediatric heart failure and shock syndromes. Here patients are profiled hemodynamically, based on presence or absence of elevated filling pressures/ pulmonary and systemic congestion (wet or dry) and adequacy of perfusion (warm or cold). Profile A (warm and dry) is the preferred or normal status, Profile B (warm and wet), Profile C (cold and wet) and Profile L (cold and dry). Clinical evidence of a “wet profile” includes orthopnea, elevated jugular venous pressure, accentuated second heart sound, edema and ascites. A “cold” profile would manifest with cold extremities, mental status changes and narrow pulse pressure or pulsus alternans.

Clinically, Profile B, wet and warm, will present with pulmonary or systemic congestion, manifesting as tachypnea, tachycardia, hepatomegaly, ascites, edema and elevated jugular venous pressures, but are adequately perfused. Intuitively, therapy calls for diuretics and standard medical management.

Profile C wet and cold, will have congestion and poor perfusion and the risk for death, where need for transplantation greater than the previous profile. These are patients with poor myocardial function and heart failure leading to shock. They will present with a picture of pulmonary edema from left ventricular diastolic failure and hypotension from low cardiac output. Management for this group would be inotropes and (judicious use of) afterload reducing vasodilators for the “cold” presentation, before diuretics for the “wet” component of pulmonary or hepatic congestion. In this situation the patient will need to warm up before you can succeed in drying out. The choice of inotropes will depend on the clinical status of the patient but milrinone intuitively would be optimal due to its inotropic, lusitropic (improve diastolic function), and vasodilatory properties. The multicenter PRIMACORP trial demonstrated a clear decrease in the incidence of post-operative low cardiac output syndrome (LCOS) with milrinone use.

Profile L so named to distance itself as a natural continuation of the three prior states is the cold and dry patient with normal filling pressures but with poor perfusion. This unfortunately is the most fragile situation where vasodilators though helpful can only be...
cautiously used with inotropic support and ultimately may require ventilatory support.

**Pharmacotherapy of shock**

Table I summarises the sites of endogenous catecholamine receptors and effects of their activation. In essence, \( \alpha \) receptor activation results in vasoconstriction. \( \beta_1 \) increases heart rate by accelerating the sino-atrial node and ectopic pacemakers while enhancing myocardial contractility while \( \beta_2 \) is essentially vaso and broncho dilatory. Dopaminergic activation causes diuresis and vasodilation.

**Types of vasoactive amines**

Table II explains the sites of action of select inotropes. Understanding their differential effects is critical in managing shock.

**Epinephrine:** By its equally potent effects on all three receptors, epinephrine causes vasoconstriction, inotropy and vasodilation. Lower dosages have predominantly \( \beta \) inotropic effects with \( \alpha \) vasoconstriction taking over at higher levels. Clinically epinephrine is best used in the patient with hypotension, myocardial failure and poor cardiac output and has special use in patients with warm septic shock and post-operative cardiac surgery. In neonates, higher dosages may cause irreversible myocardial damage. Note needs to be taken of its side effects which include hyperglycemia and leukocytosis as well as oliguria in patients with poor renal perfusion.

**Norepinephrine:** Norepinephrine clearly is the most potent \( \alpha \) stimulant vasoconstrictor, with significant increase in systemic vascular resistance, arterial blood pressure and myocardial oxygen consumption with minimal effect on contractility or cardiac output. Clinically norepinephrine is rarely used in pediatric shock unless there is no response to the usual first line medications. Occasional use maybe in the treatment of hypercyanotic spells of tetralogy of Fallot due to its impressive effect on increasing the systemic vascular resistance diverting blood through the dynamically narrowed right ventricular outflow tract. It may be briefly used in conjunction with a vasodilator in early post-operative myocardial dysfunction.

**Dopamine:** Low dosages (2-5 \( \mu \text{g/kg/min} \)) stimulate primarily the dopamine receptor which increases renal, mesenteric, cerebral and coronary flow but without effect on inotropy or systemic vasoconstriction. In the mid-range (5-10 \( \mu \text{g/kg/min} \)), through its direct \( \beta \) adrenergic effects, dopamine increases cardiac contractility without significant effects on heart rate or blood pressure. Clinically low dose dopamine is best suited for the pediatric patient who has normal blood pressures with oliguria and increased to medium dose when hypotension or lower heart rates set in. Dopamine should be used with caution in patients with pulmonary hypertension and congestive heart failure. Since 30% is protein bound, its efficacy is compromised in children who are malnourished or have defective hepatic function. In the neonatal heart, the \( \alpha \) effects of dopamine may precede its \( \beta \) effects due to variable maturation combined with decreased norepinephrine stores.

**Dobutamine:** As noted in the accompanying tables, dobutamine stimulates the \( \beta_1 \) receptors three times as much as it does the \( \alpha_1 \) and \( \beta_2 \) receptors. Hence its actions will primarily increase myocardial contractility. Its ability to enhance chronotropy by accelerating the sino-atrial node and atrioventricular conduction is dose related. Dobutamine - “the great balancer”, by its \( \beta_2 \) activities, promotes some vasodilation which cancels out \( \alpha_1 \) induced vasoconstriction and establishes balanced peripheral and systemic vascular resistances. This makes it optimal in post-operative pulmonary hypertensive pediatric patients by not increasing pulmonary vascular resistances and pressures.
Table I. Sites of endogenous catecholamine receptors and effects of activation

<table>
<thead>
<tr>
<th>Site</th>
<th>Receptor type</th>
<th>Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus node</td>
<td>(\beta^1)</td>
<td>Increased Heart rate</td>
</tr>
<tr>
<td>Atrioventricular node</td>
<td>(\beta^1)</td>
<td>Increased Heart rate</td>
</tr>
<tr>
<td>Atria + ventricles</td>
<td>(\beta^1)</td>
<td>Increased contractility</td>
</tr>
<tr>
<td>Coronary circulation</td>
<td>(\alpha)</td>
<td>Vasconstriction</td>
</tr>
<tr>
<td>Coronary circulation</td>
<td>DA</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td><strong>Peripheral Vasculature</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>(\alpha)</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>(\alpha)</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Renal</td>
<td>DA</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Mesenteric + splanchnic</td>
<td>(\beta^2, DA)</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>(\beta^2)</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td><strong>Nonvascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal tube</td>
<td>DA</td>
<td>Diuresis</td>
</tr>
<tr>
<td>Bronchial tree</td>
<td>(\beta^2)</td>
<td>Bronchodilatation</td>
</tr>
</tbody>
</table>

Table II. Sites of action

<table>
<thead>
<tr>
<th>Drug</th>
<th>(\alpha)</th>
<th>(\beta^1)</th>
<th>(\beta^2)</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It also facilitates a nice myocardial equilibrium by balancing its inotropic demand with increasing coronary blood flow. This is achieved by dobutamine not having any action on dopaminergic receptors which induce norepinephrine, the potent a stimulant coronary vasoconstrictor.

As a bonus it also improves diastolic relaxation. These attractive features of dobutamine makes its use preferable in cardiogenic shock and severe congestive cardiac failure. To summarize, dobutamine at doses of 2 to 8 mg/kg/min improves symptoms, increases cardiac output and stroke volume while decreasing pulmonary capillary wedge pressures without significant effect on heart rate, systemic and pulmonary vascular resistances. Of note, dobutamine is less effective than dopamine in raising the blood pressure without enhancing tachycardia in premature neonates, because of the unique properties of the immature myocardium.

**Isoproterenol:** Isoproterenol has limited use in pediatric shock states due to its unfavorable myocardial demands. However, it does have special use in patients with bradycardia or atrioventricular block, even in the transplanted heart. It is occasionally used in post-operative right heart failure states to help maintain heart rate and cardiac output. Its use should be avoided in left ventricular outflow tract obstructive lesions like subaortic stenosis and hypertrophic cardiomyopathy as it may potentiate the outflow gradient. It could also exacerbate hypercyanotic spells in tetralogy of Fallot, because of its effect on reducing systemic resistance. Since it can decrease diastolic pressure, avoid using isoproterenol in systemic to pulmonary shunts and severe aortic regurgitation as this could lead to increased aortic runoff and reduced coronary perfusion in diastole.

**Milrinone:** Milrinone belongs to a specific class of phosphodiesterase 3 inhibitors (PDEI 3) that results in increased contractility without an appreciable effect on chronotropy. PDEI 3s are also potent peripheral and pulmonary vasodilators. Its ability to reduce pulmonary artery pressure is through reduction in left ventricular end-diastolic pressure.4

**Vasopressin:** Arginine vasopressin is a non-catecholamine systemic vasoconstrictor which is synergistic with the other pressors, and acts by enhancing the sensitivity of the vasculature to catecholamines. Vasopressin has been shown to help in neonates with post-cardiopulmonary bypass-vasodilatory shock.5

**Levosimendan:** Levomisendan belongs to a new category of drugs called calcium sensitizers which increase myofilament sensitivity to calcium without increasing intracellular calcium through binding to Troponin C. This leads to increased inotropy and vasodilation without the increased oxygen consumption, impaired relaxation and tachyarrhythmias that elevated calcium in the cells usually induces.

**Nesiritide:** Nesiritide works to facilitate homeostasis through counter regulation of the renin-angiotensin-aldosterone system leading to smooth muscle cell relaxation. In simpler terms, it promotes vasodilation, natriuresis, and diuresis without significant hypotension.6

Algorithm for management of post-operative low cardiac output states (LCOS)

1) Initial baseline assessment after ensuring airway, breathing and circulation.

- Cardiopulmonary monitoring of HR, BP, Oxygen saturations, vital signs trends
- Laboratory parameters: tissue perfusion markers- ABG- serum pH, base deficit, bicarbonate, lactate
- Monitor for electrolyte imbalances especially calcium, magnesium and glucose.
- Assess oxygen utilization via mixed venous saturations which should be > 70%.
- Obtain chest X-ray to evaluate heart size, pulmonary blood flow, pneumonia-consolidation and pleural effusions/ pneumothorax.
- Echocardiography for cardiac function, pericardial effusion, valvular stenosis or regurgitation besides assessment of pulmonary artery systolic pressure utilizing the tricuspid regurgitant jet.
- ECG to assess atrio-ventricular synchrony.
- Evaluate if there are any significant residual anatomic lesions or surgical complications necessitating re-operation or cardiac catheterization for diagnosis or intervention.
- Assess central venous pressure, pulmonary capillary wedge pressures and cardiac index if indwelling catheters are available and interpret data based on clinical situation.
- Near infra red spectroscopy (NIRS): NIRS is being increasingly used in intraoperative as well as critical care units for monitoring cerebral and tissue perfusion.

2) Respect hemodynamic principles of maintaining adequate preload, improving contractility and decreasing afterload besides recognizing pulmonary hypertension and compromised coronary perfusion.

3) Minimize oxygen consumption by treating fever/infection and ensuring adequate sedation and paralysis. Consider mild hypothermia to reduce the metabolic rate.

4) Maintain CVP appropriate for the lesion, with colloids or crystalloids.
   - Isotonic saline or colloid boluses up to 60cc/kg

5) If the shock is unresponsive to fluid challenge, and hypotension is mild (10-20% decrease in normal mean arterial pressure for age), start with dopamine as first line inotrope at 5 μg/kg/min under central venous and arterial monitoring
   - If tachycardia persists consider milrinone load with 50 μg/kg IV over 20 minutes and infuse 0.25-0.5 mcg/kg/min or add dobutamine 5-10 μg/kg/min
   - If SVR increased in cold and dry shock (profile L) attempt combination therapy with a vasodilator like milrinone plus inotrope.

6) For fluid refractory - dopamine resistant severe shock (more than 30% decrease in mean arterial pressure) - Consider epinephrine at 0.05-0.1 μg/kg/min for cold shock in combination with vasodilators like milrinone.

Vasopressin in the dose range of 0.0003 to 0.008 units/kg/minute may help as rescue therapy in fluid and catecholamine refractory shock and post-operative shock.
   - Norepinephrine 0.01 -0.2 μg/kg/min for septic warm shock or as a bridge to mechanical support. Use with caution due to its potent vasoconstrictor effect.

7) For sinus node dysfunction or atroventricular block, consider isoproterenol (0.01-0.05 μg/kg/min) if atrial pacing unavailable. Use with caution in hypotensive or hypovolemic states.

8) If persistent fluid and catecholamine resistant shock, consider mechanical support.

Goal should be normalization of capillary refill < 2 seconds, adequate urine output >1ml/kg/hour, normal mental status and an improving shock index which is the HR/SBP ratio. 7-13

**Conclusion**

Management of shock requires an in-depth understanding of the pathophysiology and mechanisms of shock as well as the crucial role
of decision making in the appropriate choice of inotropic agent used in treating the patient. A quick history even in an emergency situation helps in directing the physician towards a possible etiology of shock and helps in appropriate management measures.

Points to Remember

- **Hypotension is a late sign of hypotensive shock in children and a normal blood pressure should not be used as an indicator of adequate hemodynamics.**

- **Knowledge of the pharmacology of vasoactive amines and their combined judicious use in individualized situations is critical in the management of cardiogenic shock.**

- **Failure to understand the special connotations of the use of inotropes in neonates and preterm infants may prove catastrophic.**

- **While a paradigm has been suggested in the management of low cardiac output after cardiac surgery, inspired, stylistic and intelligent use of these medications is the privilege of our profession.**

References


CARDIAC INVOLVEMENT IN SYSTEMIC INFECTIONS

* Amar Taksande
** Shakuntala Prabhu

Abstract: Cardiac involvement in systemic infection presents either as: (i) pericarditis; (ii) myocarditis or myocardial fibrosis due to myositis or vasculitis with rhythm and conduction disturbances and diastolic or systolic heart failure; (iii) endocardial involvement with valvular disease; (iv) pulmonary hypertension secondary to concomitant lung disease or recurrent lung embolism; (v) syncope; and (vi) arterial hypertension. Cardiomyopathy is common in several infections and it is caused by either diffuse myocardial ischemia due to vasculitis of small epicardial vessels or by granulomatous or eosinophilic infiltration depending upon the type of vasculitis. Myocarditis and pericarditis is caused by many infectious agents and may produce ECG abnormalities.

Keywords: Cardiac manifestation, Bacterial, Viral, Fungal, Infection.

The cardiovascular system is rarely involved in certain systemic infections. In children, the cardiac manifestations mainly in the form of chest pain, dyspnoea, palpitation, cardiogenic shock etc. The infection may be viral, bacterial or due to others and sometimes is caused by specific bacterial toxins, in the blood or tissues. Electrocardiography and echocardiography are essential tools for diagnosing the cardiac changes in systemic infection.

Tuberculosis (Mycobacterium Tuberculosis)

Tuberculosis primarily involves the lungs; 15%–20% of all cases are extrapulmonary, the most common sites being the lymph nodes, pleura, abdomen and central nervous system. TB is a common cause of pericardial disease in our country but myocardial involvement may occur rarely. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. Involvement of the myocardium occurs due to direct extension from the pericardium or spread from mediastinal lymph nodes or hematogenous dissemination. Pathologically, there are three patterns of involvement; these are as follows: (i) miliary tuberculosis, with the heart being just one of the many organs involved; (ii) diffuse infiltrating interstitial disease; and (iii) caseating nodular disease (tuberculoma).

Clinical features

Symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. Disseminated miliary tuberculosis is usually evident and cardiovascular symptoms are mainly in the form of rhythm
disturbances. Sudden death has been attributed to a fatal ventricular arrhythmia or a conduction defect. Clinically, tuberculomas may be asymptomatic or may present with arrhythmias, complete heart block, congestive heart failure, superior vena caval obstruction, right ventricular outflow obstruction, aortic insufficiency and sudden cardiac death.

Investigation

- ECG shows supraventricular arrhythmias, ventricular tachycardia or atrioventricular block. PR prolongation is seen in the early phase of pericarditis and is followed by changes such as ST segment elevation, normalization of the ST segment, T-wave inversion, and normalization of all changes over several days to weeks. Low-voltage complexes are seen in pericarditis with pericardial effusion.
- Echocardiography may show an echogenic immobile mass in the ventricular myocardium in the case of a calcified myocardial tuberculoma.
- Cardiac MRI shows a characteristic T2 shortening in tuberculous involvement.
- The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30-70% of cases.

Treatment

- Corticosteroids can help relieve symptoms and constriction associated with acute tuberculous pericardial effusion. Prednisone, 1–2 mg/kg/day in 1–2 divided doses orally for 4–6 wk, followed by gradual tapering.
- Regression of disease has been reported in response to antituberculous therapy.
- Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lyme Disease (Borrelia burgdorferi) 3

Lyme disease (LD) is caused by the spirochete Borrelia burgdorferi, which is spread by the Ixodes scapularis tick (deer tick). It affects the cardiovascular, musculoskeletal, and nervous systems. Lyme carditis occurs in about 10% of patients with LD. The clinical manifestations are categorized into early disease, disseminated and persistent infection. Stage 1 (early disease) occurs a few days to 1 month after the tick bite, manifests as localized infection and an erythematous rash with central clearing at the site of the tick bite, called erythema migrans. Stage 2 (disseminated infection) starts 2 to 12 weeks after the tick bite and neurologic (10% to 15%) and cardiac (10%) manifestations occur in this stage. The classic triad of Lyme neuroborreliosis includes aseptic meningitis, cranial nerve palsies (Bell’s palsy) and peripheral radiculoneuropathy. Patients with cardiac involvement may be asymptomatic or complain of lightheadedness, syncope, shortness of breath, palpitations, and/or chest pain. The most common cardiac manifestation is varying degrees of AV block. First-degree AV block can change to complete heart block within minutes. Complete heart block typically resolves within one week, and more minor conduction disturbances within six weeks and rarely requires a permanent pacemaker. Less common cardiac manifestations have included arrhythmias (supraventricular tachycardia and premature ventricular contractions) and myopericarditis with transient cardiomegaly and left ventricular dysfunction. Stage 3 (persistent infection) manifests as large-joint arthritis weeks to years after stage 2 and is seen in about 50% of the patients not previously treated. Enzyme-linked immunosorbent assays (ELISAs) are probably
more accurate than indirect immunofluorescence assays.

**Treatment**

Mild carditis is treated with oral antibiotics (Age >8 years: Doxycycline 100 mg bd and age <8 years: Amoxicillin 25 to 50 mg/kg bd, for 2 to 3 weeks) and severe carditis with intravenous antibiotics in an effort to eradicate the infection and prevent late complications of Lyme disease. For patients allergic to penicillin, cefuroxime axetil is an alternative. For high-level AV block, temporary pacing may be indicated.

**Influenza virus (Swine Flu)**

Swine flu is a respiratory disease of pigs caused by type A influenza. Humans do not normally get swine flu however in the recent past person to person spread is reported. It is contagious and spreading fast particularly among young people. Influenza is a recognized cause of myocarditis which can lead to significant impairment of cardiac function and mortality. Uncomplicated influenza may present with symptoms include: fever, cough, sore throat, nasal congestion or rhinorrhea, headache, muscle pain, and malaise, gastrointestinal illness, such as diarrhoea and/or vomiting. Complicated or severe influenza may present with lower respiratory tract infection, encephalitis, or secondary complications, such as renal failure, multiorgan failure and septic shock. Cardiovascular involvement in acute influenza infection can occur through direct effects of the virus on the myocardium or through exacerbation of existing cardiovascular disease. Cardiac involvement occurred between 4 and 7 days after the onset of influenza symptoms. All patients had preceding flu-like symptoms and fever. Worsening dyspnea is the most common symptom. Fulminant myocarditis is characterised by profound left ventricular dysfunction and cardiogenic shock. In some cases, pericardial effusions may result in cardiac tamponade.

**Investigation**

This reveals at least a four-fold increase in influenza A virus titers using paired sera. Increased creatine kinase levels. ECG abnormalities show ST elevation with Q wave and LBBB. Echo shows global hypokinesia of left ventricle.

**Treatment**

Use of oral oseltamivir in those with serious illness or pneumonia may be beneficial. In patients of fulminant myocarditis, use of inotrope drugs and intra arterial ballon counter pulsation (IABP) should be used and steroids use is discouraged.

**Dengue fever**

Dengue fever is an acute febrile infectious disease, caused by any of the four serotypes (1, 2, 3 or 4) of a virus from the genus flavivirus, called dengue virus. Dengue is transmitted by mosquitoes of the genus Aedes, which are widely distributed in subtropical and tropical areas of the world. It is characterized by biphasic fever, myalgia or arthralgia, rash, leucopenia, and lymphadenopathy. The World Health Organization criteria for dengue hemorrhagic fever are fever, minor or major hemorrhagic manifestations, thrombocytopenia (≤100,000/mm3) and objective evidence of increased capillary permeability (hematocrit increased by ≥20%), serosal effusion (by chest radiography or ultrasonography), or hypoalbuminemia. Dengue shock syndrome criteria include those for dengue hemorrhagic fever as well as hypotension or narrow pulse pressure (≤20 mm Hg). Cardiac manifestations are uncommon. The cardiac rhythm disorders, such as atrioventricular blocks and ventricular ectopic beats, can appear during infection and are attributed to viral myocarditis. These cardiac manifestations are invariably benign, transient and have a self limiting course. They tend to resolve as infection subsides and have been attributed to sub clinical viral
myocarditis but the exact mechanism is unknown. The circulatory collapse seen in the more severe dengue shock syndrome is often attributed to intravascular volume depletion consequent to capillary fragility and leakage. Dengue pericarditis can be seen but it is very rare and in the form of myopericarditis. The pathogenesis is believed to be the extension of dengue myocarditis into the pericardium rather than circulating immune complex. The accumulation of fluid in serous body spaces such as pleural, peritoneal and peritoneal cavities is reported in acute shock in severe dengue hemorrhagic fever. Thrombocytopenia may occur. Roentgenograms of the chest reveal pleural effusions (left > right) in nearly all patients with dengue shock syndrome. Electrocardiogram may show sinus bradycardia, prolonged PR interval, ectopic ventricular foci and nonspecific ST segment and T wave changes. An echocardiographic anomaly shows pericardial effusion, abnormal systolic and diastolic function, acute reversible hypokinesia and reduction in left ventricular ejection fraction. Virus-specific immunoglobulin M (IgM) antibodies only become detectable after 5-7 days. Antipyretics should be used to keep body temperature <40°C (104°F). Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs.

Human immunodeficiency virus (HIV) 7-9

Infection with HIV has become a major pediatric health concern around the world. The incidence of cardiovascular disease reported amongst HIV infected children ranges from 72% to over 90%. The exact causes of these cardiac abnormalities are unknown and probably multifactorial. Common cardiac abnormalities include cardiomyopathy, myocarditis, pericardial effusion and pulmonary hypertension. A prospective study of young children with symptomatic HIV infection revealed that dilated cardiomyopathy and left ventricular hypertrophy were common. Risk factors for cardiac complications include rapid progression of HIV infection, wasting, low CD4 count, previous serious cardiac event, and advanced neurologic disease (e.g., encephalopathy). Pathogenesis is uncertain may be related to autoimmunity, autonomic dysfunction and abnormal ventricular growth as the possible mechanisms.

**Clinical Manifestation**

Cardiac involvement in HIV infected children is sub-clinical and progressive. Sub-clinical manifestations such as left ventricular dilatation, hypertrophy and decreased systolic dysfunction can be detected only by echocardiography. Progressive left ventricular dilatation is common and may be a harbinger of congestive cardiac failure. Cardiac examination may reveal signs of CHF as sinus tachycardia, gallop rhythm, tachypnea and hepatomegaly.

- **Left ventricular dysfunction** is asymptomatic early in the course but may result in heart failure with progression.
- **Myocarditis** can be the result of infection of the myocardium with viruses such as parvovirus, cytomegalovirus, enterovirus, and adenovirus, have been implicated.
- **Pulmonary arterial hypertension** has not been well established but is probably related to an immunological process related to HIV infection, leading to chronic changes in pulmonary vasculature with resultant increase in pulmonary vascular resistance. Longstanding PAH can lead to right ventricular failure and cor pulmonale.
- **Pericardial effusions** is related to opportunistic infections, malignancies (e.g., Kaposi sarcoma, non-Hodgkin’s lymphoma) or HIV itself, or idiopathic.
Pericardial effusions are frequent, caused by opportunistic viral and bacterial infections, including mycobacteria. It may present with a pericardial friction rub and distant heart sounds on cardiac auscultation or signs of hemodynamic compromise with impending cardiac tamponade. Occasionally, cardiac tamponade develops, which requires emergency pericardiocentesis.

Other Cardiac Abnormalities: Coronary artery disease, Aortic root dilation and abnormalities of the great vessels also occur in children.

Investigations

ECG shows sinus tachycardia, low-voltage QRS complex, nonspecific ST-segment and T-wave changes, poor R-wave progression, and prolonged QTc interval. An asymptomatic prolonged QTc interval is associated with increased cardiovascular mortality in HIV infection. An echocardiogram is indicated in children with suspected LV dysfunction or any other child with significant cardiac disease. It demonstrates diminished LV contractility, dilated cardiomyopathy and hypertrophy of the LV.

Management

Monthly IV infusion of immune globulin improves LV function. Antibiotics are indicated when there is a bacterial infection of the pericardium. Emergency pericardiocentesis may be required when tamponade is present. If CHF develops, anticongestive measures, including diuretics, inotropic agents, and ACEI (e.g., enalapril, captopril) are indicated.

Malaria (Plasmodium)  

Malaria is caused by intracellular Plasmodium protozoa transmitted to humans by female Anopheles mosquitoes. The majority of morbidity and mortality from malaria is caused by infection with P. falciparum. The mechanism of cardiac complication associated malaria is not clear and proposed pathogenesis is the mechanical blockage of capillaries by malarial parasites and parasitized red blood cells. Cardiovascular manifestations include mainly hypotension and acute pulmonary oedema. In malaria, the cardiovascular problems are mainly contributed by severe falciparum parasitaemia, secondary infections, severe anemia, hyperpyrexia, dehydration, metabolic acidosis, hypoxia, and disseminated intravascular coagulation. Pericardial effusion, bundle branch block, cardiomyopathy, and myocarditis have been reported as cardiac complications. In severe falciparum malaria, cardiac arrhythmias are very rarely observed. Commonly the use of antimalarial drugs causes prolongation of QT interval. Echocardiography may reveal the regional wall motion abnormalities. Cardiac adverse events may require temporary discontinuation of the antimalarial drug.

Fungal infection

Fungi are ubiquitous, living in soil, decaying matter and may act as opportunistic organisms ready to attack when human immune system goes down. They may produce simple skin infection to very dreadful local and systemic diseases. Persistence of fever and worsening general status in spite of appropriate treatment, and peripheral embolization as well as presence of large vegetations or perivalvular aggressive invasion evident during echocardiography or intraoperatively should arouse the suspicion of a fungal infection. The progress in invasive procedures, increased use of intracardiac prosthetic devices, prolonged use of intravenous catheters, administration of multiple wide-spectrum antibiotics, and immunosuppressive therapies are among the reported risk factors. The organisms include the following: Candida species, Aspergillus species, Histoplasma...
capsulatum, Blastomyces dermatitidis, Cryptococcus neoformans, Mucor species, Torulopsis glabrata, Fusarium species (rare). Cardiac fungal infection is relatively uncommon, but its incidence is increasing. Fungal endocarditis remains a rare infection, although its incidence is increasing because more neonates are in intensive care and more neonates are undergoing cardiac surgical procedures and central hyperalimentation. It rarely affects native valves and occurs most frequently in neonates as part of a disseminated fungal infection, in patients following cardiac surgery, or in those who develop an intracardiac thrombus or valvular injury due to a central venous catheter. On rare occasions, fungal endocarditis presents as typical bacterial endocarditis, with fever, weight loss, splenomegaly, splinter hemorrhages, Roth spots, Osler nodes, petechiae, Janeway lesions, arthritis and a new or changing heart murmur. The treatment approach to fungal endocarditis is surgery combined with prompt use of amphotericin B.

**Echinococcosis (Hydatid disease)**

Hydatid disease due to Echinococcus granulosus is endemic in cattle and sheep raising regions of the world. The cyst occurs mainly in the liver and lungs and rarely involving the heart. The helminth usually reaches the heart via the coronary circulation. It grows slowly in myocardial tissue and within 1 to 5 years, it forms the actual cyst. Left ventricular myocardium is the most common site for cardiac echinococcosis because of its relatively greater blood supply. Patients may be asymptomatic or having nonspecific complaints such as fever, chest pain, weakness, and eruptions. It may manifest with anaphylactic shock due to cyst rupture into the bloodstream, systemic hydatid embolism, hydatid pulmonary embolism, atrioventricular conduction defects, pericarditis with effusion, and cardiac tamponade due to sudden cyst rupture into pericardial space. CBC shows eosinophilia. Chest x-ray shows abnormal shape of the heart shadow, or sometimes a calcified spherical mass. ECG shows low voltage graph and non-specific ST–T wave change. Echocardiography reveals a unilocular cyst with well-defined margins and internal trabeculations corresponding to daughter cysts is diagnostic of a hydatid cyst. Noncomplicated cysts usually appear hypodense and well marginated on non contrast CT. Serological tests include indirect haemagglutination (IHA) test, enzyme-linked immunosorbent assay (ELISA) and latex agglutination test. The World Health Organization guidelines recommended that: for patients with operable disease, surgical resection of the parasitic lesion, followed by medical therapy for a limited time (minimum of 2 years), long-term medical therapy (Albendazole 10–15 mg/kg or 400 mg twice a day) is indicated in inoperable disease or after incomplete resection of lesions.

**Leptospirosis**

Leptospirosis is caused by spirochetes of the genus Leptospira and most widespread zoonosis in the world. It is an occupational hazard for people who work with animals. This disease is acquired by direct or indirect contact with urine or tissues of infected animals and characterized by subclinical illness followed by self-limited systemic illness in most patients.

**Clinical manifestation**

The spectrum of human leptospirosis ranges from asymptomatic infection to a severe syndrome of multiorgan dysfunction with high mortality. After an incubation period of 7–12 days, the initial or septicemic phase begins in which leptospires can be isolated from the blood, cerebrospinal fluid (CSF) and other tissues. Symptomatic infection may present as an acute febrile illness with nonspecific signs and
symptoms (70%), as aseptic meningitis (20%), or as hepatorenal dysfunction (10%).

**Anicteric Leptospirosis**: The onset of the septicemic phase is abrupt, with fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe myalgia. Some patients have bradycardia and hypotension but circulatory collapse is uncommon. Extreme muscle tenderness, most prominent in the lower extremities. Conjunctival suffusion with photophobia and orbital pain, generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient rash, lasting <24 hour, may occur in 10% of cases, and usually consists of a truncal erythematous maculopapular rash but may be urticarial, petechial, purpuric or desquamating. Less common manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis and orchitis.

**Icteric Leptospirosis (Weil Syndrome)**: This severe form of leptospirosis occurs in <10% of cases and is less common in children. The initial manifestations are similar to those described for anicteric leptospirosis. In fulminating cases, hemorrhagic phenomena and cardiovascular collapse also occur. Abnormal electrocardiograms include first-degree AV block and changes due to acute pericarditis. Electrocardiographic abnormalities in leptospirosis represent definite involvement of the myocardium and are possibly caused by interstitial myocarditis; they indicate a poor prognosis.

**Diagnosis**

Warthin-Starry silver staining, polymerase chain reaction, and immunofluorescent and immunohistochemical methods permit identification of leptospires in infected tissue or body fluids. Spirochetes may also be demonstrated by phase-contrast or dark-field microscopy, but these are insensitive.

**Treatment**

Parenteral penicillin G (6–8 million U/m2/ day divided every 4 hours IV for 7 days) is recommended, with tetracycline (10-20 mg/kg/day divided every 6 hr PO or IV for 7 days) as an alternative for patients allergic to penicillin. Oral amoxicillin is an alternative therapy for children <9 years of age.

**Rickettsiae**

The rickettsiae are a heterogeneous group of small, obligately intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a vector tick, mite, flea, or louse. It affects the endothelium of small blood vessels and releases cytokines which damage endothelial integrity. Then it causes increased vascular permeability, platelet aggregation and polymorph and monocyte proliferation, leading to focal occlusive endangiitis, causing microinfarctions. This process especially affects the brain, cardiac and skeletal muscle, the skin, lungs and kidneys, and may cause venous thrombosis and peripheral gangrene. The clinical manifestations are: fever, severe frontal headache, and generalized myalgia especially in muscles of the lumber region, thigh and calf. As the course progresses, macular, maculopapular, or vesicular rash; necrotic eschar; pneumonitis; and meningoencephalitis can occur. Generalised lymphadenopathy and hepatosplenomegaly are also seen. Cardiac complications are seen in 5-25% of patients including hypotension due to shock, myocarditis and arrhythmias. Pericardial effusion has been reported as a manifestation of scrub typhus. Myocarditis and pericarditis are usually associated with Rickettsia rickettsii and Rickettsia conorii. Hemorrhagic pericardial effusion occurs due to vasculitis because of endothelial cell invasion by rickettsia during infection. The other complications include secondary bacterial infection, leading to
bronchopneumonia, parotitis or otitis media; venous thromboembolism; disseminated intravascular coagulation. No single laboratory finding is specific for early diagnosis. Specific diagnosis can be made by: (1) The Weil-Felix test, involving the demonstration of heterophile antibodies to strains of Proteus mirabilis (OX-19, OK-2, OX-K); (2) Group specific microagglutination test or species specific immunofluorescent antibody test (IFAT) or enzyme linked immunoabsorbent assay (ELISA). (3) Polymerase chain reaction assay can be used to detect rickettsial DNA in whole blood, buffy coat fraction or tissue specimen. Doxycycline is the drug of choice and it can be used safely even in children below 8 years of age.

Points to Remember

- **Heart is not an innocent bystander in most systemic infections of childhood.**

- A high index of clinical suspicion and timely evaluation to diagnose the underlying cardiovascular involvement is advised so as to reduce the morbidity and mortality.

References


RECENT TRENDS IN INTERVENTIONAL CARDIOLOGY

* Sivakumar K

Abstract: The role of interventional techniques in pediatric cardiology is increasing by the day. Rapid technological advances and improved diagnostic modalities has made management of congenital heart diseases more easier. This article gives a birds eye view of pediatric interventional cardiology.

Keywords: Balloon dilatation, Device closure, Coil embolisation, Hybrid interventions.

Advances in cardiac catheter based technology, improved understanding of the cardiac anomalies, modern three-dimensional cardiac imaging tools with echocardiography and computed tomography have contributed to development of various forms of non-surgical catheter based cardiovascular interventions. Interventions originated from the days of balloon angioplasty of stenotic vessels by Gruentzig and stenotic valves by Kan in 1980. Even though balloon atrial septostomy for transposition of great arteries was introduced by William Rashkind 20 years earlier, it was not considered as beginning of the interventional era due to its palliative nature. Newer hardware like low profile balloons, stents to keep dilated vessel open, devices used for closing atrial and ventricular septal defects have shown promising intermediate term results over couple of decades.

The rewarding results achieved by non-surgical treatment for many congenital heart lesions have encouraged many centers to adopt these methods and that has increased experience in use of these devices. The cost of treatment has also substantially reduced due to reuse of balloons, guide wires in developing countries with effective sterilization strategies. This article will discuss the established indications of catheter-based interventions, evolving technologies and new hybrid interventions.

Balloon dilation of stenotic valves

Balloon valvotomy works by splitting the fused commissures through circumferential wall stress. Balloon pulmonary valvotomy (BPV) is the treatment of choice for typical isolated valvar pulmonary stenosis. The presence of thick, dysplastic and less mobile valves and severe organic subvalvar obstruction portend disappointing results. Peak echo doppler gradients of 50 mmHg or more is an indication for BPV that carries a success rate of 98%. Complications like severe infundibular spasm referred as suicidal right ventricle can be avoided if patients are adequately hydrated during the procedure. Congenital aortic valve stenosis with gradients more than 50 mmHg can be progressive with a high incidence of sudden death. Valvotomy aims at reducing the gradients, improving left ventricular function and reducing left ventricular hypertrophy, and delay ultimate aortic valve replacement. Impaired left ventricular function will be an indication for balloon aortic valvotomy, even if the gradient across the valve is low. A successful valvotomy

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is defined as fall in gradients of more than 50% of pre-dilation values. New or increase in aortic regurgitation occurred in 10% of cases.

**Neonatal balloon dilatation**

Safety of neonatal pulmonary valvotomy is facilitated by maintaining adequate preprocedural pulmonary blood flow using infusion of prostaglandin E1 to keep ductus arteriosus open, and use of low profile polyethylene balloons. In pulmonary atresia with intact ventricular septum, perforation of the atretic valve is achieved with radio frequency perforation or with the stiff ends of the guide wires. In these neonates, if hypoplasia and non-compliance of the right ventricle results in poor antegrade flows even after relief of the gradients, ducal stent with 4 mm coronary stents may help to wean the baby from PGE1 infusions.² These ductal stents will be a nonsurgical alternative to a Blalock Taussig shunt that may be needed in these neonates. Neonatal aortic stenosis is associated with high mortality whatever the mode of treatment. Balloon dilation can be offered as the initial modality of treatment. The procedural risk is higher if there is cardiogenic shock at the time of presentation, endocardial fibroelastosis causing severe and persistent left ventricular dysfunction, hypoplasia of left ventricle and associated cardiac anomaly.

**Balloon dilation of coarctation of aorta**

Balloon angioplasty as the procedure of choice for patients with surgical re-coarctation is generally agreed, however it is debated in native coarctation of the aorta. This is primarily related to the issues regarding re-coarctation and aneurysm formation. Balloon size is chosen to the size of isthmus of aorta or descending thoracic aorta beyond the post stenotic dilatation. Successful dilatation is defined as a residual gradient below 20 mmHg. The factors, which contributed to suboptimal outcome in 19% of cases, were higher pre-dilation gradients, isthmus hypoplasia, long tubular obstruction, increasing age and institutional experience.

The late results of balloon dilation in neonates are uniformly poor with a recurrence rate of 80%. Most centers would opt for surgical resection of neonatal coarctation. Neonatal balloon dilatation is resorted to only in poor surgical candidates like cardiogenic shock, very severe left ventricular dysfunction, metabolic acidosis and anuria. The incidence of re-coarctation beyond neonatal period in less than 1 year of age remains high at around 30% and so is a controversial method of treatment. In coarctation balloon dilated beyond 1 year of age, recoarctation is very low at 8%. Ballooning is accepted as procedure of choice in patients of re-coarctation following surgery because previous scar formation at the time of surgery reduces incidence of aortic rupture and aneurysm formation. Aneurysm formation in the site of balloon dilatation occurs in about 6% of patients and femoral vascular injury in around 5% of patients.

**Stents in native / re-coarctation**

Stents may decrease the rate of restenosis by preventing recoil thereby giving good procedural results (Fig.1). It may also help in preventing acute or sub-acute dissection and prevent aneurysm formation by providing circumferential support to the wall of the aorta. They have now been used to treat native coarctation as well as re-coarctation. However the theoretical objection to its use in young age is that the larger stents cannot be deployed and there is a limit to which the smaller stents, deployed at younger age, can be re-dilated. Thus surgical removal of the stents may be required while correcting the lesion at a later age. Once somatic growth is achieved, larger stents can be used which can be dilated up to 18-25 mm. The chances of aortic rupture is largely minimized by the use of covered stents that are
Fig. 1. Coarctation stenting: The figure on the left is an aortic angiogram in anteroposterior view showing severe postsubclavian coarctation. The figure on the right shows wide aortic lumen after stenting.

Fig. 2. Device closure of distal aortopulmonary window: The figure on the left shows aortic angiogram, there is a distal aortopulmonary window between the left wall of ascending aorta to the main pulmonary artery leading to a continuous left to right flow. Figure on right shows cessation of left to right shunt after device closure.
covered with polytetrafluoroethylene in the past few years and they have increased the indications for interventional therapy. Research on bioabsorbable magnesium based stents in neonates and young infants are yet to be converted to clinical practice.

Device closure of atrial septal defects

Interventional therapy in ostium secundum ASD with right atrial and ventricular dilatation is widely adopted in the absence of associated heart disease that would merit surgical intervention like partial anomalous pulmonary venous connection and mitral valve disease. Sinus venosus, primum ASD, coronary sinus and the IVC type of ASD are not amenable for device closures. A very careful preoperative evaluation by echocardiography is very essential for planning the procedure. The defect should have adequate rims of septal tissue all around separating it from vital structures such as mitral valve, pulmonary veins, coronary sinus, etc. Patent foramen ovale in patients who have had cerebro-vascular accident due to paradoxical embolism from venous side (with demonstrable right to left shunting on contrast echocardiography) can also be closed using current devices. In view of the safety of these devices used for more than 20 years in over 100000 patients, interventional device closure of ASD is now a routine practice. Currently devices find extended indications and are also used in patients with deficient margins, patients with multiple defects, associated defects like ventricular septal defects, patent ductus arteriosus, and valvar stenosis (e.g. Lutembacher syndrome – ASD device closure and balloon mitral valvotomy) that are amenable for interventional therapy (Fig.2). Another extended indication for device closures are patients with severe pulmonary hypertension with elevated pulmonary vascular resistance where fenestrated devices are used and patients under 1 year of age weighing under 10 kg who have heart failure or growth failure.4

VSD device closure

A majority of large ventricular septal defects that lead to heart failure in infancy are large and they need surgical closure. Small to moderate sized defects that allow the infant to reach childhood without significant heart failure or pulmonary hypertension may lead to persistent left ventricular dilatation, and are at risk of endocarditis. Such defects merit closure. Inlet and sub pulmonary VSD are not amenable for interventional therapy since their margins are shared by the tricuspid and pulmonary annulus respectively. A majority of defects are perimembranous and a small proportion is in muscular location. These are considered for device closure. Asymmetric nitinol double disc occluder devices have been used to close the perimembranous VSD without affecting the aortic valve closure mechanism for over a decade in a large number of young patients. One of the problems with perimembranous devices are early and late occurrence of atrioventricular nodal conduction disturbances that may manifest as complete heart block, bradycardia or Stokes Adams attacks. This complication is due to stretch of the infranodal conduction through the bundle of His along the margins of the defect. Muscular defects are also suited for device closures using symmetric devices. In very small infants who have muscular defects, per ventricular device closure after sternotomy using a catheter advanced from the right ventricular anterior wall with avoidance of cardiopulmonary bypass has been practiced in the recent years.

Coil embolization therapy

Transcatheter embolization with a variety of materials have been used to occlude abnormal channels but stainless steel or platinum coils have
emerged more popular and have assumed an important role in congenital cardiovascular interventions. They are used in closure of patent ductus arteriosus, aorto pulmonary collaterals in cyanotic heart diseases, pulmonary arteriovenous malformations, systemic and coronary arteriovenous fistulae (Fig.3). Stainless steel coils made thrombogenic by inserting dacron strands along its length used in the past are increasingly replaced with MRI compatible platinum coils since ferromagnetic stainless steel coils may pose problems with cardiac magnetic resonance imaging evaluation in future. Coil closure of small to moderate sized ductus arteriosus have been achieved by deployment of single or multiple coils from either venous or arterial end. The availability of thicker (0.052 " coils) and multiple coils have substantially simplified coil closure of large PDA.  

**Device closure of PDA**

Use of embolization coils in patients with large ducts may be complicated by (1) coil migration and embolism to pulmonary bed or distal aorta and (2) left pulmonary artery stenosis in small children. Nitinol based duct occluders have replaced coils in moderate to large ducts and are associated with a very high rate of closure approaching 100% in 3 months. This device has the potential to close ducts even larger than 12mm in size (Fig.4). Even though there is a possibility of aortic protrusion in infants weighing less than 5 kg, these devices have been extensively used in these very small infants too. New modifications in device shape and design like Amplatzer duct occluder II and vascular plugs have been used in various ductal shapes through smaller delivery sheaths in the recent years. With extensive use of these coils and devices in ducts, surgery seem to be indicated only in the neonates or premature babies with large ducts, where again interventional therapy is done in experienced centers in many instances.

**Pulmonary artery and conduit dilatation**

Native and postoperative pulmonary artery stenoses are usually not good surgical candidates due to very high incidence of restenosis. Balloon dilatation and stenting of pulmonary arteries are technically highly challenging and demanding interventions that need very meticulous planning of the hardware and technique. After surgical reconstruction of right ventricle to pulmonary arteries using homografts and xenograft conduits in various forms of cyanotic heart diseases, including tetralogy, pulmonary atresia, truncus arteriosus and double outlet right ventricles, the conduits degenerate over time and lead to stenosis and calcification as age advances. Conduits may also become inadequate due to smaller luminal diameter. Conduit change will necessitate redo sternotomy through the mediastinal adhesions. Balloon dilatation and stenting hence will offer a valuable nonsurgical palliation since it may effectively postpone conduit replacement. The distal conduit anastomosis is prone for stenosis due to fibrotic strictures and are effectively relieved by balloon dilatation.

**Atrial septostomy**

Balloon atrial septostomy, a neonatal intervention done to improve intercirculatory admixture in transposition of great vessels with an intact inter-ventricular septum before surgical correction has been in clinical practice for nearly 5 decades. Specially designed balloon tipped septostomy catheters are used for these purposes; these procedures are done in many neonatal ICU without fluoroscopy and under echocardiographic guidance. The procedure enlarges an already existing patent oval foramen and increases mixing of blood, thus allowing more saturated blood to reach the systemic circulation. The effective pulmonary blood flow is also increased because of right to left flow. In patients
Fig. 3. Coil closure of Blalock Taussig Shunt: Injection in left subclavian artery on left shows flows through the left BT shunt to the left pulmonary artery. The figure on right shows closure of BT shunt flows with a couple of embolization coils.

Fig. 4. Device closure of a massive PDA. Figure on left is a computed tomogram image after contrast injection, showing location of a fully endothelialized large 24 mm device in the ductal ampulla in relation to the bifurcation of the main pulmonary artery. Figure on right shows the relation of the device to the aortic arch.
with transposition and large VSD and/or PDA, balloon atrial septostomy relieves symptoms of heart failure by reducing the elevated left atrial pressure created by the large pulmonary blood flow. In spite of reports that septostomy may increase particulate and thromboembolism to the brain and potentiate left ventricular early regression, it stabilizes patients before the arterial switch operation. A successful septostomy gives an arterial saturation of 75% or more and less than 2mm Hg gradient across the atrial septum. In a small percentage no improvement in mixing occurs for unexplained reasons in spite of adequate septostomy. In patients with rigid interatrial septal tissues, more aggressive interventions like blade atrial septostomy using 10-15 mm blades, static dilatation of interatrial septum using larger balloons is utilized, often in univentricular palliations with associated stenosis or atresia of one of the atrioventricular valves.

**Neonatal stenting of ductus arteriosus**

In neonates with pulmonary atresia and critical right ventricular outflow tract obstruction, ductus arteriosus may be the main source of pulmonary blood flow to maintain systemic oxygenation. In these neonates, the natural duct closure that occurs in the first week may lead to calamitous drop in oxygen saturation that leads to severe acidosis and death. These neonates are maintained on PGE1 infusion till they are operated upon with a BT shunt. These surgeries in smallest of the neonates are morbid with chances of pulmonary over and under circulation, ventilatory dependency, shunt thrombosis and other neonatal complications. Transcatheter ductal stenting with coronary 4 mm stents will circumvent many of the problems of thoracotomy and may provide a less morbid alternative especially in the compromised neonate.\(^2\) Larger stents are used in the patients with duct dependent systemic circulation as in hypoplastic left heart syndrome, since the systemic circulation is dependent on these ducts.

**Post operative interventions**

In view of the complexity of congenital cardiac surgical procedures, there are increasing recognition of postoperative residual hemodynamically significant defects.\(^8\) Redo surgery to correct many of them will be technically be more challenging and demanding. Table I details a large group of postoperative interventions utilizing off-label uses of the occluder devices, stents and coils that are done to palliate these patients from their hemodynamic disturbances.

**Hybrid interventions**

The bottleneck of application of interventional techniques in the smaller neonates and young infants is the ability to have a safe vascular access to the heart to be able to deliver the occluder devices and stents in the desired locations.\(^9\) Hybrid surgical techniques are performed with ease since the heart is directly exposed after pericardial opening after sternotomy. Utilizing the advantages of sternotomy, introducer sheaths are directly placed after placing purse string sutures on the right ventricular anterior free wall or anterior wall of the main pulmonary artery. Under fluoroscopic guidance, guide wires and short sheaths are introduced through muscular ventricular septal defects and branch pulmonary arteries. Once the sheath positions are confirmed, devices can be placed across muscular ventricular septal defects for per ventricular device closures (Fig.5). Similar placements of devices in atrial septum are referred as peratrial device closures. Branch pulmonary artery stenosis can be dealt with direct stenting through sheaths placed across the main pulmonary artery. These hybrid techniques avoid cardiopulmonary bypass in the smaller neonates and infants and circumvent systemic side effects.
Table I. Post operative residual defects and catheter based therapy

<table>
<thead>
<tr>
<th>Post operative residual defect</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Residual VSD</td>
<td>VSD device closure</td>
</tr>
<tr>
<td>2 Aorto pulmonary collaterals with large shunt</td>
<td>Coil embolization</td>
</tr>
<tr>
<td>3 Overflowing BT shunt</td>
<td>Plug or coil closure</td>
</tr>
<tr>
<td>4 Pulmonary artery or conduit stenosis</td>
<td>Balloon angioplasty, stents</td>
</tr>
<tr>
<td>5 Recoarctation of aorta</td>
<td>Balloon angioplasty, stents</td>
</tr>
<tr>
<td>6 Senning Mustard surgery baffle leak</td>
<td>Device closure</td>
</tr>
<tr>
<td>7 Mustard surgery baffle obstruction</td>
<td>Stent dilatation</td>
</tr>
<tr>
<td>8 Post Glenn decompressing venous collaterals</td>
<td>Coil embolization, devices</td>
</tr>
<tr>
<td>9 Fontan fenestration causing hypoxia</td>
<td>Device closure</td>
</tr>
<tr>
<td>10 Failing Fontan surgery with venous congestion</td>
<td>Fontan circuit fenestration</td>
</tr>
<tr>
<td>11 Conduit valve regurgitation</td>
<td>Percutaneous valve implant</td>
</tr>
<tr>
<td>12 Thrombosed or stenosed aortopulmonary shunts</td>
<td>Balloon dilatation, stents</td>
</tr>
<tr>
<td>13 Residual PDA after surgical ligation</td>
<td>Coil closure</td>
</tr>
<tr>
<td>14 Post Glenn localised lung AV malformations</td>
<td>Coil closure</td>
</tr>
<tr>
<td>15 Recurrent post operative pericardial effusions</td>
<td>Balloon pericardiotomy</td>
</tr>
</tbody>
</table>

Fig. 5. Hybrid intervention: Perventricular device closure. Figure on left is a transesophageal four chamber echocardiogram demonstrating a large 16 mm apical muscular VSD, Figure on the right side shows VSD closure by a large muscular VSD occluder device on a beating heart in the operating room after sternotomy without employing cardiopulmonary bypass.
of extra corporeal circulation. Some surgical procedures like Norwood stage I surgery in hypoplastic left heart syndromes associated with very high mortality and morbidity are considerably simplified by adopting hybrid approach by avoiding cardiopulmonary bypass and performing ductal stenting in the catheterization laboratory. These children grow for few months before an extensive stage II surgery.

Conclusions

New advances in understanding of cardiac anatomy aided by the modern imaging techniques, miniaturization of hardwares, increasing experience of catheter based interventions have widened the horizon of the interventional techniques in congenital heart diseases. Percutaneous implantations of pulmonary and aortic valves have successfully been done in over hundreds of patients using these techniques thereby avoiding surgical morbidity. The coming years is bound to see more applications of these technologies in the improvement of the quality of life of the young children handicapped with congenital heart diseases.

Points to Remember

• **Pediatric interventional cardiology is a technology driven growing field.**

• **It helps not only in managing CHD but also in the management of selected complications after cardiac surgery.**

• **Increased awareness of this field will help the suffering children to return to normalcy with less morbidity and mortality.**

References


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TIMING OF SURGERY FOR COMMON CONGENITAL HEART DEFECTS - A READY RECKONER

* Krishna S Iyer

Surgery remains the mainstay for most congenital heart defects (CHD), although many simpler CHD’s can today be treated by non-surgical catheter based interventions. Optimal results can be obtained with surgery only if it is at an appropriate time in the natural history of the defect. Guidelines for management are important for decision-making, however each patient needs to be evaluated on an individual basis. A prerequisite for any management plan is an accurate anatomic and pathophysiologic diagnosis, which ideally should be confirmed by a pediatric cardiologist. A surgical plan should then be made in conjunction with the surgeon who is likely to do the surgery. It is not recommended that the treating pediatrician take a decision on the treatment plan for any CHD in isolation, lest a disastrous error in the timing of intervention occur.

Broad guidelines on optimal timing of intervention in common CHD’s are given in Table I. These are presented keeping the Indian scenario in mind and guided by current practice in the active pediatric cardiac units.

### Table I. Optimal timing of intervention in common CHDs

<table>
<thead>
<tr>
<th>Defect</th>
<th>Recommended timing of surgery</th>
<th>Earlier if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect (ASD) – secundum type</td>
<td>2 – 3 years. If asymptomatic and no failure to thrive (FTT) or pulmonary artery hypertension (PAH)</td>
<td>Symptoms of congestive heart failure (CHF), FTT or PAH on echo</td>
</tr>
<tr>
<td>ASD of sinus venosus type</td>
<td>3 – 4 years if asymptomatic and no FTT or echo evidence of PAH</td>
<td>Symptoms of CHF, FTT or PAH on echo</td>
</tr>
<tr>
<td>ASD of primum type (partial AVSD)</td>
<td>As for ASD secundum</td>
<td>As for ASD secundum, significant mitral regurgitation</td>
</tr>
<tr>
<td>Ventricular septal defect (VSD)</td>
<td>Depends on size: If VSD is large (＞2/3 size of aorta), associated with severe PAH – surgery between 3 – 6 months.</td>
<td>Uncontrolled CHF, FTT, additional defect like coarctation, PDA or double outlet right ventricle (DORV)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Defect</th>
<th>Recommended timing of surgery</th>
<th>Earlier if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent ductus arteriosus (PDA)</td>
<td>If VSD is moderate (less than size of aorta, right ventricle (RV) pressure 1/2 to 2/3 of left ventricle (LV) – surgery between 1 - 2 years. If VSD is restrictive (less than 1/3 of aorta, normal RV pressure) - but L-R shunt &gt;1.5:1 If VSD restrictive and shunt &lt;1.5:1 - No surgery</td>
<td>One episode of severe LRTI or infective endocarditis (IE), FTT Presence of aortic valve prolapse and onset of regurgitation, progressive RV outflow obstruction (Gasul’s syndrome)</td>
</tr>
<tr>
<td>Atrio-ventricular septal defect (AVSD) – Complete</td>
<td>Depends on size : Large (associated with severe PAH and CHF) – closure as early as possible after diagnosis Moderate (mild to moderate PAH, no CHF) – closure at 6 – 12 months. Small (no PAH, no LA/LV enlargement) – elective closure at 1-2 years</td>
<td>Failure of pharmacologic closure in preterm baby FTT, clinical CHF, associated lesion Single episode of IE</td>
</tr>
<tr>
<td>AVSD – Partial</td>
<td>3 – 6 months.</td>
<td>FTT, uncontrolled CHF, significant Atrio-ventricular valve regurgitation</td>
</tr>
<tr>
<td>Co-arctation of aorta</td>
<td>With LV dysfunction and CHF – urgent surgery after diagnosis</td>
<td>FTT, PAH, significant mitral regurgitation, single episode of IE</td>
</tr>
<tr>
<td></td>
<td>With normal LV function – surgery between 3-6 months.</td>
<td>Associated VSD, PDA or upper limb hypertension</td>
</tr>
<tr>
<td>Valvar aortic stenosis</td>
<td>With LV dysfunction, CHF – urgent intervention. No LV dysfunction or CHF - Intervention whenever peak Doppler gradient exceeds 80 mm. Hg.</td>
<td>ST – T changes in ECG, symptoms of angina and/or syncope – intervention indicated if gradient exceeds 50 mm.Hg.</td>
</tr>
<tr>
<td>Sub-aortic stenosis</td>
<td>Intervention when peak gradient exceeds 64 mm. Hg.</td>
<td>Onset of secondary aortic regurgitation</td>
</tr>
</tbody>
</table>

Contd..
<table>
<thead>
<tr>
<th>Defect</th>
<th>Recommended timing of surgery</th>
<th>Earlier if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot (TOF) and double outlet right ventricle (DORV) with PS</td>
<td>Asymptomatic child with minimal cyanosis– elective total correction at about 1 year of age. Symptomatic child (spells or saturation &lt;70%) – intervention as soon as possible – BT shunt if less than 3 months of age, total correction beyond 1 year of age. Between these ages either procedure depending on institutional expertise.</td>
<td>Can be done as early as 6 months depending on institutional policy.</td>
</tr>
<tr>
<td>TOF with pulmonary atresia (PA)</td>
<td>If asymptomatic with minimal cyanosis– repair with RV to PA conduit at 3-4 years of age. If spells or saturation &lt;70 % before that age – BT shunt.</td>
<td>Anatomy suitable for conduitless repair</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous connection (TAPVC)</td>
<td>Obstructed TAPVC – emergency repair as soon as diagnosed. Unobstructed TAPVC – elective repair as early as possible.</td>
<td>Uncontrolled CHF, significant truncal valve regurgitation, associated defects.</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>Repair with RV – PA conduit at 1 – 3 months.</td>
<td>Uncontrolled CHF, significant truncal valve regurgitation, associated defects.</td>
</tr>
<tr>
<td>Transposition of great arteries (TGA) with intact ventricular septum (IVS) or restrictive VSD</td>
<td>Arterial switch operation (ASO) within 4 weeks of age. Beyond that age LV status determines surgery. If not regressed – ASO. If regressed - atrial switch or LV retraining followed by ASO.</td>
<td>Emergency ASO indicated for failure of stabilization with prostaglandin and/or balloon atrial septostomy.</td>
</tr>
<tr>
<td>TGA with VSD (unrestricted)</td>
<td>ASO and VSD closure at 3 – 6 weeks</td>
<td>Uncontrolled CHF, failure to thrive, associated large PDA</td>
</tr>
<tr>
<td>TGA with VSD and PS</td>
<td>If asymptomatic with minimal cyanosis – Rastelli repair (intracardiac LV to aorta tunnel and RV to PA conduit) at 3-4 years of age. If spells or saturation &lt;70 % before that age – BT shunt.</td>
<td>If a conduitless type of reparative surgery is planned (REV procedure or Nikaidoh procedure)</td>
</tr>
<tr>
<td>Defect</td>
<td>Recommended timing of surgery</td>
<td>Earlier if</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Single ventricle (includes tricuspid atresia, mitral atresia, univentricular hearts, unbalanced ventricles, straddling AV valves, DORV and TGA with unroutable VSD)</td>
<td>With PS: Bidirectional Glenn shunt (BDG) at 6 – 12 months followed by Fontan completion at 2 – 4 years. Without PS: PA band at 3 – 6 weeks of age followed by BDG at 6 – 12 months followed by Fontan completion at 2 – 4 years.</td>
<td>BT shunt if significant cyanosis less than 6 months of age Uncontrolled CHF, need for ventilatory support</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>Norwood or Sano procedure as soon as possible after birth, followed by BDG and Fontan completion as for single ventricle.</td>
<td></td>
</tr>
</tbody>
</table>

For further reading


**NEWS AND NOTES**

**IAP - PALS Provider Course**

Organized by
Institute of Child Health, Sir Ganga Ram Hospital, Delhi and IAP Delhi

**Date:** 26th & 27th, 2011

**Registration Fee:** Rs 3000/- by cash or demand draft in favor of “Ambulatory Pediatrics” at Delhi

**Course Coordinator**

**Dr Suresh Gupta**
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Institute of Child Health, Sir Ganga Ram Hospital, New Delhi
Mobile: 9811426628, Email: sureshgupta62@gmail.com
APPROACH TO HEADACHE IN CHILDREN AND ADOLESCENTS – A REVIEW

* Archana B Netto  
** Lakshmi Achar

Abstract: Headache/migraine remains under recognised, underdiagnosed and undertreated in children. The impact of untreated disease has long term consequences on the developing brain, including the development of comorbidities. At the end of the article, one should be able to differentiate primary from secondary headache and be able to recognize and manage common primary headaches like migraine and tension – type headache. The impact of migraine on the child with the use of Ped MIDAS and Pediatric QOL Inventory will be discussed.

Keywords: Headache, Migraine, Children.

Headaches are a universal feature of the human experience. Headache prevalence rates among children range from 5.9% to 37.7% and increase in school age (40 – 50%) and adolescent children (80%). Prepubertal boys are more often afflicted than girls, whereas after puberty, headaches occur more often in girls. An attack of severe headache represents one of the most common reasons for a visit to a pediatric emergency department (ED). In a pediatric ED, the primary objective is to recognize the serious life-threatening conditions requiring immediate medical care among the wide spectrum of headache diagnoses. Chronic recurrent headache may result in missing school days and lead to severe interruption in learning and education. Chronic untreated headache might lead to developmental regression, depression, other behavioral problems, and can severely affect a child’s daily activities and future life. Every headache in a child may not be explained, but evaluation of a child’s headache is important in order to arrive at the proper diagnosis and start appropriate treatment.

All headaches do not necessarily mean an underlying serious structural disease of the brain. It is important for the treating pediatrician to be aware of the types of headache, the clinical characteristics, diagnostics tests (where secondary headaches are suspected) and treatment modalities.

Pathophysiology

The brain and most of the overlying meninges have no pain receptors and are therefore insensitive to pain. Table I lists the pain sensitive structures in the cranium. Pain arising from the cranial circulation and supratentorial structures travels in the trigeminal nerve. This pain is referred to the front of the head. Pain arising from the posterior fossa travels in the first three cervical nerves and is referred to the back of the head and neck. Because the posterior fossa is also innervated by the glossopharyngeal and vagus nerves, pain arising...
### Table I. Pain sensitive structures

<table>
<thead>
<tr>
<th>The intracranial pain sensitive structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries of the Circle of Willis and first few centimeters of their medium sized branches</td>
</tr>
<tr>
<td>Meningeal (dural) arteries</td>
</tr>
<tr>
<td>Large veins and dural venous sinuses</td>
</tr>
<tr>
<td>Portions of dura near blood vessels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The extracranial pain sensitive structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>External carotid artery (ECA) and its branches</td>
</tr>
<tr>
<td>Scalp and neck muscles</td>
</tr>
<tr>
<td>Skin and cutaneous nerves</td>
</tr>
<tr>
<td>Cervical nerves and nerve roots</td>
</tr>
<tr>
<td>Mucosa of sinuses</td>
</tr>
<tr>
<td>Teeth</td>
</tr>
</tbody>
</table>

### Table II. Causes of secondary headache in children

<table>
<thead>
<tr>
<th>Head trauma (acute or chronic posttraumatic headache)</th>
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</thead>
<tbody>
<tr>
<td>Ocular headache (glaucoma, hypermetropia, astigmatism)</td>
</tr>
<tr>
<td>Noncephalic infections (viral fever, sinusitis, adenoiditis; fever is the most common cause of benign paroxysmal headache)</td>
</tr>
<tr>
<td>Vascular disorders - Arterial hypertension, intracranial hematoma, arteriovenous malformations, subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Nonvascular intracranial disorders – Neoplasms, abscesses</td>
</tr>
<tr>
<td>Neuroinfections – Meningitis, encephalitis</td>
</tr>
<tr>
<td>Disorders of CSF circulation - Pseudotumor cerebri, postlumbar puncture headache, hydrocephalus</td>
</tr>
<tr>
<td>Metabolic disorders – Hypoxia, high altitude, hypoglycemia, porphyria</td>
</tr>
<tr>
<td>Headache associated with substance exposure – Carbon monoxide poisoning, monosodium glutamate (Chinese restaurant syndrome), nitrate or nitrite, alcohol, ergotamine, analgesic abuse</td>
</tr>
<tr>
<td>Headache associated with substance withdrawal - Alcohol (hangover), ergotamine, caffeine, narcotics</td>
</tr>
<tr>
<td>Psychological – Depression, school phobia</td>
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</tbody>
</table>
from the posterior fossa also may be referred to the ears and throat.

**Mechanisms of headache**

The major mechanisms by which head pain is caused are inflammation (meningitis, sinusitis, etc.), traction (Post lumbar puncture headache, tumor, abscess), compression (Space occupying lesions, Chiari type I causing foramen magnum compression) and malignant infiltration (meningeal carcinomatosis). Headache can also result from increased cerebral blood flow caused by fever due to any infection and hypoxia due to any cause. Sustained contraction of the head and neck muscles is the mechanism that causes ‘muscle contraction’ headache.

**Approach to headache in children**

The first step in diagnosis headache is to exclude a secondary cause. Ten percent of headaches seen in a neurology/speciality clinics are secondary. Causes of secondary headache in children are summarized in Table II.

A thorough history is most essential to establishing the diagnosis. Interview of a child and/ or parent with headache should include the questions listed in Table III. History is the key to diagnosing the cause of headache and identifying those children with symptomatic (secondary) headache who need to be investigated. In addition to the checklist provided in the box, questions need to be specifically asked about other symptoms that suggest raised intracranial pressure or progressive neurological disease such as unsteadiness, seizures or visual disturbances. Subtle behavioral disturbances or scholastic difficulties can be early warning symptoms of a structural etiology, though it may also occur when the pain becomes severe and chronic. School absence can be a useful proxy measure for the problem. Timing of headache, postural maneuvers and associated symptoms should be enquired. Morning headache before rising suggests raised ICP, while morning headache after rising points towards headache of low CSF pressure. Maneuvres like coughing, straining and bending worsen that headache of raised ICP and a low pressure headache is relieved by lying down. The goals of clinical examination of a patient with headache are to support the clinical impression made on history, to rule out other differentials and to adhere to parents’ expectations (to be taken seriously and to be able to ask for complimentary testing only wherever necessary).

The general physical examination must include determination of vital signs, including blood pressure and temperature. Careful palpation of the head and neck should be performed in a search for sinus tenderness, thyromegaly, or nuchal rigidity. Head circumference must be measured, even in older children, because slowly progressive increases in intracranial pressure cause macrocrania. The skin must be examined for signs of neurocutaneous syndrome, particularly neurofibromatosis and tuberous sclerosis, which are highly associated with intracranial neoplasms.

A detailed neurologic examination is essential. More than 98 percent of children with brain tumors have objective neurologic findings. Key features in children with intracranial disease include altered mental status, abnormal eye movements, optic disc distortion, motor or sensory asymmetry, coordination disturbances, and abnormal deep tendon reflexes. Warning symptoms/ signs of secondary headaches are summarized in Table IV.

The choice of laboratory testing rests squarely on the differential diagnosis. Skull radiographs and electroencephalography are rarely useful in the diagnosis of headache. Sinus radiography may be indicated for the
<table>
<thead>
<tr>
<th><strong>Table III. Key information required from medical history</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal pattern or pace of onset of the headache</strong></td>
</tr>
<tr>
<td>Acute, acute-recurrent, chronic progressive, chronic nonprogressive, or mixed</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td><strong>Quality and severity of pain</strong></td>
</tr>
<tr>
<td>Associated symptoms, including nausea, vomiting, photophobia, phonophobia</td>
</tr>
<tr>
<td>Exacerbating/alleviating factors</td>
</tr>
<tr>
<td>Response to treatments</td>
</tr>
<tr>
<td>Aura</td>
</tr>
<tr>
<td><strong>Past history of headache</strong></td>
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<tr>
<td>Changing quality/location/severity of pain</td>
</tr>
<tr>
<td>Family history of headache</td>
</tr>
<tr>
<td>Toxic exposure</td>
</tr>
<tr>
<td><strong>Drugs (prescribed or recreational)</strong></td>
</tr>
<tr>
<td>Anticoagulants, anticonvulsants, birth control pills, asthma medicines, stimulants, antihypertensives, analgesics, carbon monoxide, lead</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td><strong>Neurologic symptoms</strong></td>
</tr>
<tr>
<td>Seizure, syncope, altered consciousness, declining school performance, neck pain or stiffness, vertigo, visual changes, diplopia, hearing loss or change, ataxia, disequilibrium, weakness, gait difficulty, back pain</td>
</tr>
<tr>
<td>Sinus or dental pain, nasal discharge, facial pain</td>
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<tr>
<td><strong>Past medical history</strong></td>
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<tr>
<td>Neurosurgical procedures (ventriculoperitoneal shunt)</td>
</tr>
<tr>
<td>Sinus disease</td>
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<tr>
<td>HIV</td>
</tr>
<tr>
<td>Endocrine disorders (hyperthyroidism)</td>
</tr>
<tr>
<td>Congenital heart disease (increased risk for brain abscess or hypertension)</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Coagulopathy</td>
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<tr>
<td>Pregnancy and last menstrual period</td>
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<tr>
<td>Rheumatologic or collagen vascular disease (lupus)</td>
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<tr>
<td>Psychiatric disorders, such as depression, suicide, anxiety disorder</td>
</tr>
</tbody>
</table>
Table IV. Worrisome headache - Red flags - SSNOP

| Systemic symptoms (fever, weight loss) |
| Secondary risk factors (HIV, systemic cancer) |
| Neurologic symptoms or abnormal signs (confusion, impaired consciousness, papilledema, cranial nerve palsies, hemiparesis, incoordination, etc.,) |
| Onset: Sudden, abrupt or split second |
| Previous history of headache: Change in attack frequency, severity or clinical features |

Table V. Indications for neuroimaging in children with headache

| Children less than 6 years |
| Worst headache of life |
| Chronic-progressive pattern (steadily worsening over time) |
| Focal neurologic symptoms |
| Abnormal neurologic exam – papilledema, abnormal eye movements, hemiparesis, ataxia, pathological reflexes, cranial nerve palsies |
| Presence of ventriculoperitoneal shunt |
| Presence of neurocutaneous syndromes |
| Headaches or vomiting on awakening |
| Meningeal signs |

A febrile patient with headache if the clinical history and physical examination suggest acute sinusitis, although clinical judgment may justify treatment without imaging.\(^9,10\) Brain imaging studies (e.g., CT scanning and MR imaging) are almost always performed in children who are less than 6 years of age.\(^11\) In the majority of patients with acute-recurrent headache or chronic-nonprogressive headache patterns and normal findings from neurologic examinations, no imaging is warranted.\(^12\) The overwhelming majority of studies evaluating the role of neuroimaging in young patients with headache have demonstrated no diagnostic abnormalities or incidental (nonpathologic) findings.\(^13\)

The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society reviewed the literature on the evaluation of the child with recurrent headaches and concluded that routine laboratory investigations, lumbar puncture and EEG are not necessary.\(^14\) Indications for neuroimaging in children with headache are summarized in Table V.

Lumbar puncture is effective in determining the presence of an infectious process; increased intracranial pressure (ICP), particularly pseudotumor cerebri; and demyelinating diseases. Nevertheless, if increased ICP is
suspected from an intracranial space-occupying lesion, lumbar puncture is contraindicated because it may lead to brain herniation. Fig.1. summarises the diagnostic evaluation of headache.

Points to Remember

- **Contrary to popular belief, headaches are very common in children. The primary headache disorders, which include migraine and tension-type headache, account for the majority of headaches, while secondary headaches, i.e. those with underlying pathology, are much less common.**

- **Untreated children with headache experience substantial disability, school absenteeism and impaired quality of life.**

- **To manage childhood headache one needs to be able to distinguish the painful from the harmful and recognize the common headache patterns and the signs and symptoms that may indicate serious intracranial disease.**

- **A thorough history and examination is the key in determining the cause and should be the most important means of reassuring the child and family that there is no serious cause for the headaches.**
A comprehensive treatment approach is required to treat headaches of childhood and relieve parental anxiety.

References


NEWS AND NOTES

SECOND ADVANCED VACCINIOLOGY COURSE IN INDIA

INDVAC 2011

From 27th September to 6th October, 2011

Venue: Community Health Training Centre (CHTC), Centre for Stem Cell Research (CSCR), Christian Medical College, Vellore.

Contact: Dr. Anuradha Bose, Course Director INDVAC 2011,

Department of Community Health, Christian Medical College, Vellore,
Tamil Nadu 632 002, Phone: 91-416-2284207, Email: indvac.cmc@gmail.com
MIGRAINE IN CHILDREN

* Archana B Netto
** Lakshmi Achar

Abstract: Pediatric migraine is now distinctly recognized among the primary headache disorders. Adequately addressing this disorder has as much importance on the patient’s overall well-being as immunizations and nutrition do. Diagnosing migraine in children can be very challenging. Its manifestations vary widely through childhood. Mimics of migraine also emerge during childhood to complicate the diagnostic landscape. Episodic symptoms, including headache are caused by entities such as mitochondrial/metabolic disorders, epilepsy, vascular disorders and congenital malformations. In addition, the medical history can be limited by the child’s inability to articulate the symptoms, coupled with parental interpretation, distortion and editorial. This article reviews classification and treatment of pediatric migraine with an emphasis on entities peculiar to children.

Keywords: Migraine, Children, Management, Headache.

Migraine is a chronic, progressive and debilitating disorder that has an impact on the lives of millions of individuals. The origin of the disability can be traced into childhood and adolescence for most adult migraine sufferers. Migraine affects 1–3% of children by age 7 years and 4–11% by age 15 years. Abu-Afereh and Russell estimated the prevalence of tension-type headaches in school children to be 0.9%. Prevalence increases from 3% in the preschool years, to 4% to 11% by the elementary school years, and then up to 8% to 23% during the high school years. Before puberty, boys have more headaches than girls, but after puberty, migraine headaches occur more frequently in girls. The incidence of migraine peaks earlier in boys than in girls. The mean age of onset of migraine is 7 years for boys and 11 years for girls; the gender ratio also shifts during the adolescent years (Table I). The incidence of migraine with aura peaks earlier than the incidence of migraine without aura. Secondary headaches are rare, and brain tumour as a cause of headache even rarer. For every child with a brain tumor there are around 5000 children with recurrent headaches, including 2000 children with migraine.

Classifying pediatric headaches

In 1988, the International Headache Society published a classification scheme for headaches, including complex diagnostic criteria. In essence, it divided headache into two categories - primary and secondary. Primary headache disorders, i.e. those that have no other underlying cause, include migraine, tension type headache and cluster headache. Secondary headaches are associated with underlying central nervous system (CNS) or other pathology. This classification needed fine tuning, especially in relation to headaches in children and
adolescents, and the revised classification was published in 2004\(^8\) (Table II). Notably absent in this are several clinical entities peculiar to childhood, such as “Alice in Wonderland” syndrome, benign paroxysmal torticollis, confusional migraine, and ophthalmoplegic migraine (OM), which are discussed for completeness.\(^9\)

### Table II. Migraine classification

<table>
<thead>
<tr>
<th>Migraine with aura</th>
<th>Table III</th>
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<tbody>
<tr>
<td>Typical aura with migraine headache</td>
<td>Focal symptoms, such as visual disruptions, hemiparesis and aphasia are manifestations of the regional neuronal depolarization and oligemia caused by cortical spreading depression (CSD). Clinical entities of childhood with focal neurologic symptoms, previously termed migraine variants, such as hemiplegic and basilar type, now are included within this category of migraine with aura. Approximately 15% to 30% of children and adolescents who have migraine report visual disturbances, distortions, or obscurations before, or as, the headache begins. The visual symptoms begin gradually and last for several minutes (typical aura). The most frequent forms are binocular visual impairment with scotoma (77%), distortion or hallucinations (16%) and monocular visual impairment or scotoma (7%).(^10) Formed illusions (eg, spots, balloons, colors, rainbows) or other bizarre visual distortions (eg, Alice in Wonderland syndrome) may be described, albeit infrequently.</td>
</tr>
<tr>
<td>Typical aura with non migraine headache</td>
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<tr>
<td>Typical aura without headache</td>
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<tr>
<td>Familial hemiplegic migraine</td>
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<tr>
<td>Sporadic hemiplegic migraine</td>
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<tr>
<td>Basilar-type migraine</td>
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<tr>
<td>Childhood periodic syndromes that are commonly precursors of migraine</td>
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<tr>
<td>Cyclic vomiting</td>
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<tr>
<td>Abdominal migraine</td>
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<tr>
<td>Benign paroxysmal vertigo of childhood</td>
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<tr>
<td>Retinal migraine</td>
<td></td>
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<tr>
<td>Complications of migraine</td>
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<tr>
<td>Chronic migraine</td>
<td></td>
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<tr>
<td>Status migraine</td>
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<tr>
<td>Persistent aura without infarction</td>
<td></td>
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<tr>
<td>Migrainous infarction</td>
<td></td>
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<tr>
<td>Probable migraine</td>
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</table>

### Table I. Prevalence of migraine headache through childhood\(^6\)

<table>
<thead>
<tr>
<th>Age</th>
<th>3-7 Years</th>
<th>7-11Years</th>
<th>15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>1.2%–3.2%</td>
<td>4%–11%</td>
<td>8%–23%</td>
</tr>
<tr>
<td>Gender ratio</td>
<td>Boys &gt; girls</td>
<td>Boys = girls</td>
<td>Girls &gt; boys</td>
</tr>
</tbody>
</table>

Focal symptoms, such as visual disruptions, hemiparesis and aphasia are manifestations of the regional neuronal depolarization and oligemia caused by cortical spreading depression (CSD). Clinical entities of childhood with focal neurologic symptoms, previously termed migraine variants, such as hemiplegic and basilar type, now are included within this category of migraine with aura. Approximately 15% to 30% of children and adolescents who have migraine report visual disturbances, distortions, or obscurations before, or as, the headache begins. The visual symptoms begin gradually and last for several minutes (typical aura). The most frequent forms are binocular visual impairment with scotoma (77%), distortion or hallucinations (16%) and monocular visual impairment or scotoma (7%).\(^10\) Formed illusions (eg, spots, balloons, colors, rainbows) or other bizarre visual distortions (eg, Alice in Wonderland syndrome) may be described, albeit infrequently.

Sudden images and complicated visual perceptions should prompt consideration of benign occipital epilepsy, specifically Panayiotopoulos syndrome.\(^11\) Transient visual obscurations may also be described with idiopathic intracranial hypertension; thus, not all visual symptoms with headache are attributable to migraine with aura.

**Basilar-type migraine:** Basilar-type migraine (BM) represents 3% to 19% of childhood
Table III. Diagnostic criteria for migraine with and without aura

<table>
<thead>
<tr>
<th>Migraine without aura</th>
<th>Migraine with aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At least five attacks fulfilling B-D</td>
<td>A. In addition to above criteria, at least two attacks fulfilling B</td>
</tr>
<tr>
<td>B. Duration between 1 and 48 h</td>
<td>B. At least three of the following:</td>
</tr>
<tr>
<td>C. At least two of the following:</td>
<td>• One or more fully reversible aura symptoms indicating focal cortical or brainstem dysfunction</td>
</tr>
<tr>
<td>• Bilateral or unilateral</td>
<td>• Aura developing gradually over minutes, or two or more symptoms occurring in succession</td>
</tr>
<tr>
<td>• Pulsating</td>
<td>• Aura lasts no more than 1 h</td>
</tr>
<tr>
<td>• Moderate to severe in intensity</td>
<td>• Pain follows aura after &lt;1 h</td>
</tr>
<tr>
<td>• Aggravation by routine physical activity</td>
<td>E. Not attributable to another disorder</td>
</tr>
<tr>
<td>D. During the headache at least one of the following:</td>
<td>Migraine with aura</td>
</tr>
<tr>
<td>• Nausea or vomiting</td>
<td>A. In addition to above criteria, at least two attacks fulfilling B</td>
</tr>
<tr>
<td>• Photophobia or phonophobia</td>
<td>B. At least three of the following:</td>
</tr>
<tr>
<td>E. Not attributable to another disorder</td>
<td>• One or more fully reversible aura symptoms indicating focal cortical or brainstem dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Aura developing gradually over minutes, or two or more symptoms occurring in succession</td>
</tr>
<tr>
<td></td>
<td>• Aura lasts no more than 1 h</td>
</tr>
<tr>
<td>Table IV. Diagnostic criteria for basilar type migraine</td>
<td>C. At least one of the following:</td>
</tr>
<tr>
<td>A. Fulfills criteria for migraine with aura</td>
<td>1. At least one aura symptom develops gradually over 5 minutes or more, and different aura symptoms occur in succession over 5 minutes or more.</td>
</tr>
<tr>
<td>B. Accompanied by two or more of the following types of symptoms:</td>
<td>2. Each aura symptom lasts more than 5 minutes and 60 minutes or less.</td>
</tr>
<tr>
<td>• Dysarthria</td>
<td>D. Headache-fulfilling criteria: migraine without aura begins during the aura or follows aura within 60 minutes.</td>
</tr>
<tr>
<td>• Vertigo</td>
<td>Familial hemiplegic migraine (FHM):</td>
</tr>
<tr>
<td>• Tinnitus</td>
<td>FHM, type 1, is an uncommon autosomal dominant form of migraine with aura caused by a missense mutation in the calcium channel gene (CACNA1A) linked to chromosome 19p13. Clinically, FHM is a migraine headache heralded by an aura of “stroke-like” qualities, producing some degree of hemiparesis (Table V). The transient episodes of focal neurologic deficits precede the headache phase by 30 to 60 minutes but, occasionally, extend well beyond the</td>
</tr>
<tr>
<td>• Hypacusia</td>
<td>mean age onset of 7 years. Attacks are characterized by episodes of dizziness, vertigo, visual disturbances, ataxia, or diplopia as the aura, followed by the headache phase. The pain of BM may be occipital in location, unlike the usual frontal or bitemporal pain of typical migraine. The diagnostic criteria require two or more symptoms and emphasize bulbar and bilateral sensorimotor features (Table IV). Familial forms of BM have recently been reported.</td>
</tr>
<tr>
<td>• Diplopia</td>
<td></td>
</tr>
</tbody>
</table>
**Table V. Diagnostic criteria for familial hemiplegic migraine**

| A. Fulfills criteria for migraine with aura |
| B. Aura consisting of fully reversible motor weakness and at least one of the following: |
| 1. Fully reversible visual symptoms, including positive features (eg., flickering lights, spots, lines) or negative features (eg., loss of vision) |
| 2. Fully reversible sensory symptoms, including positive features (eg., pins and needles) |
| 3. Fully reversible dysphasic speech disturbance |
| C. At least two of the following: |
| 1. At least one aura symptom develops gradually over more than 5 minutes |
| 2. Aura symptom lasts more than 5 minutes and less than 24 hours |
| 3. Headache that fulfills criteria for migraine without aura begins during the aura or follows the onset of aura within 60 minutes |
| D. At least one first-degree or second-degree relative has had an attack |
| E. At least one of the following: |
| 1. History and physical and neurologic examinations not suggesting any organic disorder |
| 2. History or physical or neurologic examination suggesting such a disorder, which is ruled out by appropriate investigations. |

Headache itself (hours to days). The location of headache is often (but not invariably) contralateral to the focal deficits. Many children and adolescents report transient somatosensory symptoms heralding an attack with focal paresthesias around the mouth and hand (eg, chiro-oral) without weakness; this does not fulfill the criteria for hemiplegic migraine. FHM types 2 and 3 are clinically quite similar but have distinctly different molecular mechanisms: FHM type 2 attributable to point mutation of the α2-subunit of the sodium-potassium pump (ATP1A2) gene on chromosome 1q21 to 23 and FHM type 3 attributable to sodium channel gene mutation (SCN1A).

Sporadic hemiplegic migraine includes those patients who present with the abrupt onset of focal neurologic signs or repetitive episodes of focal neurologic symptoms without a family history.

**Migraine variants / periodic syndromes of childhood**

Formerly called ‘migraine variants’, they are now more appropriately categorized according to IHS criteria. Three childhood conditions included in the category of periodic syndromes are benign paroxysmal vertigo, cyclic (or cyclical) vomiting syndrome (CVS) and abdominal migraine. A fourth, benign paroxysmal torticollis, has demonstrated linkage to migraine and is also discussed.

**Benign paroxysmal vertigo (BPV)** occurs in young children with abrupt episodes of unsteadiness or ataxia. The child may appear...
startled or frightened by the sudden loss of balance. Witnesses may report nystagmus or pallor. Verbal children may describe dizziness and nausea. The spells may occur in clusters that typically resolve with sleep. The diagnosis of benign paroxysmal vertigo is based on a characteristic clinical history, but caution must be exercised to exclude seizure disorders (eg, benign occipital epilepsy), otologic pathologic conditions, posterior fossa lesions, cervical spine abnormalities or metabolic disorders. See Table VI for diagnostic criteria.

**Cyclical vomiting syndrome**: A pattern of cycling episodes of vomiting may be seen with a variety of gastrointestinal, neurologic, and metabolic disorders, but a significant subset of children with stereotyped episodes of vomiting have a migrainous basis for their symptoms, which represent CVS. The key clinical feature of CVS is recurrent episodes of severe vomiting with interval wellness (Table VII). The episodes occur on a regular, often predictable, basis every 2 to 4 weeks, lasting 1 to 2 days, and commencing in the early morning hours. The age of onset is approximately 5 years and boys and girls are affected equally. Most children “outgrow” their symptoms by the age of 10 years; a small proportion of patients have symptoms through adolescence and even as young adults. After a complete diagnostic investigation has excluded other causes of the cyclic vomiting pattern, a comprehensive treatment plan, including acute and prophylactic measures, may be instituted. For acute treatment of attacks, aggressive hydration, sedation, and an antiemetic agent represent the mainstays. Oral or intravenous hydration with a glucose-containing solution is essential. Antiemetic choices include Ondansetron (0.3–0.4 mg/kg IV or 4–8 mg PO), Promethazine (0.25–0.5 mg/kg per dose IV or PO), Metoclopramide (1–2 mg/kg up to 10mg BD, IV or PO), Prochlorperazine (2.5–5 mg BD IV). Migraine prophylaxis for CVS should be strongly considered because CVS is an extraordinarily disabling condition for the child and the family.

**Abdominal migraine (AM)** is characterized by episodic, vague, midline, or periumbilical abdominal pain (Table VIII). It includes a subset of patients with chronic recurrent abdominal pain with features overlapping those of migraine without aura. It usually occurs in children aged between 5 and 9 years. Most children affected have a strong family history of migraine with or without aura and eventually develop migraine. AM is a diagnosis of exclusion, and other diagnoses should be considered and eliminated first (peptic ulcer disease, cholecystitis, gastroesophageal reflux, gastrointestinal obstruction especially duodenal, irritable bowel syndrome, etc.,) by appropriate investigations. Migraine therapy is effective.

**Benign paroxysmal torticollis** is a rare paroxysmal dyskinesia characterized by attacks of head tilt alone or tilt accompanied by vomiting and ataxia that may last hours to days. Other tortional or dystonic features, including truncal or pelvic posturing, may be seen.

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**Table VI - ICHD II definition of BPV**

- A At least five attacks fulfilling criterion (B–D).
- B Multiple episodes of severe vertigo occurring without warning and resolving spontaneously after minutes or hours.
- C Normal CNS exam and audiometric/vestibular functions between attacks.
- D Normal electroencephalogram.
Attacks first manifest during infancy between 2 and 8 months of age. Paroxysmal torticollis is likely an early-onset variant of basilar migraine, but the differential diagnosis must include gastroesophageal reflux (Sandifer syndrome), idiopathic torsional dystonia, and complex partial seizure. However, particular attention must be paid to the posterior fossa and craniocervical junction, where congenital or acquired lesions may produce torticollis. MRI of the brain and cervical spine are recommended to evaluate any possible structural abnormality. EEG should be performed to rule out any seizure. Once the diagnosis is established and the benign nature is confirmed, there may be no requirement for treatment beyond reassurance. With time the attacks evolve into a classical migraine headache with or without aura, or into episodes characteristic of BPV. They may also cease without any further symptomatology.

**Other unusual forms of migraine in childhood**

‘Alice in Wonderland’ syndrome represents the spectrum of migraine with aura, but the visual aura is quite atypical and may include bizarre visual illusions and spatial distortions preceding an otherwise nondescript headache. Affected patients describe distorted visual perceptions, such as micropsia, macropsia, metamorphopsia, teleopsia, and macro- or microsomatognopsia. The visual symptoms likely represent CSD and oligemia involving the parieto-occipital region heralding the headache.

Confusional migraine has perceptual distortions as a cardinal feature. Affected patients, usually boys, abruptly become agitated, restless, disoriented, and occasionally combative. The confusion phase may last minutes to hours. Later, once consciousness returns to baseline, the patients describe an inability to communicate with frustration, confusion, and loss of

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**Table VII. Diagnostic criteria for CVS**

| A. At least five attacks fulfilling criteria B and C. |
| B. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting from 1 h to 5 days. |
| C. Vomiting during attacks occurs at least four times per hour for at least 1 h. |
| D. Symptom free between attacks |
| E. Not attributed to another disorder. |

Note:
1. In particular, history and physical examination do not show signs of gastrointestinal disease.

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**Table VIII. Diagnostic criteria for abdominal migraine**

| A. At least five attacks fulfilling criteria B through D |
| B. Attacks of abdominal pain lasting 1 to 72 hours |
| C. Abdominal pain has all the following characteristics: |
1. Midline location, periumbilical or poorly localized |
2. Dull or “just sore” quality |
3. Moderate or severe intensity |
| D. During abdominal pain, at least two of the following: |
1. Anorexia |
2. Nausea |
3. Vomiting |
4. Pallor |
| E. Not attributed to another disorder; |

Note: history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.
orientation to time, and they may not recall a headache phase at all. Confusional migraine often occurs after seemingly innocuous head injury occurring in sports (eg, soccer, football, skating). Clearly, any sudden unexplained alteration of consciousness after head injury warrants investigation for intracranial hemorrhage, drug intoxication, metabolic causes or epilepsy. Clinically, confusional migraine most likely represents an overlap between hemiplegic migraine and BM. Patients who present with unilateral weakness or language disorders should be classified as having hemiplegic migraine, and patients with vertiginous or ataxic patterns should be classified as having BM.

Ophthalmoplegic migraine (OM) has been removed from the migraine spectrum into the group of “cranial neuralgias” as a result of elegant neuroimaging evidence demonstrating an underlying demyelinating-remyelinating mechanism. The key clinical feature is painful ophthalmoparesis. The pain may be a nondescript ocular or retro-ocular discomfort. Ptosis, limited adduction, and vertical displacement (eg, cranial nerve III) are the most common objective findings. The oculomotor symptoms and signs may appear well into the headache phase rather than heralding the headache, contrary to the sequence of typical migraine. The signs may persist for days or even weeks after the headache has resolved. Because OM is no longer viewed as migraine, eventually, the term ophthalmoplegic migraine is likely to evolve to ophthalmoplegic neuralgia.

The migraine precursors and these unusual forms of migraine with aura are unique to children and represent a challenging group of disorders characterized by the abrupt onset of focal neurologic signs and symptoms (eg, hemiparesis, altered consciousness, nystagmus, ophthalmoparesis) followed by headache. Frequently, these ominous neurologic signs initially point to epileptic, cerebrovascular, traumatic, or metabolic causes and the migraine diagnosis becomes apparent only later.

**Management**

The treatment of migraine in children includes acute therapy, preventive therapy and biobehavioral therapy. It is important to educate the patient and the family about the diagnosis of migraine and to provide reassurance about the absence of other life-threatening disorders. In clinical practice, management of children and adolescents with headache should incorporate the addition of headache disability and quality of life assessments to the traditional outcomes of headache intensity, duration and frequency. Headache disability measures specifically designed for use in pediatrics are the PedMIDAS\(^1\) and a general quality of life measure applicable for children aged 2 to 18 years, the Pediatric Quality of Life Inventory Version 4.0 (PedsQL)\(^2\). The reliability, validity and utility of these measures have been demonstrated. The fundamental goals of long-term migraine treatment are

1. Reduction of headache frequency, severity, duration and disability.
2. Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
3. Improvement in the quality of life
4. Avoidance of acute headache medication escalation
5. Education and enablement of patients to manage their disease to enhance personal control of their migraine
6. Reduction of headache-related distress and psychologic symptoms
management and psychological intervention, including biofeedback assisted relaxation training. Treatment adherence entails an understanding by the patient and parent about the importance of their treatment. Psychological or biobehavioral intervention may be useful in assisting with adherence by identifying obstacles to the medical plan and overcoming these barriers. Biobehavioral therapy addresses adjustment of lifestyle habits. Many times, unhealthy lifestyle habits serve as a trigger for pediatric headaches: inadequate nutrition, skipping meals and altered sleep patterns. The basic recommendations given to migraine sufferers include regular sleep and exercise, moderation of caffeine intake, and adequate hydration. Somewhere between 7% and 44% of patients report that a particular food or drink can precipitate a migraine attack. In children, the principal dietary triggers are cheese, chocolates, and citrus fruits. Wholesale dietary elimination of a list of foods is, however, not recommended.

**Acute treatment of migraine**

Presently there are no Food and Drug Administration (FDA)-approved medications for the treatment of migraine in children. Primarily, over-the-counter medications are often utilized, including nonsteroidal anti-inflammatory drugs [NSAIDs: ibuprofen (10 mg/kg/dose), naproxen sodium and for older children aspirin] and general pain relievers (acetaminophen 15 mg/kg/dose). Many prescriptive medications contain sedatives or narcotics that may treat the pain, but do not allow the child to return to normal functioning. Migraine-specific medications, including the triptans and dihydroergotamine (DHE), have been approved for adult use but remain under evaluation in children. Triptans are 5HT-1B/D agonists and migraine-specific medications. There are currently seven triptans approved for use in the USA in adults. Acute medications should not roughly exceed

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**Table IX. Biobehavioral therapies for pediatric migraine**

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<thead>
<tr>
<th>Treatment</th>
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<tr>
<td>Identification of migraine triggers</td>
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<tr>
<td>Electromyographic biofeedback</td>
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<tr>
<td>Thermal hand warming</td>
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<tr>
<td>Galvanic skin resistance feedback</td>
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<tr>
<td>Relaxation therapy</td>
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<tr>
<td>Progressive muscle relaxation</td>
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<tr>
<td>Autogenic training</td>
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<tr>
<td>Meditation</td>
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<tr>
<td>Passive relaxation</td>
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<tr>
<td>Self-hypnosis</td>
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<tr>
<td>Cognitive therapy/stress management</td>
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<tr>
<td>Cognitive control</td>
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<tr>
<td>Guided imagery</td>
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<tr>
<td>Dietary measures - “Avoidance diets” - Caffeine moderation, Herbs, Butterbur root, Feverfew (Tanacetum parthenium), Ginkgo, Valerian root</td>
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<tr>
<td>Minerals - Magnesium</td>
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<tr>
<td>Vitamins - Riboflavin</td>
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<tr>
<td>Acupuncture</td>
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<tr>
<td>Aroma therapy</td>
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To achieve these goals, the treatment regimen must balance biobehavioral strategies and pharmacologic measures.

**Biobehavioral treatments (Table IX)**

Biobehavioral therapy for pediatric headaches is felt to be essential to maintain a lifetime response to the treatment and management of headaches. It can be divided into three components: treatment adherence, lifestyle
two to three days per week. Medication overuse or analgesic rebound headaches are felt to be a frequent cause of transformed migraines or chronic daily headaches.

Acute treatment represent the mainstay of migraine management. There are several basic guidelines regarding the use of acute treatment that must be included as part of the patient’s educational process. The essential message is to give enough and to give it early.

1. Take the medicine as soon as possible when the headache begins (within 20–30 minutes).
2. Take the appropriate dose.
3. Have the medicine available at the location where the patient usually has his or her headaches (e.g., school), and complete the school medicine forms.
4. Avoid analgesic overuse (more than three doses of analgesic per week).

Only sumatriptan (5 and 20 mg) and zolmitriptan (5 mg) in the nasal spray form and rizatriptan (5 and 10 mg) and almotriptan (6.25, 12.5, and 25 mg) in the tablet form have demonstrated safety and efficacy in adolescents 12 to 17 years of age. For young children less than 12 years of age, ibuprofen (7.5–10 mg/kg) and acetaminophen (15 mg/kg) have demonstrated efficacy and safety for the acute treatment of migraine.\(^{16}\)

**Prophylactic treatments of migraine**

A diverse group of medications is used to prevent attacks of migraine. To warrant use of a daily preventive medication, the headaches must occur with sufficient frequency, regularity, and severity, and must interfere with daily lifestyle and pose a functional disability. About one third of children with migraine require periodic courses of daily medication. Table X summarizes the options for prophylactic management of frequent migraine in children.\(^{17}\) Once preventive treatment is initiated, patients must be encouraged to permit enough time for the beneficial effects to be appreciated. Generally, an 8 to 12-week course is necessary before success or failure can be determined.

The duration of treatment is controversial. The general recommendation is to provide treatment through the calendar school year and then to eliminate daily agents gradually during summer vacation. Another option in younger children is to use a shorter course (e.g., 6-8 weeks), followed by slow weaning off the medicine.

For children younger than the age of 10 years who do not have problems related to being overweight, cyproheptadine at a starting dose of 2 to 4 mg as a single bedtime dose is a simple and safe strategy. The dose may gradually be elevated to two or even three times a day, but most children become too sedated at doses much higher than 4 to 8 mg/day.

Flunarizine (not available in USA) is very efficacious for pediatric migraine in doses of 5 - 15 mg, single bedtime dose.

Amitriptyline is one of the most widely used agents, though it has not been assessed in a controlled fashion. Starting doses of 5 to 10 mg at bedtime may gradually be increased toward 1 mg/kg/day.

Topiramate is gaining wide acceptance, and mounting evidence, based on well-designed controlled trials, supports its use.\(^{18}\) For teenagers, a 15- to 25-mg dose of topiramate is initiated as a single bedtime dose and then gradually titrated toward 50 mg twice a day incrementally on a weekly or every-other-week basis (titrate to effect). Cognitive effects must be monitored quite carefully, and more evidence is needed to assess the educational impact of topiramate for prevention of adolescent migraine.
Divalproex sodium has strong efficacy data in adults and is an approved drug, but no controlled trials exist in children. Open-label trials indicated that divalproex sodium was an effective and well-tolerated treatment for the prophylaxis of migraine in children.

Prognosis

Five- to 7-year follow-up studies revealed that 20% to 25% of adolescents originally diagnosed with migraine have remission of symptoms, 50% to 60% have persistence of their migraine with aura, and 25% convert to tension-type headache (TTH). Twenty percent who originally had TTH converted to migraine.\textsuperscript{20} Monastero and colleagues\textsuperscript{21} evaluated 55 adolescents with migraine who were available for 10 years of follow-up and found that 42% had persistent migraine, 38% had experienced remission, and 20% had transformed to TTH. Interestingly, only migraine without aura

<table>
<thead>
<tr>
<th>Table X. Options for prophylactic management of frequent migraine in children</th>
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<tr>
<td>Agent</td>
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<tr>
<td><strong>Antihistamine</strong></td>
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<td>Cyproheptadine</td>
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<td><strong>Antidepressant</strong></td>
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<td>Amitriptyline</td>
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<td><strong>Beta blockers</strong></td>
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<td>Propranolol</td>
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<td>Metoprolol tartrate</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<td>Valproic acid</td>
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<td>Carbamazepine</td>
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<td>Topiramate</td>
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<td><strong>NSAIDs</strong></td>
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<tr>
<td>Naproxen sodium</td>
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<td><strong>Calcium Channel Blocker</strong></td>
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<td>Flunarizine</td>
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persisted through the 10-year follow-up period, whereas other migrainous disorders and nonclassifiable headaches did not. Female gender, migraine severity at diagnosis, and longer duration from time of onset of headache until time of initial medical examination tend toward an unfavorable prognosis.

Impact of migraine

In clinical practice, management of children and adolescents with headache should incorporate the addition of headache disability and quality of life assessments to the traditional outcomes of headache intensity, duration and frequency. The commonly used tools are PedMIDAS (Pediatric Migraine Disability ASsessment), a modification of MIDAS (Migraine Disability ASsessment) of adults and Pediatric Quality of Life Inventory Version 4.0 (PedsQL). The reliability, validity and utility of these measures have been demonstrated, and they can be efficiently incorporated into day-to-day clinical care. Both tools add unique information to the determination of the outcome of intervention. Assessments should be made at initial evaluation and regularly throughout treatment.

Summary

Migraine is a common disorder in children and adolescents. There is a wide spectrum of clinical forms, but the most frequent form is migraine without aura, which is characterized by attacks of frontal or bitemporal pounding and nauseating headache lasting 1 to 72 hours. A fascinating and challenging subset known as migraine with aura and the periodic syndromes can be associated with frightening focal neurologic disturbances and may require careful consideration for the possibility of neoplastic, vascular, metabolic, or toxic disorders.

Migraine treatment philosophy now embraces a balanced approach with biobehavioral interventions and pharmacologic measures. Treatment decisions must be based on the disability produced by the headaches, the headache burden.

In the near future, further advances in understanding the molecular genetics of migraine can be anticipated, that should translate to improved care of the migraine in children. Furthermore, therapeutic energy expended for our pediatric patients should translate to decreased disability as our patients progress into adulthood, lessening the lifespan burden of migraine.

Points to Remember

- Recurrent headaches, of whatever cause, are a cause of considerable morbidity, especially in terms of school absence.
- Migraine headache, is extensively underestimated and misdiagnosed in the pediatric population.
- Understanding the impact of migraine on the quality of life can guide the decisions regarding the most appropriate therapeutic action.
- Migraine treatment philosophy embraces a balanced approach with biobehavioral interventions and pharmacologic measures.

References


LINCOSAMIDES, OXAZOLIDINONES AND STREPTOGRAMINS IN PEDIATRIC PRACTICE

* Jeeson C Unni

Abstract: Lincosamides (clindamycin), streptogramins [dalfopristin (streptogramin A) and quinupristin (streptogramin B)] and oxazolidinones (linezolid) are grouped together because they have a similar mode of antibacterial action and similar antibacterial spectra. Macrolides and the ketolide telithromycin (Telithromycin) may be included with this group for similar reasons. All inhibit protein synthesis by binding to the 50S ribosomal subunit. Cross-resistance occurs among macrolides, clindamycin, quinupristin and to some extent, telithromycin because they bind to the same target. However, cross-resistance does not occur between these antibiotics and dalfopristin and linezolid which bind to different targets on the 50S ribosomal subunit. Lincosamides and streptogramins are used for mixed infections with gram positives and anaerobes. The new antibiotic on the horizon – the oxazolidinone antibiotic, linezolid - to which no resistance has yet been described - needs to be used sparingly for infections for which no other antibiotic is effective.

Keywords: Lincosamides, Oxazolidinones, Streptogramins, Children.

The three groups of antibiotics that are to be discussed in this drug profile review article are not used often in pediatric practice. They have their limitations and special indications for use clinicians caring for children and adolescents need to be aware of their role in pediatric therapeutics. Though the drugs in these groups are unrelated compounds, they are discussed together because they possess a common mode of action and similar antibacterial spectra. The drugs that will be discussed in detail are clindamycin (prototype of lincosamides of which the only other drug is lincomycin); dalfopristin (streptogramin A) and quinupristin (streptogramin B) and a combination of the two; and linezolid (prototype of oxazolidinones).

Mechanism of action

Lincosamides and streptogramin B (quinupristin) are protein synthesis inhibitors that bind to the 23S portion of the 50S subunit of bacterial ribosomes and cause premature dissociation of the peptidyl-tRNA from the ribosome. They inhibit the late phase of protein synthesis and are bacteriostatic. Streptogramin A (dalfopristin) binds to the 70S or 50S ribosomal particle and inhibits the early phase of protein synthesis. Though both streptogramins are bacteriostatic, when used together, they can inhibit bacterial growth and are bactericidal. Streptogramin A first binds to the peptidyl transferase domain of the 50S ribosomal subunit, preventing the early events of elongation. The binding of streptogramin A causes a conformational change that increases the ribosomal binding activity of streptogramin B.
100-fold. Oxazolidinones, on the other hand, bind to the 50S subunit of the prokaryotic ribosome, preventing it from forming complexes with the 30S subunit, mRNA, initiation factors and formylmethionyl-tRNA. What this achieves is the inhibition of the production of complexes required for the initiation of protein synthesis, thus preventing translation of the mRNA. The mechanism of action of oxazolidinones therefore differs from that of other protein synthesis inhibitors like chloramphenicol, macrolides, lincosamides and tetracyclines, which do not block initiation of mRNA translation but inhibit the consequent peptide elongation. This difference may be significant in two aspects - i) prevents synthesis of staphylococcal and streptococcal virulence factors (e.g. coagulase, hemolysins and protein and ii) site of action does not overlap with that of other protein synthesis inhibitors; and as a result, rRNA methylases that modify the 23S rRNA and in turn block the binding of macrolides, clindamycin and group B streptogramins, do not affect its activity. However, prevention of the initiation of protein synthesis being no more lethal than prevention of peptide elongation, oxazolidinones are also essentially bacteriostatic.

**Pharmacokinetics**

Clindamycin is available in three salt forms: hydrochloride (oral capsules), palmitate (oral solution) and phosphate (injection). Clindamycin hydrochloride is well absorbed after oral administration, with an absolute bioavailability of 90%. Administration with food does not appear to affect absorption. It is widely distributed in body fluids and tissues, including bone and pleural fluid. It does not appreciably distributed into cerebrospinal fluid, even with inflamed meninges. It is extensively metabolized via cytochrome P450 3A4 to primarily inactive compounds, with approximately 10% excreted in the urine. The average half-life is 2 to 3 hours. The serum half-life may be slightly longer in patients with severe renal or hepatic dysfunction, but no specific dosing adjustment is recommended. Serum half-life is significantly longer (8.68 vs 3.60 hours) in premature compared with term infants less than 4 weeks of age. Both premature and term infants less than 4 weeks have significantly decreased clearance when compared with infants greater than 4 weeks (0.294 and 0.678, respectively, vs 1.58 L/hr). Clearance is significantly greater (1.919 vs 0.310 L/hr) and serum half-life less (1.75 vs 7.57 hours) in infants with body weight greater than 3.5 kgs.

Quinupristin and dalfopristin, following intra venous administration, are rapidly cleared from the blood with elimination half-lives of approximately 1 hour for quinupristin and 0.4-0.5 hour for dalfopristin. The pharmacokinetic profile of quinupristin is dose-independent and so is that of dalfopristin and when considered together. They are eliminated mainly in the faeces and to a lesser extent in the urine. A dose independent pharmacokinetic profile emerged for quinupristin, but not for dalfopristin. With increasing doses of dalfopristin, there was a significant increase in its volume of distribution without a change in clearance its elimination half-life therefore increased accordingly. Interestingly, the sum of the AUCs for dalfopristin and its metabolite RP 12536 showed dose-proportionality. They penetrate rapidly and well into non-inflammatoriy interstitial fluid. However, they do not penetrate the central nervous system or cross the placenta to any significant degree.

A major advantage of linezolid is its high bioavailability (close to 100% - similar to IV administration) when given by mouth: allowing switch to oral route at the earliest. Taking linezolid with food somewhat slows its absorption, but the area under the plasma
concentration time curve (AUC) is not affected. Peak serum concentrations (C_{max}) are reached one to two hours after administration and the drug is readily distributed to all tissues in the body apart from bone matrix and white adipose tissue. Concentrations achieved in the epithelial lining fluid of lower respiratory tract are equal to or more and that in CSF slightly less than levels attained in serum. Elimination half life is 4.5-5.5 hrs. The clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population.

**Spectrum and clinical use**

Clindamycin exhibits a broad spectrum of antimicrobial activity, including Gram-positive aerobes/anaerobes, Gram-negative anaerobes and select protozoa (Toxoplasma gondii, Plasmodium falciparum, Babesia spp.) and fungi (Pneumocystis jiroveci). It is the drug of choice for treating retropharyngeal abscess in children. It has also been used in empiric antibiotic regimens for dental infections – not only for endocarditis prophylaxis during dental procedures bone and joint infections where anaerobes and/or MRSA were likely causes as well as in the treatment of serious skin and soft tissue infections, (SSI) especially when MRSA is being considered. However, studies have shown that there is no significant difference between cephalexin and clindamycin for treatment of uncomplicated pediatric SSTIs caused predominantly by community acquired MRSA - close follow-up, fastidious wound care and appropriate drainage of wound being more

important than initial antibiotic choice. The cost of clindamycin - quinine combination limits its usefulness in areas where malaria is endemic. A combination of clindamycin and primaquine appeared superior to pentamidine as second-line therapy for pneumocystis pneumonia in patients failing or developing toxicity with trimethoprim/ sulfamethoxazole. A combination of topical benzoyl peroxide and clindamycin was found to be as effective as a combination of benzoyl peroxide and salicylic acid and better than benzoyl peroxide or clindamycin used alone in treatment of acne.

The quinupristin/dalfopristin combination (both as mesilate salt) is licensed in adults for infection due to Gram positive bacteria but there is limited information on use in children. Hence, in children, the combination needs to be reserved for treating MRSA treatment failures or in conditions when no other drug seems to be effective. The combination is ineffective against E faecalis and has to be co-prescribed with other antibiotics in mixed infections involving gram negatives. A study in adults suggests effectiveness of the combination in vancomycin-resistant E faecium infections in the critically ill with serious underlying conditions.

The anti-bacterial spectrum of linezolid was reviewed in a multi-centre, multi-national study of antibiotic sensitivity. It demonstrated an almost universal coverage for Gram positive organisms; including those that were multi-drug resistant. Linezolid also covers infections by anaerobes, atypical microbes like chlamydia and mycoplasma species, select gram negative bacilli and mycobacterium species. Recent results have demonstrated that oxazolidinone analogs related to linezolid are effective in treating pulmonary tuberculosis caused by resistant Mycobacterium tuberculosis in animal infection models and suggest additional new therapeutic applications for these
Since, till date, little resistance has been reported to Linezolid even amongst methicillin (MRSA) - and vancomycin (VRSA) - resistant staphylococcus, vancomycin-resistant enterococci (VRE) and penicillin resistant streptococcus pneumoniae (PRSP) this drug needs to be reserved for treatment of these difficult-to-treat infections.

**Dosage and administration**

**Clindamycin**

- **Neonates** - <7 days: <2000gm 10mg/kg/day divided 12th hrly IV/IM; <7 days >2000gm 15mg/kg/day divided 8th hrly IV/IM; >7 days <1200gm 10mg/kg/day divided 12th hrly IV/IM; 1200-2000gm 15mg/kg/day divided 8th hrly, >2000gm 20mg/kg/day divided 8th hrly IV/IM. Children10-40mg/kg/day divided 8th hrly IV/IM or orally. 12-18yr 150-300mg upto max of 450mg/dose 4 times daily.

- Falciparum malaria (alternate therapy) with 20mg/kg/day for 5 days. If given IM it must be given as a deep IM injection to a maximum of 600mg (4ml). It is prudent to avoid rapid IV administration. Clindamycin must be diluted before IV administration to at least 6mg in 1ml. with NaCl 0.9% or glucose 5%, and infused over 10-60 minutes. Maximum rate 20mg/kg over 1 hour.

- Acne: Topical application as thin film 2 times daily with lotion and once daily with gel.

- **Dose adjustment in hepatic failure:** Dose reduced and liver function monitored. The drug is not readily removed by dialysis or peritoneal dialysis.

**Linezolid**

- Pneumonia, complicated skin and soft-tissue infections caused by gram-positive bacteria (initiated under expert supervision) - By mouth or by intravenous infusion over 30–120 minutes - Neonate under 7 days -10 mg/kg every 12 hours, increase to every 8 hours if poor response; Neonate over 7 days - 10 mg/kg every 8 hours; Child 1 month–12 years - 10 mg/kg (max. 600 mg) every 8 hours; Child 12–18 years - 600 mg every 12 hours. Children treated initially with IV linezolid may be switched to oral therapy without dosage adjustment when clinically appropriate.

**Drug interactions**

Clindamycin enhances effects of non-depolarising muscle relaxants and suxamethonium and antagonises effects of neostigmine and pyridostigmine. Clindamycin, like all antibiotics that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk is probably small). Interactions of combined oral contraceptives may also apply to combined contraceptive patches and vaginal rings. The combination of erythromycin and clindamycin appears to produce antagonistic effects in vitro, so the concomitant use of these two antibiotics is not recommended.

Linezolid is a reversible, nonselective inhibitor of monoamone oxidase. When vasopressor or dopaminergic agents are co-administered, the initial doses should be reduced and titrated to achieve the desired response and reduce the incidence of serotonin syndrome. Adrenergic drugs such as dopamine, epinephrine, phenylpropanolamine, pseudoephedrine may cause hypertension. Monitor blood pressure and heart rate. Increased blood pressure may occur when linezolid is used with diet high in tyramine.

**Side effects**

Despite its potential to treat mixed infections involving gram positives and anaerobes, clindamycin is not a first line drug, except for retropharyngeal abscess or peritonsillar abscess, because of its association with pseudo membranous colitis. Discontinuation of
therapy is recommended if diarrhoea develops. Other side effects include nausea and vomiting, jaundice and altered LFTs, leucopenia, eosinophilia and thrombocytopenia; polyarthritis; rash, pruritus, urticaria, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection. With topical use, skin dryness and irritation may occur.

Linezolid: Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for up to 28 days. Drug-related adverse events in children are typically mild to moderate in intensity and of limited duration and include loose stools and vomiting. Pseudo membranous colitis is uncommon. There have been case reports of reversible thrombocytopenia, anaemia and neutropenia. These blood disorders and optic neuropathy have been reported in patients receiving linezolid for more than the maximum recommended duration of 28 days.

Points to Remember

- **Lincosamides, streptogramins and oxazolidinones** are unrelated compounds but common mode of action and antibacterial spectrum
- **Predominantly Gram positive coverage** – *streptococcus, staphylococcus; Clindamycin has anaerobic activity; Linezolid - MRSA, VRSA, VRE, PRSP.*
- **Clindamycin not first line drug due to association with pseudomembranous colitis;** - reserve for mixed infection in retropharyngeal abscess and endocarditis prophylaxis. It may be used for skin and soft tissue / bone and joint infections due to excellent tissue penetration if 1st line antibiotics do not give adequate response.

- **Streptogramins** - ([dalfopristin (streptogramin A) and quinupristin (streptogramin B)] – Separately or in combination are not used in pediatrics.
- **Linezolid, being one of the few drugs that may be used in VRSA, VRE, PRSP infections, must be reserved for treatment of these difficult to treat infections. Misuse of this life saving drug must therefore be avoided.**
- **Cost of linezolid should also be a deterrent to its rampant use.**

References


Abstract: Skin acts as a mirror and helps in the diagnosis of obscure internal disease. There are several conditions in which both cardiac and skin involvement are present. Congenital heart diseases are associated with dermatological manifestations such as cyanosis, clubbing, etc. There are certain dermatological conditions that are associated with cardiac defects. There are many multi system disorders in which both cardiovascular system and skin are involved.

Keywords: Skin, Cardiac, Multi system.

The skin being the largest organ in the body, many a times may throw light on the diagnosis of an obscure internal disease. There are several conditions in which both cardiac and skin involvement may be present. Either the cutaneous manifestation may be secondary to the cardiac condition, as is the case of cyanosis, polycythemia and clubbing secondary to congenital heart disease or the cardiac component may occur secondary to the dermatological condition, eg- heart failure in erythroderma. Certain congenital cardiac defects that occur in genetic disorders are associated with unique skin manifestations as in Down syndrome, Turner syndrome, multisystemic disorders like collagen vascular diseases, sarcoidosis, etc may affect the heart and skin simultaneously or in sequence. At times, the cutaneous manifestations may be a component of a systemic or vascular disorder, which also involve the cardiovascular system as another component.

In general, skin and heart may be affected in certain congenital/inherited conditions, genetic disorders, infections, inflammatory diseases, connective tissue disorders, vasculitis, metabolic and endocrine disorders etc. In this article, the dermatological manifestations of few cardio-cutaneous conditions have been discussed, while other disorders have been tabulated (Table 1).

**Congenital rubella syndrome**

Congenital rubella occurs when a non-immune pregnant woman transfers the virus to the fetus. Congenital rubella syndrome is characterised by the presence of classical triad of congenital cataract, deafness and cardiac defects (patent ductus arteriosus, peripheral stenosis of pulmonary artery, ventricular septal defect). Apart from intrauterine growth retardation, microcephaly and mental retardation, hepatospleenomegaly, thrombocytopenia, pigmentary retinopathy may be present. Characteristic cutaneous lesions, namely discrete bluish red macules measuring 2 to 8 mm in diameter, papules and nodules may be present at birth or occur within two days. While new lesions rarely occur after 48 hours, lesions fade over a few weeks. These bluish purple macules and papules that occur in a generalised pattern, due to extramedullary hematopoiesis are referred to
as the blueberry muffin lesions. Other causes of these lesions in a newborn are infections due to toxoplasma, cytomegalovirus, enterovirus and Parvovirus B19, erythroblastosis foetalis, hereditary spherocytosis, ABO incompatibility (twin-twin transfusion syndrome), neoplasia like neuroblastoma, leukemia and histiocytosis.

Other dermatological manifestations may include cutis marmorata, seborrhoea, hyper pigmentation of the forehead, cheeks and umbilical area, recurrent urticaria and discrete deep dimples over bony prominences, particularly patellae. Vasomotor instability that presents as generalised mottling and acral cyanosis may occur.\textsuperscript{1,2}

**Chromosomal disorders**

**Trisomy 21 (Down’s syndrome)**

Down’s syndrome is the most common example of aneuploidy that occurs due to an extra copy of chromosome 21 resulting in multi system involvement, with an incidence of 1 in 700 live births.\textsuperscript{3} The characteristic clinical features were first described by John Langdon Down in 1866.\textsuperscript{4}

Morphological features and cardiac involvement being well known, focus would be only on the dermatological manifestations of Down’s syndrome. The skin is normal at birth and in early childhood becomes soft and velvety. Dryness of skin is seen to slowly increase from 5 years onwards and by 15 years, generalised xerosis is observed in over 70% of children. Premature wrinkling of the skin may occur. Patchy lichenification is present in 30% under 10 years and in 80% over 20 years.\textsuperscript{3} A south indian study reported lichenification to be the most common disorder among the dermatological manifestations.\textsuperscript{5} Increased incidence of auto immune conditions like alopecia areata and vitiligo have been reported, which may be related to the immunological deficiency in T-cell function in Down’s syndrome. Alopecia areata when present is severe and refractory to treatment.\textsuperscript{3} Atopic dermatitis is not as common as previously considered. However, patients with lichenification, xerosis and palmoplantar keratoderma may represent an atopic diathesis.\textsuperscript{5} Malassezia folliculitis presents as a chronic follicular papular eruption in the presternal and interscapular regions. Seborrhoetic dermatitis is frequently seen.

Hair is fine and sparse in these children. They may be more prone for bacterial and fungal infections. There is a high prevalence of onychomycosis. Children with Down’s syndrome are predisposed to the development of norwegeian scabies, which presents as generalised scaling, hyperkeratotic crusted plaques on the palms, soles, flexure aspects of the wrists, buttocks and the sacrum. This predisposition is the result of immunologic dysfunction and poor cutaneous sensation.\textsuperscript{4} Angular chelitis, fissured scrotal tongue and chronic blepharitis are common.

Dermatoglyphic studies have revealed the occurrence of simian palmar crease, a single flexion crease on the fifth finger and an increased incidence of ulnar loops on the fingers. Elastosis perforans serpiginosa characterised by reddish to skin coloured hyperkeratotic 1-3mm papules with a central keratotic plug that occur singly or in circinate patterns has been reported. These lesions are usually seen on the nape of the neck and upper extremities, but are occasionally seen on the face and trunk. Though usually asymptomatic, it may occasionally produce pain and pruritus.\textsuperscript{6}

There is an increased prevalence (19-37%) rate of syringomas in children with Down’s syndrome compared to the general population. Lesions usually present as 1-3mm asymptomatic flat topped, flesh coloured papules in a
widespread pattern. An association between perforating milia like calcinosis cutis lesions and periorbital syringomas has been reported in patients with Down’s syndrome.\textsuperscript{7} Vasomotor instability may present as acrocyanosis and cutis marmorata. Children with Down syndrome have an increased risk of leukemia, leukemoid reaction and transient myeloproliferative disorder. The latter two conditions may present as pustular or vesicopustular skin eruptions which resolve without therapy as the hematologic disorder subsides.\textsuperscript{8}

**Trisomy 18 (Edward’s syndrome)**

Cutaneous features include nail hypoplasia, cutis laxa of the neck, hypertrichosis of the forehead and back, and capillary haemangiomas. Dermatoglyphics reveals a low arch dermal ridge pattern. Camptodactyly of the fingers will be present along with absence of distal flexion creases of the little finger and often also of the third and the fourth fingers. The hand is usually clenched with fixed overlapping of the index over middle finger and the fifth over the fourth finger. Hypoplasia of subcutaneous and adipose tissue is common.\textsuperscript{3,9}

**Trisomy 13 (Patau syndrome)**

Cutaneous lesions are localized defects of the scalp, capillary haemangiomas particularly in the glabellar region, hyper convex nails and postaxial polydactyly, often with a rudimentary postminimus sixth finger. Cutis laxa and recurrent chronic cellulitis affecting the parotid region, axilla, abdominal wall and groin has been reported.\textsuperscript{3,9}

**Cutis laxa (Generalised Elastolysis)**

This belongs to a group of heterogenous disorders of elastic tissue, characterised by loose, inelastic skin that is pendulous and hangs in folds, resulting in a prematurely aged or blood hound appearance. It may be congenital or inherited. Skin is hyperextensible and does not resume the normal shape unlike in Ehler Danlos syndrome. Systemic involvement occurs in the form of aortic dilatation, pulmonary stenosis, pulmonary emphysema, gastrointestinal and genitourinary diverticulae and ventral hernia.\textsuperscript{10}

**Ehlers Danlos Syndrome**

It is characterised by abnormal collagen synthesis or processing. There are 12 sub types. Cutaneous features include skin hyperextensibility and fragility. The skin recoils back to the original shape. Hypermobility of the joints is present. Fragile skin with easy bruisibility and cigarette paper scar are the characteristic lesions. Cardiac involvement limited to the classical, hypermobility and vascular types, comprises of aortic and pulmonary artery dilatation, arterial rupture, mitral and tricuspid valve prolapse.\textsuperscript{11,12}

**Multisystem diseases with involvement of skin and heart**

**Rheumatic fever**

Erythema marginatum and subcutaneous nodules are the cutaneous manifestations of rheumatic fever that are included as 2 of the 5 Jones major criteria for the diagnosis of rheumatic fever.

**Erythema marginatum** is an asymptomatic, evanescent, migratory annular erythema seen in 10-20% of children with acute rheumatic fever, that occurs in conjunction with the carditis, preceding the joints manifestations. It is characterised by erythematous, polycyclic, serpigenous plaques with central clearing that disappear without pigmentation or scaling. The most common sites to be involved are the trunk, axillae and proximal extremities, but face and hands may be rarely involved. Lesions migrate by 2mm -12mm over 12 hours and may disappear within few hours to few days. Recurrent crops occur over several weeks.\textsuperscript{13,14}
Subcutaneous nodules seen in a frequency of 0-8% occurs primarily on the bony prominences namely the occiput, wrist and the extensor surfaces of the elbows, knees, ankles, knuckles attached to the tendon sheath and spinous processes of the lumbar and thoracic vertebrae. The nodules are firm, non tender, free from the overlying skin and vary in size between a few millimeters to 1-2 cm. They are smaller and more transient than the nodules seen in rheumatoid arthritis. Nodules resolve within a month and are strongly associated with severe rheumatic carditis.13,14,15

**Infective endocarditis**

Cutaneous manifestations of subacute bacterial endocarditis which occur as a result of septic emboli or immune complex deposition due to bacterial focus, act as important clues to the diagnosis. They include cutaneous purpura and petechiae, Roth’s spots, Osler’s nodes, Janeway lesions and subungual splinter haemorrhages. Petechiae are the most common mucocutaneous manifestations of bacterial endocarditis, with an incidence of 20-40% among the patients with acute and subacute bacterial endocarditis. They occur as small, red or violaceous macules that do not blanch and subsequently fade. Petechiae may be seen, especially on the heels, legs and shoulders. Purpura (flat and elevated) occur without evidence of platelet dysfunction, and may represent leukocytoclastic vasculitis. Roth spots (conjunctival petechiae) observed in 5% of patients are oval, retinal hemorrhages with a clear, pale center. Osler nodes are small, tender nodules that develop distally on the digital tufts and toe pads. They persist for hours to days. Janeway lesions are faint red macular lesions that occur on the palms and soles. Splinter hemorrhages are subungual, linear, dark-red streaks. Osler’s nodes and Janeway lesions have also been reported in systemic lupus erythematosus, gonococccemia, haemolytic anemia and enteric fever.17,18

**Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is a chronic inflammatory small vessel vasculopathy of unknown etiology, involving multiple organ systems. Approximately 15-20% of all patients of systemic lupus erythematosus occur within the first two decades of life. Of these, 60% occur between the ages of 11-15 years, 35% between 5-10 years and 5% in less than 5 years. Apart from neonatal SLE, this disorder is rarely seen below 3 years. A child is diagnosed as having SLE if any four out of the 11 ARA criteria are present. Children often present with fever, arthralgia/arthritis, rash and fatigue.19,20

In about 25% of the patients, cutaneous lesions are the presenting features. Classical discoid lupus erythematosus lesions are the most common cutaneous manifestations of childhood SLE. These lesions occur as well defined, erythematous plaques with adherent scales, telangectasia and follicular plugging and atrophy. Discoid lesions of LE may be seen without serologic or systemic manifestations of SLE. Erythematous, mildly scaly eruption that occurs over the cheeks and bridge of the nose, the malar rash is seen in 30 - 60% of patients with SLE. Subacute cutaneous lupus erythematosus (SCLE) lesions characterized by polymorphic, psoriasiform lesions with thin and easily detached scales. Other cutaneous lesions that may be present are erythematous, edematous non-scarring plaques in sun exposed areas (lupus erythematosus tumidus), petechiae, purpura, livedo reticularis, urticaria like vasculitis lesions, erythema nodosum, oral and nasal ulcers, nail fold telangiectasia, small digital ice pick infarcts, scarring or non-scarring alopecia.19,20,21

Cardiac involvement may occur in about 50% of childhood SLE patients. It includes pericarditis, myocarditis, vasculitis affecting the coronary arteries and Libman-Sachs endocarditis.
Cardiac failure from myocarditis or infarction may be present.\textsuperscript{19,20,21}

**Neonatal Lupus Erythematosus**

Neonatal lupus erythematous (NLE) caused by maternal transmission of autoantibodies is seen in infants born to mothers with or who have a tendency for SLE, rheumatoid arthritis, Sjogren syndrome, mixed connective tissue disease.\textsuperscript{20} Anti-Ro antibody is present in more than 95\% of NLE infants, while anti-La antibody is seen in 60 - 80\% of them. Mothers of affected infants, who are asymptomatic, will later develop LE or Sjogren’s syndrome, the risk being estimated between 2\% to more than 70\%. Cardiac disease begins in utero and affects the conduction system of the heart permanently.\textsuperscript{22}

About 50\% of babies with NLE have cutaneous manifestations, with the lesions occurring within the first few days of life. However, they may be seen at birth. New lesions do not occur after approximately 3 months of age. Erythematous sharply demarcated, non scaly lesions may occur on all parts of the body, including the scalp with a strong predilection for the periorbital areas causing the characteristic “raccoon eyes” appearance. NLE lesions may resemble the papulosquamous (erythematous, nonindurated, scaly plaques) and annular polycyclic lesions of subacute cutaneous lupus erythematosus. Discoid lesions, scaly atrophic patches and telangectasia have been described. Telangiectasia may be an initial sign of NLE.\textsuperscript{22} Mucosal ulceration has been reported in severely affected babies.\textsuperscript{20} The skin lesions generally disappear by 7 months of age, corresponding to the disappearance of the maternal IgG antibodies.\textsuperscript{21} NLE is the most frequent cause of congenital heart block. Unlike the cutaneous lesions of NLE, congenital heart block is irreversible. Associated congenital heart defects such as patent ducus arteriosus, septal defects, transposition of the great vessels, coarctation of the aorta, tetralogy of Fallot, tricuspid and mitral insufficiency have been reported in 30\% of affected infants.\textsuperscript{21}

**Kawasaki disease**

Kawasaki disease (KD) is an acute febrile mucocutaneous lymph node syndrome with multisystem vasculitis affecting infants and children less than 5 years of age, that has become one of the leading causes of acquired heart disease in the world. Diagnosis of KD is based on the clinical features including fever for 5 days or more and four of the following five signs: 1) bilateral conjunctival injection, 2) oral mucosal changes - pharyngeal erythema, cheilitis, strawberry tongue, 3) acute hand and foot edema with erythema followed by periungual desquamation (convalescent), 4) erythematous, polymorphous generalised skin eruption and 5) cervical lymphadenopathy (at least 1.5 cm).\textsuperscript{23,24}

The conjunctival injection is unique with involvement of the bulbar conjunctiva, absence of exudate and perilimbal sparing. Periungual desquamation that begins during the convalescence (10-15 days after the onset) begins at the tips of the digits, after which membranous desquamation spreads over the palms up to the wrist, to be followed by the desquamation of the toes after several days. Cutaneous features of KD include a polymorphic exanthem that may be morbilliform, maculopapular, scarlatiniform, urticarial or erythema multiforme like with targetoid lesions. Accentuation of the skin eruption in the folds, especially the groin, resulting in an erythematous desquamation is an important finding.\textsuperscript{25}

Cardiac involvement includes coronary arteritis, coronary artery aneurysms, pericardial effusion, myocarditis, endocarditis, congestive heart failure, arrhythmias and valvular reguritation.\textsuperscript{25}
Table I. Cardiocutaneous associations\textsuperscript{26-31}

<table>
<thead>
<tr>
<th>Disease /Syndrome</th>
<th>Cardiovascular/ other components</th>
<th>Cutaneous features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner syndrome</td>
<td>Coarctation of Aorta</td>
<td>Triangular facies, micrognathia, lymphedema, hypoplastic, hyperconvex nails, multiple naevocellular naevi etc</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Aortic aneurysm</td>
<td>Typical facies with dolichocephaly, malar hypoplasia and enophthalmos, ectopia lentis, long, thin extremities</td>
</tr>
<tr>
<td>Ellis-van Crewald syndrome</td>
<td>AV septal defects</td>
<td>Ectodermal dysplasia affecting nails and teeth, polydactyly, chondrodysplasia,</td>
</tr>
<tr>
<td>William syndrome</td>
<td>Supravalvular aortic stenosis</td>
<td>Elfin facies - high prominent forehead, stellate iris patterns, epicanthal folds, underdeveloped mandible and bridge of the nose, overhanging upper lip, strabismus, and dental abnormalities, skeletal defects</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Truncus arteriosus, interrupted/double aortic arch, aberrant subclavian artery.</td>
<td>Thick, dry, scaly skin, sparse hair and eyebrows, thin, short, brittle nails, hypoplasia of teeth, calcification of skin and subcutaneous tissues</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>Cardiomyopathy/ cerebellar ataxia, retinitis pigmentosa, peripheral polyneuropathy, sensorineural deafness, anosmia</td>
<td>Fine, white scales over trunk and extremities resembling ichthyosis vulgaris</td>
</tr>
<tr>
<td>Entero viral exanthems ( Groups A&amp; B Coxsackie virus, ECHO virus)</td>
<td>Pericarditis, myocarditis/ gastrointestinal symptoms, neurological ( aseptic meningitis. Encephalitis &amp; paralysis)</td>
<td>Maculopapular , petechial &amp; vesicular rash, haemorrhagic conjunctivitis</td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td>E-ECG abnormalities O- ocular hypertelorism, A- abnormalities of the genitalia, R- retardation of growth, D-Deafness</td>
<td>Multiple lentigines</td>
</tr>
<tr>
<td>Myxomas (Carney’s complex, NAME and LAMB syndromes)</td>
<td>Atrial myxomaPituitary, thyroid and testicular tumours</td>
<td>Naevi, mucocutaneous myxomas, myxoid neurofibroma, lentigines, blue nevi, ephelides</td>
</tr>
<tr>
<td>Disease /Syndrome</td>
<td>Cardiovascular/ other components</td>
<td>Cutaneous features</td>
</tr>
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<td>--------------------------</td>
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<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Selenium deficiency</td>
<td>Cardiomyopathy/ Muscle pain and weakness, elevated creatine kinase and transaminase levels,</td>
<td>Hypopigmentation of skin and hair, white nails</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Cardiac rhabdomyomas</td>
<td>Angiofibromas, ash –leaf macules, Shagreen patch, periungual &amp; subungual fibromas</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Hypertension (renovascular or phaeochromocytoma)</td>
<td>CALM, Neurofibromas</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Pericardial effusion, conduction defects, myocardial fibrosis, cardiomyopathy, cor pulmonale</td>
<td>Cutaneous sclerosis , Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Conduction defects, cardiomyopathy, pulmonary hypertension</td>
<td>Gottron’s papules, heliotrope rash, poikiloderma</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Conduction defects, arrhythmias, CCF</td>
<td>Papules, plaques, nodules and or lesions in scars</td>
</tr>
<tr>
<td>Erythroderma ,any cause</td>
<td>High output cardiac failure</td>
<td>Exfoliation</td>
</tr>
</tbody>
</table>

**Conclusion**

Skin and cardiovascular system are involved in many conditions, either as in congenital heart disease, genetic disorders or as concomitant components of multi system disease. Cutaneous associations of cardiac conditions will enable the physicians to make an early diagnosis of the underlying condition, provided one is aware of them as “The Eyes do not see, what the mind does not know”.

**Points to Remember**

- **Chromosomal disorders such as Down’s syndrome, Turner syndrome have unique morphological features and specific cardiac defects.**
- **Erythema marginatum and subcutaneous nodules in rheumatic fever are associated with acute carditis.**
- **Neonatal lupus erythematosus is the most frequent cause of congenital heart block. Most of the mothers of affected babies are asymptomatic and must be evaluated and followed for the development of lupus erythematosus, Sjogren’s syndrome, mixed connective tissue disease and rheumatoid arthritis.**
• Cutaneous markers may facilitate the diagnosis of underlying cardiac condition.

References


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**CLIPPINGS**

Iramain, Ricardo, López-Herce, Jesús; Coronel, Julia; Spitters, Cristopher; Guggiari, Jaime; Bogado, Norma. Inhaled Salbutamol Plus Ipratropium in Moderate and Severe Asthma Crises in Children. *Journal of Asthma, April 2011.*

The combination of inhaled β₂ agonists and anticholinergics is recommended for children with acute asthma. This was a prospective study of children aged 2-18 years to determine whether salbutamol plus ipratropium bromide improves oxygenation and lung function and reduces the frequency of hospitalization in children with asthma crises. Patients were evaluated using the asthma score and spirometry. They received six nebulizations of salbutamol plus placebo or salbutamol plus ipratropium and were re-evaluated at 30, 60, 90, 120, and 240 minutes, at which time it was decided whether they were to be admitted. A total of 97 patients completed the study, 49 in the salbutamol plus ipratropium group and 48 in the salbutamol-only group. There were no differences in the status at baseline between the two groups. Children treated with salbutamol plus ipratropium presented a greater improvement in clinical state and lung function and required hospitalization less frequently (18.4%) than children in the salbutamol group (43.8%) (p = .007). Improvement was more marked in children with severe asthma crises than in those with moderate crises. The effect of salbutamol plus ipratropium was similar in children over 8 years of age and in younger children. Salbutamol plus ipratropium bromide improves lung function in asthmatic children with moderate to severe asthma crises, independently of age. The effect is greater in children with severe crises, with a substantial reduction in the need for hospitalization.
PARASELLAR TUMORS

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**** Elavarasu MD

In the last issue we saw sellar tumors. Now we will focus on some tumors around the sella. We have already seen the boundaries of the sella which are the cavernous sinus and its contents, the sphenoid bone including the sphenoid sinus and the brain tissue in the middle and posterior fossa. The possible tumors and tumor like lesions arising from these structures include aneurysms arising from the internal carotid artery and the circle of Willis, cavernous sinus hemangiomas and Schwannomas arising from adjacent cranial nerves like the trigeminal schwannoma. Chondromas and chondrosarcomas can arise from the sphenoid bone, while chordomas arise from primitive notochord cell rests at the base of the skull notably the clivus. Superiorly is the hypothalamus where hypothalamic glioma, hamartomas and germinomas are possibilities.

Meningiomas are rare in children, constituting less than 1% of childhood intracranial neoplasms. Meningiomas are slow growing tumors. They arise from the arachnoid cells in the arachnoid villi that project into the dural sinuses. So, these tumors are dural based and therefore have a very rich blood supply from the meningeal arteries. This accounts for their brilliant enhancement following contrast. Another interesting aspect of meningiomas is adjacent hyperostosis which is due to invasion of dura that provokes an intense osteoblastic response. Hyperostosis is seen in about 15 to 20% of patients. The tumor may show punctate calcifications and cysts. The tuberculum sellae, anterior clinoid, adjacent medial sphenoid wing, superior orbital fissure and cavernous sinus are common sites at the skull base. In the vault they occur parasagittally, from the falx or anywhere along the convexity of the brain.

Fig.1 shows an almost isodense mass near the sella to the right. The tumor is seen to arise from the petrous ridge and has grown through the tentorial hiatus into the posterior fossa. The edges of the tentorium pinches the mass giving it a dumb-bell shape. The pressure on the brain stem has compressed the 4th ventricle and dilated the superior ventricles. The cerebral cisterns are widened on that side proving the extra-axial origin of the mass. There is no surrounding edema. 50% of meningiomas produce brain edema. On contrast injection the tumor enhances very well (Fig.2). It is well circumscribed and low grade meningiomas can be resected completely with little chance of recurrence.

MRI is useful for showing the relationship with neighbouring brain, arterial encasement and venous invasion. Tumors are isointense and enhance brilliantly with gadolinium just as in CT.
Fig. 1 Right parasellar hyperdense meningioma

Fig. 2 Homogenously and brilliantly enhancing meningioma

Fig. 3 Small aneurysm of the right anterior communicating artery

Fig. 4 Trigeminal schwannoma coronal section

Fig. 5 Trigeminal schwannoma axial section
The circle of Willis is closely related to the sella. Aneurysms commonly involve these arteries, commonest sites being the anterior cerebral artery and anterior communicating artery. These sites are followed by bifurcation of the internal carotid, posterior communicating artery, middle cerebral artery and basilar artery bifurcations. Fig.3 is a contrast CT showing a small aneurysm in the right anterior communicating artery. Small aneurysms are less than 1.5cm, large are 1.5 to 2.5 cm and giant aneurysms are greater than 2.5 cm.

Most aneurysms in the pediatric age group are congenital. Traumatic dissecting aneurysms can involve the cavernous carotid or the basilar arteries. Mycotic aneurysms resulting from septicemia are usually multiple and are found in the peripheral vascular bed commonly in the posterior fossa.

Fig.4 and Fig.5 shows a clearly defined hypodense lesion just posterolateral to the sella, to the right of the sphenoid bone. The white line around the tumor denotes the dural reflection and therefore tells us it is an extradural mass. This is the typical location for trigeminal schwannoma arising from trigeminal ganglion in the Meckel’s cavity. The Meckel’s cavity is a CSF containing pouch with the trigeminal ganglion. Medial to the ganglion is the internal carotid artery in the posterior portion of the cavernous sinus which will serve as a good landmark for identifying the location of the Meckel’s cavity. Schwannomas are hypodense lesions that show moderate enhancement. When the tumor is large it erodes the surrounding bone. Here it has eroded the petrous apex and sphenoid bone. The Meckel’s cavity can also be involved in bony metastases, expanding chordoma and chondrosarcoma.

The chordoma is primarily a midline mass with a large posterior fossa component. It causes irregular bone destruction of the clivus unlike the schwannoma that shows a smooth erosion. It is isodense or hyperdense and shows mild enhancement with contrast. Calcification is often present.

Another parasellar mass is the cavernous hemangioma occurring in the cavernous sinus. They are isodense with normal brain in plain CT and enhance intensely and homogenously on contrast CT. They can encase the cavernous carotid artery and cause mild erosion of bone.

The parasellar masses that we saw in this issue are rare but they show some distinctive features that help us make the diagnosis.

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**NEWS AND NOTES**

**MYOCON 2012**

Hosted by
Muscular Dystrophy Association, India

**Date:** 21st & 22nd January, 2012

**Venue:** Hotel GRT GRAND, Thyagaraya Nagar, Chennai.

For Further details Contact : Muscular Dystrophy Association, India
C/o. V.J.Clinic, New No.8, Old No.21, 4th Cross Street, Sastri Nagar, Adayar, Chennai - 600 020. Tamil Nadu. Email: myocon2012@gmail.com
CASE STUDY

CONSTIPATION IN AN ADOLESCENT - BEWARE

* Senthilnathan Ramaswamy
** Ravindar Anbarasan

Abstract: Constipation is a common problem in children. Development of constipation in an adolescent must be viewed with suspicion as this may be due to a mechanical cause. We report three adolescents with constipation, who were evaluated and surprisingly found to have carcinoma of the colorectum. Adenocarcinoma of the colon is the third common malignancy in adults. It is extremely rare in children. Though several case reports of occurrence in children are reported in the literature, new insights in the understanding about the pathogenesis of this malignancy is forthcoming only in this decade.

Keywords: Constipation, Adolescents, Adenocarcinoma colorectum, Hereditary nonpolyposis colon cancer.

Carcinoma of the colorectum is an important type of gastrointestinal malignancy in adults. It forms approximately 15% of cancer deaths in adults.1 Colorectal cancer is an extremely rare form of cancer in children and adolescents, hence most of the literature on this subject are single case reports. We did review of 53 case records of adolescent children presenting with constipation of short duration from May 1998 to September 2008. We had three cases of colorectal cancer and the remaining 50 children had either fissure in ano, a bleeding pile mass or no discernable cause for constipation.

Case Reports

Case 1

A 11 year old boy presented to us with history of recurrent attacks of abdominal pain and bilious vomiting. Examination revealed visible intestinal loops suggestive of an acute intestinal obstruction. Four weeks prior to this episode, he took treatment elsewhere for pain abdomen and progressive constipation and was managed conservatively. There was no past history of pain abdomen or bleed per rectum. A skiagram of the abdomen showed features of intestinal obstruction. Chest skiagram and routine blood counts were normal. An ultrasonogram of the abdomen showed dilated fluid filled bowel loops with solid organs being normal. He was taken up for an emergency laparotomy which revealed dilated bowel loops and a firm mass at the splenic flexure of the colon causing intestinal obstruction (Fig.1). Distal bowel was collapsed and transverse mesocolon had prominent lymph nodes. Patient underwent near total colectomy with nodal clearance. Ileo-pelvic colon anastamosis was done and intestinal continuity was reestablished. His post operative period was uneventful. Histopathological examination of the resected specimen showed a poorly differentiated mucinous adenocarcinoma and nodes were positive for malignancy (Fig.2). The boy has
Fig. 1. Resected specimen of a growth at the splenic flexure of the colon.

Fig. 2. Mucinous adenocarcinoma of the colon.
completed 1 year of follow-up and is on chemotherapy consisting of cisplatin and 5-fluorouracil.

Case 2

A 11 year old boy presented with history of constipation, pain abdomen and bleed per rectum for 2 months. He was treated elsewhere for fissure in ano with no significant improvement in symptoms. On admission to our institution, rectal examination revealed bleeding per rectum. Sigmoidoscopy revealed a proliferative growth at 10 cm from anal verge and later confirmed by biopsy to be a mucin secreting adenocarcinoma of the rectum. Patient underwent an anterior resection of rectum using a stapler. Nodal status was positive for malignancy. Patient died 9 months later with liver metastasis and pleural effusion.

Case 3

A 12 year old boy with history of constipation and abdominal pain was evaluated and subsequently operated elsewhere and found to have colonic cancer. He was referred to us for chemotherapy. The histopathology was a poorly differentiated mucinous adenocarcinoma of the colon with metastasis to the lymph nodes. He succumbed to the advanced disease 6 months later.

Discussion

The signs and symptoms of colorectal cancer in children are not routinely considered as a cause of constipation, recurrent abdominal pain, bleed per rectum or intestinal obstruction. This is due to the rarity of occurrence of colonic carcinoma in children. Acute intestinal obstruction is an important mode of presentation in 70% of the cases. It is common in the 11-16 year age group, though case report of this occurrence is reported in a 9 month old child. All the children in our review belong to the hereditary non polyposis colonic cancer group (HNPCC). HNPCC is now described as Lynch syndrome, named in honor of Dr. Henry T. Lynch, of Creighton University Medical Center. All three patients in our review did not have a pedigree of cancer occurring in the parents or siblings at the point of their presentation and seem to be isolated occurrence. Lynch syndrome survivors are more prone for developing a second malignancy like uterine or ovarian cancer.

Genetic studies on colonic adenocarcinoma (HNPCC) now focus on mutations in genes involved in the DNA mismatch repair pathway. These include MLH1 located on chromosome 3p21, MSH2 located on chromosome 2p21 responsible for 90% of the mutations. But this study is cumbersome and time consuming. Hence techniques have been evolved to identify cancer patients who are likely to be HNPCC carriers for genetic testing. Amsterdam criteria is useful in identifying high-risk candidates for molecular genetic testing which is as follows.

1. Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first degree (parent, child, sibling) relative of the other two. 2. Two successive affected generations of colon cancer. 3. One or more colon cancers diagnosed under the age 50 years. 4. Familial adenomatous polyposis (FAP) has been excluded.

An indirect method to identify DNA mismatch repair gene dysfunction is to measure the microsatellite instability (MSI) in the resected colon cancer specimens. If MSI is identified there is a higher likelihood of Lynch syndrome being diagnosed. Recently immunohistochemistry is also employed to identify DNA mismatch repair gene expression. These two tests in combination are able to identify majority of Lynch syndrome carriers.
This paves way for the confirmatory genetic testing for Lynch syndrome. HNPCC is inherited as an autosomal dominant disorder. Most children with HNPCC inherit the condition from one of the parent. However, due to incomplete penetrance, variable age of cancer diagnosis, cancer risk reduction, or early death, not all patients with an HNPCC gene mutation have a parent who had cancer. Some patients develop HNPCC de-novo in a new generation, without inheriting the gene. These patients are identified only after developing an early-life colon cancer. Parents with HNPCC have a 50% chance to pass the gene on to each child. We were not able to do genetic studies in our patients due to lack of facilities.

Adenocarcinoma of the mucinous type in children has a poor prognosis, as the presence of mucin prevents the natural immunity against the tumour cells and paves way for the spread of the malignancy. All our patients were in stage C of Dukes classification on presentation. Survival following complete excision for dukes stage A is 80% and is only 30-50% for stage C. This explains the 2 deaths we had in our cases. Adjuvant chemo and radiotherapy do not offer great benefits in pediatric colon carcinoma. A 10 cm margin of resection of the tumour with nodal clearance is recommended for curative resection.

Conclusion

Adolescent constipation must be diligently evaluated to rule out a sinister cause of constipation like colorectal cancer. Colonic adenocarcinoma can be the underlying cause. Only a high index of suspicion and early intervention will help in improving the survival and offer a better prognosis in children who develop abdominal symptoms in the 11-16 age group. Genetic studies will also help to identify HNPCC carriers who will need a close follow up in order to establish the later risk of developing second malignancy.

References

PICTURE QUIZ

Three days old, term, 2.2 kg, male baby, second born to third degree consanguinous parents, presented with bowing of both lower limbs since birth. Antenatal, natal and family history were not contributory. His both lower limbs were short with bowing of thighs. He had bilateral club feet and lateral two toes were absent bilaterally. All nails were dysplastic. Roentgenogram showed right angled bowing of both femora with absent fibulae bilaterally. Upper limb bones were normal. Sonogram of abdomen and cranium were normal; and echocardiogram showed a small patent ductus arteriosus. Can you spot the diagnosis?

Fig. 1

Fig. 2

*Srinivasan K, **Ramesh S, ***Natarajan B, ****Parvathy M, *****Lavanya BS
*Prof of Neonatology, **Resident in Neonatology, ***Radiologist, ****Assistant Professor, *****Resident in Pediatrics, Department of Neonatology, Institute of Child Health & Hospital for Children, Chennai.

Answer on page 329


Answer for picture quiz

**Fuhrmann syndrome** consists of bowing of both femurs, aplasia/hypoplasia of fibulae and poly/syn/oligodactyly. Other findings include absent/coalescent tarsal bones, absent metatarsals, hypoplasia of fingers and fingernails and postaxial polydactyly.¹

Antenatal diagnosis is possible with ultrasonography detecting bowed femora in the fetus.

Woods CG, et al. found that Fuhrmann Syndrome develops from partial mutation in exon 3 of the WNT7A gene². The chromosome locus is 3p25 and inheritance is autosomal recessivel. The gene is responsible for chondrogenesis in the limbs.

Reference


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Use of CT in the evaluation of suspected appendicitis in children is common. Expanding the use of Ultrasound (US) would eliminate the radiation exposure associated with CT. The present study tries to describe new criteria which would improve ultrasonogram’s diagnostic accuracy for diagnosing appendicitis.

A retrospective review of 304 consecutive patients undergoing US for the diagnosis of appendicitis during 2006 was done. The sensitivity, specificity and accuracy of the maximal outer diameter (MOD) at various measurements was calculated and compared to pathology results. Additional variables (appendiceal wall thickness, fecalith, hyperemia, fat stranding, free fluid, age and weight) were also evaluated.

The highest sensitivity (98.7%) and specificity (95.4%) were identified when MOD was e7 mm or wall thickness was >1.7 mm. These values resulted in correctly classifying 96.6% of cases, with 1 (0.5%) false-negative and 6 (2.9%) false-positive studies. Incorporating secondary signs of appendicitis, age or weight did not alter accuracy.

These findings identify new US criteria that compare favorably to CT. In children with suspected appendicitis, using US as the initial imaging study will ultimately lead to improved accuracy, lower cost and the elimination of ionizing radiation exposure.
Q. At present many pharmaceutical companies are marketing combination of two antimicrobials like cefixime + ofloxacin, ceftizidime+tobramycin.

1. Are these combinations rational?

2. Give your message on rational pediatric practice

Dr.Ashok Singhal
Gwalior, MP

A. Many fixed dose combination (FDC) of drugs / medicines have hit the Indian pharmaceutical market in recent years. Fixed dose combination drugs are acceptable for treatment of single disease like AIDS, TB and malaria. According to Warren Kaplan, combinations make therapeutic sense for these three illnesses, but the evidence for the utility of combinations is still largely circumstantial.

In the WHO list of essential medicines, around 6.5% of the medicines listed therein are FDCs. The anti-infectious disease FDCs listed other than for the three above mentioned conditions are (1) Antibacterials, β Lactam medicines (Amoxicillin + Clavulanic acid, Imipenem + Cilastatin (Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection), (2) other antibacterials are (Sulfamethoxazole + Trimethoprim) and (3) anti-pneumocystosis and antitoxoplasmosis medicines (Sulfamethoxazole + Trimethoprim injection). The studies on which the combination of cefixime and ofloxacin and ceftizidime and tobramycin were formulated are very recent reports and not yet supported by systematic reviews. The BNF for children and IAP Drug Formulary do not mention these combinations. Hence, it is suggested that more RCTs on the use of these new antibiotic combinations that are available in the Indian market today are needed before they are recommended for use in children.

References


Dr Jeeson C Unni
Editor-in-chief, IAP Drug Formulary, Cochin.
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