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- Editorial Board
The present issue of IJPP is dedicated to topics in “Hematology”. Hematology has emerged as a highly developed super specialty in all aspects, including molecular genetics.

All the components in blood are essential to maintain the health of an individual. Blood components in single or in combination can be affected either primarily or secondarily leading on to disease status. For example congenital red cell aplasia which is a primary disorder and anemia of chronic renal failure which is a secondary problem affecting red blood cell. Bleeding disorder can be primary or secondary due to disseminated intravascular coagulation.

There are many hematological disorders which are of great interest to practicing pediatricians. As it is impossible to cover all those in a single issue of the journal, most common and interesting conditions are covered in this issue. There are many conditions like anemia which can be managed by a general pediatrician himself, if he is equipped with the basic knowledge and simple laboratory support. The most frequent hematological disorders which are faced by a practicing pediatrician are due to derangements in RBC and hemoglobin. It is so common that it gives an impression that the entire hematology revolves around anemia and nothing else. Most common cause of anemia in developing countries is nutritional deficiency involving many micro nutrients. These micronutrients are misused many times and under used on a few occasions. The article “Hematinics” in this issue will demystify the doubts in the minds of practicing pediatricians.

Next to RBCs, WBCs can be considered as an important cellular component of blood. Among them neutrophils play a vital role by tackling the micro organisms which enter the body. Neutropenia or defective function of neutrophils makes the individual more prone for infection and a severe infection by itself can lead on to neutropenia. The management of neutropenia is a challenging one. A clear cut idea on how to manage these children efficiently is given in this issue.

Coagulation is a fascinating area in hematology in view of its unique cascade. A systematic approach will lead on to a correct diagnosis when coagulation disorder is suspected. This issue covers the pathophysiology in DIVC as well as how to approach a child with thrombotic disorders.

One other important cause of bleeding diathesis is thrombocytopenia. Idiopathic thrombocytopenic purpura if it runs a chronic course, is a problem to both the parents and physicians. A brief article on the approach to the same will be an eye opener to our readers.

Hemophagocytic syndrome, another interesting condition which is under diagnosed is dealt with briefly in this issue.

Approach to hematological conditions which can be diagnosed prenatally is also covered in this issue.

Articles on acute myocarditis and skeletal dysplasias attempt to give an overview on these conditions. Use of radiological investigations for evaluation of seizures is covered in this issue.

Urticaria is dealt with in this issue under dermatology series. A case study on McCune Albright syndrome illustrates the important clinical aspects of the condition. We hope you will find this issue to be practical and useful.

Dr. K. Nedunchelian,
Editor-in-Chief
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Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1”) in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript. They are considered for publication on the understanding that they are contributed to this journal solely. All pages are numbered at the top of the right corner, beginning with the title page. All manuscripts should be sent to: The Editor-in-Chief, Indian Journal of Practical Pediatrics

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200 – 250 words pertaining to the articles published in the journal or practical viewpoints with scientific backing and appropriate references in Vancouver style.

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HEMATOLOGY

HEMATINICS IN CHILDREN

* Naithani R
** Saxena R

Abstract: Iron deficiency anemia is very common in children and is usually secondary to dietary deficiency and worm infestation. Correct choice of hematinics is important as most iron preparations cause gastric irritation and staining of teeth leading to poor compliance. The discussion below will clarify all queries related to ideal choice of hematinics.

Keywords: Iron Deficiency, Children, Hematinics

Nutritional anemia is a major public health problem in India. The prevalence of anemia under 15 years is 50-70%. Predominant cause of these anemias is nutritional in this age group and hence is easily amenable to supplementation of the deficient factor. Diet, however needs to be modified in these children to prevent relapses of anemia.

Iron deficiency

Iron deficiency is the most common preventable nutritional deficiency in the world, especially among infants and young children. Anemia secondary to iron deficiency is linked with depressed mental and motor development during infancy and early childhood. It may be reversible if detected and treated adequately. Iron deficiency anemia (IDA) during childhood also results in decreased physical activity and decreased interaction with the environment. Learning capability and school achievements are adversely affected in presence of severe and persistent IDA.

Magnitude of problem

Prevalence of IDA among children under 5 years of age has been estimated to be 75% in India. The 1998-99 National Family Health Survey-2 (NFHS-2) in India documented a prevalence of IDA as 75% among children between 6-35 months of age.

Causes

Although malabsorption and bleeding are described as causes of iron deficiency, the overwhelming cause is dietary in origin. The main reason for this high rate is the undue reliance on fresh unmodified cows’ milk and non-iron containing convenience foods. Much of this is the result of late or inappropriate weaning. It has been shown that iron intake is low in the first four years of life. Iron intake is lowest in families with lower income and in poorer areas. Presence of worm infestation, hookworm or mixed infections, serve as a major cause of blood loss. Poor hygienic habits result in recurrent gastrointestinal infection. Recurrent episodes of diarrhea and amoebic dysentery increase the risk of development of IDA. A term baby is born with sufficient iron stores for 6–8 months. Assuming that the mother has sufficient iron stores and the child is on breast milk which has got a higher bioavailability of iron, though the iron content is low, if appropriate weaning has taken place at
6 months of age, with iron containing weaning foods, significant iron deficiency should not occur. In chronic inflammatory disease, absorption of iron appears to be reduced which would limit the growth of microbes in chronic infections. Recently an acute phase protein hepcidin has been identified, which plays a major role in iron absorption. Hepcidin over expression in the liver leads to decreased iron uptake by the duodenum. Most of the iron that is absorbed is directed into the RES while only minor amounts may reach the sites of erythropoiesis.

Clinical consequence

It was earlier believed that the clinical symptoms of anemia (such as fatigue, headache, dizziness, shortness of breath or tachycardia) occur only when the hemoglobin level dropped abruptly. Asymptomatic anemia presents with impairments in physical condition, quality of life, and cognitive function which may be unrecognized by both patients and even by their doctors. The adaptation to chronic anemia is in fact adaptation to lower quality of life. Fatigue is associated with significant physical, emotional, psychological and social consequences, with virtually every aspect of daily life being affected. Surprisingly, over the range 8-14g/dL, the largest improvement in quality of life occurred when hemoglobin levels increased from 11 to 13 g/dL. In addition, children who are iron deficient tend to be shorter than non-iron deficient children and there is some evidence that they may be more prone to infections, although this remains speculative.

Children learn from play and interaction and iron deficient children are always tired and clingy and do not interact with other children. In addition, they have a short attention span, unhappiness, and increased fearfulness. However, these changes have been attributed to “social isolation” rather than secondary to IDA.

Treatment of IDA

The objectives of therapy in IDA are i) To restore the hemoglobin to normal ii) replenish the depleted iron stores iii) treat etiologic factors and prevent their recurrence.

Oral iron supplements should be started as soon as a diagnosis of IDA is established. The standard dose is 3 mg/kg of elemental iron per day up to a maximum of 180 mg/day. Higher doses (6mg/kg body weight) were previously used; but were associated with more frequent gastrointestinal side effects. Single daily doses are as effective, but 2-3 divided doses are better tolerated by children. Ideally, oral iron should be given at least half an hour before a meal to ensure maximal absorption. It can also be given 1-2 hours after meals. Oral iron therapy must continue for a period of at least four months to replenish depleted iron stores, if an adequate response to therapy is seen. Stoppage of iron, once anemia is corrected, is the most frequent cause for recurrence of IDA.

Dramatic improvement in sense of well-being is usually observed within first 12-24 hours of starting therapy. An increase in reticulocyte count is observed in 48-72 hours and peaks in 5-7 days. The height of response is inversely proportional to the severity of anemia. The hemoglobin level rises at an average rate of 0.15 g/dl per day, usually commencing about one week after the institution of therapy. The rate of regeneration is most marked in early stages.

Choice of iron preparations

i) Ferrous sulphate tablets are available in two forms: a) Routinely available tablet has 333mg of ferrous sulphate (adult) with elemental iron of 100mg and 66mg (Pediatric) with 20mg elemental iron and b) The exsiccated form of ferrous sulphate is used in the MCH programme. The total strength of ferrous sulphate is 200 mg. The content of elemental iron remains 60 mg per
tablet. Pediatric iron tablets of 100 mg with elemental iron content of 20 mg are also available in MCH programme.

Since various commercial preparations contain elemental iron ranging from 25mg/ml to 250mg/5ml, lack of awareness often results in over dosage. There are several iron / hemoglobin / vitamin cocktails which are expensive and contain sub optimal amounts of elemental iron.

Various salts have been used. Ferrous sulphate is used most frequently, is least expensive and causes few side effects if administered in appropriate doses. Ferric-hydroxide polymaltose complex, a recently introduced salt in the market, has fewer gastrointestinal side effects. As maximum iron absorption occurs in the duodenum and proximal jejunum, enteric-coated tablets should not be used. Nausea, vomiting, abdominal discomfort, diarrhea and constipation occur in some patients. These side effects are dose related and can be minimized by adhering to standard doses, gradual hiking up of dose and administration of iron with or after meals.\textsuperscript{21}

### Oral iron preparations

Tables 1 and 2 show elemental iron content of various iron salts and different iron preparations. All ferrous compounds are oxidized in the lumen of the gut or within the mucosa with release of activated hydroxyl radicals, which will attack the gut wall and produce a range of gastrointestinal symptoms and discomfort.\textsuperscript{13,22} Enteric coated ferrous formulations attempt to avoid this by minimizing iron release in the stomach but the absorption of iron may be compromised. The newer non-ionic iron polymaltose has been shown to have no oxidative potency on lipoproteins in healthy subjects and a better compliance than ferrous sulphate but data on efficacy are lacking.\textsuperscript{23} Haem iron polypeptide has an advantage of alternative absorption pathways. This product is thought to have improved bioavailability\textsuperscript{24} and promises lower side effects.

### Table 1. Iron compounds and elemental iron content

<table>
<thead>
<tr>
<th>Iron Preparation</th>
<th>% Elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>20</td>
</tr>
<tr>
<td>Exsiccated ferrous sulfate</td>
<td>30</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>23</td>
</tr>
<tr>
<td>Ferrous carbonate</td>
<td>16</td>
</tr>
<tr>
<td>Ferrous lactate</td>
<td>19</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>12</td>
</tr>
<tr>
<td>Ferric ammonium citrate</td>
<td>18</td>
</tr>
<tr>
<td>Ferrous glycine sulfate</td>
<td>18</td>
</tr>
</tbody>
</table>

### Table 2: Iron preparations and elemental iron content

<table>
<thead>
<tr>
<th>Iron Preparation</th>
<th>Elemental iron (per tab/cap or per 5 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fersolate Tab</td>
<td>66 mg</td>
</tr>
<tr>
<td>Tonoferon syrup</td>
<td>250 mg</td>
</tr>
<tr>
<td>Tonoferon pediatric syrup</td>
<td>80 mg</td>
</tr>
<tr>
<td>Tonoferon drops</td>
<td>25 mg/ml</td>
</tr>
<tr>
<td>Fefol Z, Fesovit, Dexorange, Hepatoglobine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Livogen hemtonic</td>
<td>42 mg</td>
</tr>
<tr>
<td>Autrin</td>
<td>113 mg</td>
</tr>
<tr>
<td>Vitcofol syrup, Hemsi syrup, Fesovit syrup</td>
<td>33 mg</td>
</tr>
<tr>
<td>Jectofer injection</td>
<td>50 mg/ml</td>
</tr>
<tr>
<td>Imferon injection</td>
<td>50 mg/ml</td>
</tr>
</tbody>
</table>
a) **Ferrous salts:** All dietary iron has to be reduced to ferrous form to enter the mucosal cells. Hence bivalent iron salts like ferrous sulfate, fumarate, gluconate, succinate, glutamate and lactate have been preferred over ferric salt preparations. In addition, these salts are amongst the cheapest preparations of iron available for medicinal use. Ferrous sulfate (FS) (20% elemental iron) is commonly used in tablet preparations. However, liquid formulations of the salt are only available as elixirs in sorbitol base as syrup preparations are unstable (the salt is easily oxidizable in moist environment) which negates the cost advantage. Ferrous fumarate (FF) (33% elemental iron) has a similar efficacy and gastrointestinal tolerance to ferrous sulphate. FF salt is moderately soluble in water, environmentally more stable and is tasteless. These salts have uniformly good bioavailability. However, the bioavailability decreases markedly in the presence of dietary inhibitors like phytates, tannic acid, etc. They cannot be added to other foods/milk/fortified formulas for the same reason.

b) **Iron amino-acid chelates:** Iron amino-acid chelates are conjugates of the ferrous or ferric ion with amino-acids. They have no effect on the color or taste of food products and have high bioavailability in the presence of dietary inhibitors. It is hypothesised that the chelates prevent iron from binding to inhibitors in food or precipitating as insoluble ferric hydroxide in the pH of the small intestine. Comparison of ferrous sulphate with ferrous bisglycinate in infants of 6 to 36 months of age showed equivalent rise in hemoglobin in the two groups. However, the group receiving ferrous bisglycinate had a higher rise in serum ferritin. Also, a lesser incidence of side effects was observed in this group. Ferrous glycine sulphate (FGS) is the only salt of this group available in India.

c) **Iron polymaltose complex:** Iron polymaltose complex contains non-ionic iron and polymaltose in a stable complex. Its absorption is not affected by food or milk. These salts are better absorbed and have lesser side effects. They are expensive and improvement in hemoglobin level is not as expected compared with other iron preparations.

**Packed red cell transfusions**

Red-cell transfusions should not be recommended routinely in IDA. Transfusions are indicated only if there is evidence of impending or overt cardiovascular decompensation. If patient is in congestive cardiac failure, a partial exchange transfusion may be required.

**General measures**

Deworming at initial diagnosis and then periodically at 3-6 monthly intervals helps in improving the iron status. Children should be encouraged to wear shoes while going to the fields to prevent infestation with the infective form of hookworm larvae. Table 3 shows the various sources of iron and Table 4 shows factors affecting iron absorption.

**Failure of response**

Failure to attain adequate response to therapy in 2-3 weeks is designated as failure to respond. Poor compliance and inadequate doses are the most important causes of failure to respond to iron supplements, if the diagnosis of IDA is correct. Usually stools turn black on iron supplements and this can be used as an easy measure to detect poor compliance. Certain preparations containing ferric hydroxide
polymaltose complex have been associated with poor response, even when given in adequate doses. Associated folic acid deficiency also hinders response to iron therapy. If all these causes have been ruled out, one must think of malabsorption and chronic blood loss. Celiac disease may present with nonresponsive IDA. Other features of malabsorption may be subtle or altogether absent. Serological tests and duodenal biopsy may clinch the diagnosis. Chronic blood loss from gastrointestinal tract and lungs is another major cause of nonresponsive IDA.  

2) Complementary foods: To improve the nutritional value of home-based complementary foods, “micronutrient Sprinkles” in a powder form were developed as a home-fortification strategy for improving the nutritional quality of home-based complementary foods. The formulations of these sprinkles contain microencapsulated ferrous fumarate along with other micronutrients such as zinc, vitamins A, C and D or folic acid. Sprinkles are packed in single-dose-sachets. Entire contents of one sachet need to be sprinkled daily onto any semi-solid food for infants. The iron in sprinkles is encapsulated with a thin coating of a vegetable-based hydrogenated lipid that prevents the iron from oxidizing the food so as not to change the color, texture or taste of the food to which Sprinkles are added. The consumption of 60 sprinkles sachets (each containing 12.5 mg of elemental iron) over at least 2 months should be adequate for repletion and to maintain sufficient iron stores and normal hemoglobin levels in young children.

Prevention of IDA

1) Diet: Daily iron requirement in first year of life is 5-7 mg. Preterm and low birth weight infants with low iron stores should receive 10-15 mg iron per day. In childhood, 10 mg elemental iron is required per day with increased requirements during pubertal spurt. Tables 3 and 4 show the diet sources and different factors affecting its absorption.

Table 3. Sources of dietary iron

<table>
<thead>
<tr>
<th>Chemical form and type of iron</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haem iron</td>
<td>- Meat, fish, poultry and blood products</td>
</tr>
<tr>
<td></td>
<td>- 10-15% of iron intake in industrialized countries.</td>
</tr>
<tr>
<td></td>
<td>- Less than 10% of total intake in developing countries.</td>
</tr>
<tr>
<td></td>
<td>- Bioavailability high: absorption 20-30%</td>
</tr>
<tr>
<td>Non-haem iron – Food iron</td>
<td>- Cereals, tubers, vegetables and pulses.</td>
</tr>
<tr>
<td></td>
<td>- Bioavailability determined by the presence of enhancing and inhibiting factors consumed in the same meal</td>
</tr>
<tr>
<td>- Contamination iron</td>
<td>Soil, dust, water, iron pots, etc.</td>
</tr>
<tr>
<td>- Fortification iron</td>
<td>- Bioavailability usually low.</td>
</tr>
<tr>
<td></td>
<td>- Various iron compounds used</td>
</tr>
<tr>
<td></td>
<td>- varying potential bioavailability</td>
</tr>
<tr>
<td></td>
<td>- bioavailability of soluble fraction determined by composition of meal.</td>
</tr>
</tbody>
</table>
3) **Food fortification:** Iron fortification involves the addition of iron, usually with folic acid, to an appropriate food vehicle that is made available to the population at large. In developed countries, cereal flour is the most common food vehicle but other foods, such as noodles, rice, and various sauces, have also been used. Iron supplementation has a major impact on population health. Iron supplementation would avert almost 2.5 million disability adjusted life years (DALYs) in the Southeast Asian sub region. On the other hand, fortification is less costly than supplementation of any iron preparation. Consumption of fortified foods is generally limited to the middle- and high-income groups who are not always at greatest risk of micronutrient deficiencies. Key factors in the selection of the right food vehicle include that the vehicle must be consumed regularly and in predictable amounts, and must be affordable by the target population. It must be processed in large central mills so that quality control can be effectively implemented. The fortified food should not undergo changes in color, taste, or appearance as a result of the addition of these micronutrients. Stability and bioavailability of the micronutrients added to the food must remain high under standard under local conditions of storage and use. Other fortificants have been suggested, such as ferrous fumarate or ferrous sulfate, which are more costly but also more bioavailable.29,30

The recent WHO/UNICEF review of complementary foods in developing countries concluded that iron requirements may be difficult to meet from non-fortified complementary foods, especially if animal products are not widely consumed.2,29-31 In addition, prolonged exclusive breastfeeding, delayed introduction of weaning foods (which are often of poor quality) and feeding of small amounts of foods to infants are responsible for higher prevalence of iron deficiency.

Table 4. **Major determinants of iron absorption**

<table>
<thead>
<tr>
<th>Dietary factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Haem iron is better absorbed</td>
</tr>
<tr>
<td>(2) Factors that enhance non-haem iron absorption:</td>
</tr>
<tr>
<td>- Ascorbic acid (vitamin C)</td>
</tr>
<tr>
<td>- Meat, poultry, fish and other seafood</td>
</tr>
<tr>
<td>- Low pH (e.g., lactic acid)</td>
</tr>
<tr>
<td>- Histidine, cystine, lysine</td>
</tr>
<tr>
<td>(3) Factors that inhibit non-haem iron absorption:</td>
</tr>
<tr>
<td>- Calcium</td>
</tr>
<tr>
<td>- Phytates</td>
</tr>
<tr>
<td>- Tannins in tea and coffee specially after food</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Host Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Iron Status</td>
</tr>
<tr>
<td>(2) Health Status</td>
</tr>
<tr>
<td>- Infections</td>
</tr>
<tr>
<td>- Chronic diarrhea</td>
</tr>
<tr>
<td>- Short bowel</td>
</tr>
</tbody>
</table>

Though iron deficiency anemia has been recognized as a major public health problem among children in India, low priority has been given for its prevention and control. In 1998-99, for example, the National Anemia Control Program reached fewer than 28% of Indian children 1-5 years of age.23 Two Combination of low coverage and poor adherence to the intervention and poor quality of iron preparations were the major reason for failure of programme. Prevalence of IDA remains high among young children in India even after the implementation of the National Anemia Control Program. Technical disadvantages associated with the use of liquid iron preparations are limited shelf life...
and expensive transportation costs due to the weight of the bottles. National Institute of Nutrition, Hyderabad successfully fortified salt with iron (ferrous sulphate 3.2g, sodium acid sulfate 5.0g and orthophosphoric acid 3.2g in one kg of common salt). Multiple studies have been conducted showing that iron fortified salt successfully prevented the development of IDA and was also able to correct mild IDA. Since iodine deficiency is also common, salt was also fortified with iodine. Iron fortified salt needs to be utilized throughout the country as prophylaxis and control of IDA.

Current WHO and UNICEF guidelines recommend that interventions for the prevention and control of iron deficiency should follow an integrated, long-term approach. IDA must be addressed by a multidisciplinary approach, including the following elements: 1) increased iron intake (i.e., iron-rich diets, increasing iron absorption, and iron and folate supplements, fortification of wheat flour and other complementary foods with iron and other micronutrients, where appropriate); 2) infection control (i.e., public health measures to control hookworm infestations, malaria, and schistosomiasis); 3) improved nutritional status (i.e., control of major nutrient deficiencies, diet diversification, and infection prevention).

**VITAMIN B\textsubscript{12} AND FOLATE DEFICIENCY**

Megaloblastic anemia (MA) is the most common result of deficiency of these vitamins. Other less common manifestations in children include neuro-developmental effects and abnormal movements. Neural tube defects result from deficiency in mothers during pregnancy. The commonest age is 3-18 months with maximum number of cases being in 9-12 months. These children are generally exclusively breast-fed by mothers who are undernourished and have poor blood levels of folate and cobalamin.

**Prevalence of megaloblastic anemia**

The increase in prevalence of MA is also supported by observation that MA accounts for maximum/a large number of cases of pancytopenia in many Indian series. Estimation of serum levels are required to be certain of the deficient micronutrient. Sarode et al reported B12 deficiency in nearly 85% cases with megaloblastic anemia. Chandra et al observed folate deficiency in 50%, cobalamin deficiency in 62% and combined deficiency of both cobalamin and folate in 30%. Gomber et al. found even lower prevalence of folate deficiency in a study on preschool children from Delhi.

**Etiology**

In India, most cases of MA are caused by nutritional deficiency of folate, B\textsubscript{12} or both. Pernicious anemia due to intrinsic factor deficiency, malabsorption resulting in folate deficiency (celiac disease) and certain inborn errors of metabolism eg. methylmalonic aciduria (B\textsubscript{12} deficiency) and methylene tetrahydrofolate reductase deficiency (folate) account for minority of cases.

Nutritional deficiency is far more common in vegetarian than in non-vegetarian families. B\textsubscript{12} deficiency seen in infants and young children has been particularly related to maternal deficiency which results in poor body stores at the time of birth. These infants who are exclusively/predominantly breastfed for prolonged period tend to develop B\textsubscript{12} deficiency as the breast milk content of B\textsubscript{12} in these mothers is far below normal. Chandra et al have documented a good co-relation between serum levels of the mothers and their suckling infants and young children. From the developed countries, cases of MA are being reported among infants born to vegetarian mothers.

Giardia infection has been demonstrated to cause folate malabsorption. H.pylori infection has
been incriminated to cause $B_{12}$ malabsorption among adults.\textsuperscript{11}

**Clinical consequences**

Symptoms of anemia such as fatigue, headache, dizziness, shortness of breath, or tachycardia may occur. Most cases tend to be moderately or severely malnourished.

Some features peculiar to MA include hyperpigmentation of knuckles and terminal phalanges and mild enlargement of liver and spleen. Petechial and other hemorrhagic manifestations have been reported in up to 25\% cases. Presence of bleeding with severe anemia makes them clinically indistinguishable from aplastic anemia.\textsuperscript{6,11,12}

Some cases of MA exhibit developmental retardation/regression in association with severe anemia. The infantile tremors syndrome cases have macrocytic anemia and developmental regression in addition to tremors. Occurrence of abnormal movements in association with hypotonia, psychomotor retardation, apathy and failure to thrive is being reported.\textsuperscript{16,17} Impairment of cognitive function is also described in children and adolescents with $B_{12}$ deficiency even in absence of anemia.\textsuperscript{18}

**Treatment**

Like any other deficiency state replacement therapy is required. Anemia and other cytopenias respond to administration of very small doses of drugs. However, since folate is available as a 5 mg tablet and its over dose is not associated with adverse effects; 5 mg daily dose has been used.

For $B_{12}$ deficiency, parenteral administration of $B_{12}$ is usually recommended. A dose of 10 $\mu$g cyanocobalmine (CNCbl) subcutaneous daily is sufficient to correct metabolic abnormalities like increased LDH and iron levels and in increasing the reticulocyte counts with maximum count attained on 5-7 days. For smaller children the dose of CNCbl is 0.2 $\mu$g/kg. It acts as a therapeutic test of vit $B_{12}$ deficiency. This does not restore the plasma methylmalonic acid and total homocysteine levels to normal. Dementia and depression may improve rapidly with therapy while other neurologic abnormalities usually show slow improvement over 6 months and may not improve at all. Decrease in MCV, reticulocytosis, and improvement in platelet and neutrophil counts are observed within few days. Subsequently 1000 $\mu$g CNCbl daily for 7 days followed by 100 $\mu$g weekly for 1 month is required. Six to eight weeks treatment is usually described as sufficient.\textsuperscript{19}

In pernicious anemia 1000 $\mu$g of hydroxycobalamine (OHCbl) every 3 months or 1000 $\mu$g daily for 1-2 weeks every 6-12 months is given. A small number of children may develop antibodies against OHCbl. In children with inherited defects of cobalamine metabolism higher doses of OHCbl i.e 1000 $\mu$g OHCbl 2-3 times every week is required.\textsuperscript{19}

Chandra et al\textsuperscript{20} observed development of tremors in 6 out of 51 cases within few hours of administration of 1000 $\mu$g dose. However, these tremors and other neurological signs have been self-limiting but their appearance may influence the compliance. They recommend a dose of 250 $\mu$g in infants and 500 $\mu$g in older children. Sudden increase in the levels of neurotransmitters has been offered as the plausible explanation for this neurological phenomenon.\textsuperscript{9}

They also noticed that some cases have developed thrombocytosis which resulted in stroke in one patient.\textsuperscript{20} Hence careful monitoring of blood counts is required during treatment.

**Deficiency of other micronutrients**

Usually the children presenting with dietary iron deficiency or vitamin $B_{12}$ or folic acid deficiency also have other micronutrient
deficiencies as diet is likely to be deficient in other micronutrients also. A holistic approach is required in treatment of these children.

Points to Remember

- **Iron deficiency is the most common preventable nutritional deficiency in the world, especially among infants and young children.**

- **Prevalence of IDA among children under 5 years of age has been estimated to be 75% in India.**

- **Oral iron supplements should be started as soon as a diagnosis of IDA is established.**

- **The standard dose is 3 mg/kg of elemental iron per day up to a maximum of 180 mg/day.**

- **Ferrous sulphate is used most frequently, is least expensive and causes few side effects if administered in appropriate doses.**

- **Failure to attain the adequate response to therapy in 2-3 weeks is designated as failure to respond.**

- **Poor compliance and inadequate doses are the most important causes of failure to respond to iron supplements, if the diagnosis of IDA is correct.**

- **Chronic blood loss from gastrointestinal tract and lungs is a major cause of nonresponsive IDA**

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**CHALLENGES IN THE MANAGEMENT OF FEBRILE NEUTROPENIA IN CHILDREN**

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** Kurkure P  
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**Abstract:** Managing febrile neutropenia in children is a challenge. Although, improved understanding of risk factors and better diagnostic as well as therapeutic options have improved the outcome of febrile neutropenia, newer emerging risk factors, changing epidemiology of infections and increasing bacterial resistance continue to pose serious challenges. The present focus is to develop new, effective antimicrobials for resistant pathogens, refine the existing risk-stratification models to reliably identify patients for outpatient treatment and employ novel nonculture-based tools to replace empirical therapy with pathogen-directed, preemptive therapy. Existing challenges and possible strategies in the management of febrile neutropenia in children are discussed.

**Key words:** Febrile neutropenia, Children, Challenges

Fever in a neutropenic patient is the most common oncologic emergency and demands urgent medical intervention. It occurs in 10-15% of patients with solid tumors and in more than 80% of patients with hematological malignancies. It is associated with a mortality rate of 5-10%. Managing infections in neutropenic patients is a dynamic process. On one hand, there is an improved understanding of risk factors and a greater availability of diagnostic and treatment options. On the other hand, newer risk factors are emerging, epidemiology of infections are constantly changing, bacterial resistance is increasing and with intensification of chemotherapy, the immunosuppressed hosts are increasing in number. Hence, infection in the immunocompromised host continues to pose serious challenges. The Infectious Diseases Society of America (IDSA) has established guidelines for the treatment of febrile neutropenic patients. However, these guidelines fail to address the specific needs of pediatric patients. Existing challenges in the management of febrile neutropenia and strategies to overcome them in pediatric cancer patients are presented.

**Febrile neutropenia and its importance**

Febrile neutropenia is defined as development of fever in a neutropenic patient.

Fever is defined as a single oral temperature measurement of more than 38.3°C (101°F) or axillary temperature of more than 37.5°C, in the absence of obvious environmental causes. Neutropenia is defined as neutrophil counts of less than 500 cells/mm³ or a count of less than 1000 cells/mm³ with a predicted decrease to less than 500 cells/mm³ in the immediate future.
Bodey and colleagues demonstrated that the risk of infection clearly increased when absolute neutrophil count (ANC) dropped below 1000/mm³, with a marked increase when the ANC was below 500/mm³. This study laid the foundation of contemporary therapeutic paradigms in the management of febrile neutropenia². In addition to the absence of granulocytes; the disruption of the integumentary, mucosal and mucociliary barriers and inherent microbial flora shifts as well as antimicrobial usage predispose the neutropenic patient to infections. It is noteworthy that the signs and symptoms of infection are often absent or muted in the presence of neutropenia with fever remaining the only consistent early sign. Approximately 48 to 60% patients who become febrile have an established or occult infection. Common sites of infection are the alimentary tract (i.e., mouth, pharynx, esophagus, large and small bowel and rectum), sinuses, lungs and skin¹.

**Spectrum of pathogens**

There is a myriad of pathogens described in neutropenic hosts and the main source is the host’s endogenous flora. The pathogens responsible for initial infections are primarily bacteria; whereas antibiotic-resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections. The range of infecting pathogens is detailed in Table 1¹³.

Bacterial pathogens: Gram-negative bacilli especially Escherichia coli, Klebsiella species and Pseudomonas aeruginosa have been the prominent pathogens in neutropenic hosts in the past. The incidence of blood stream infections due to gram positive bacteria is increasing, since the introduction of extended-spectrum β-lactams, use of central venous catheters (CVCs), use of quinolone prophylaxis, administration of high-dose, cytarabine-containing regimens, and the increased use of proton pump inhibitors. The most common infections in neutropenic patients are tissue-based infections which are predominately caused by gram-negative rods. Anaerobic bacteremia occurs in less than 5% of patients. It is particularly common in patients with intra abdominal infections, perirectal abscesses, or periodontal disease¹³.

Fungal pathogens: The most common fungal infections in febrile neutropenic patients are candidiasis and aspergillosis. The clinical spectrum of candidiasis is broad, ranging from superficial to disseminated disease. Candida species also are common causes of catheter-related infections. The most common Candida species that cause candidemia are Candida albicans followed by Candida glabrata, Candida tropicalis and Candida parapsilosis. Aspergillosis is the most common invasive mold infection. Aspergillosis initially affects the lungs or sinuses and later disseminates to other organs. Aspergillus fumigatus is the most common species that causes invasive disease¹.

Emerging challenge of superbugs: Emergence of multidrug-resistant, gram-negative rods, such as P. aeruginosa, E. coli, Citrobacter and Acinetobacter species is of serious concern. This is partly as a consequence of antibiotic selection pressure and induction of extended-spectrum chromosomal β-lactamases (ESBL) after the use of β-lactams. Similarly, the resistance of the gram-positive cocci to β-lactams is increasing. Infections by methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis, and penicillin-resistant streptococci have become common in these patients. Furthermore, there is emergence of resistance to vancomycin in some bacteria, most notably VRE (vancomycin resistant enterococci). In India too, increasing reports of ESBL producing gram-negative infections are of particular concern. A total of 81.9% of gram-negative isolates in a countrywide multicentric
study were reported to be ESBL producers and ESBL production was seen in 86, 89 and 77% of E. coli, Klebsiella sp. and P. aeruginosa isolates respectively. Similarly, staphylococcal methicillin resistance has become as high as 80 to 87% in some centres. In fungal pathogens, non-albicans Candida spp., azole-resistant Candida infections and non-fumigatus Aspergillus species resistant to amphotericin B deoxycholate (AMB), such as Aspergillus terreus, appears to be increasing.

### Table 1. Common pathogens and resistant organisms in febrile neutropenic children

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>Resistant pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive bacteria</strong></td>
<td>Penicillin-resistant streptococci, VRE, MRSA</td>
</tr>
<tr>
<td>Staphylococcus spp. (e.g. S. epidermidis and S. aureus)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp. (alpha-hemolytic; e.g., S. mitis)</td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp. (e.g. E. faecium, E. faecalis)</td>
<td></td>
</tr>
<tr>
<td>Clostridium spp. (C. difficile, C. septicum, C. tertium)</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-negative bacteria</strong></td>
<td>ESBL, Multidrug resistant pseudomonas and Acinetobacter</td>
</tr>
<tr>
<td>Enterobacteriaceae (E. coli, Klebsiella spp., Enterobacter spp.)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td></td>
</tr>
<tr>
<td>Anaerobes (e.g. Bacteroides spp. and Prevotella spp.)</td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>Amphotericin resistant candida, Aspergillus</td>
</tr>
<tr>
<td>Candida spp. (e.g. C. albicans, C. glabrata, C. tropicalis, C. krusei)</td>
<td></td>
</tr>
<tr>
<td>Aspergillus spp. (e.g. A. fumigatus, A. flavus, and A. terreus)</td>
<td></td>
</tr>
<tr>
<td>Fusarium spp. (e.g. F. solani and F. oxysporum)</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jiroveci (formerly, P. carinii)</td>
<td></td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Ganciclovir resistant cytomegalovirus</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td></td>
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<tr>
<td>Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>Parvovirus</td>
<td></td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td></td>
</tr>
</tbody>
</table>

Note: ESBL: extended spectrum beta-lactamase, MRSA: Methicillin resistant S. aureus, VRE: vancomycin resistant enterococci

### Baseline assessment in febrile neutropenia

#### Physical examination

The initial evaluation should focus on determining the potential sites and causative organisms of the suspected infection. It should also include assessment of the patient’s risk of developing an infection-related complication. A site-specific history and meticulous physical examination should be performed promptly.
Thereafter, cultures should be taken and empiric antibiotics started as soon as possible. Due to absence of frank inflammatory signs, physicians should attempt to elucidate subtle signs and symptoms of infection and investigate them. Physical examination should be repeated daily especially focusing on sites of persistent symptoms and should always include examination of the skin, skin folds, IV sites, genitalia, perianal region, sinuses, oropharynx and fundi.

**Laboratory evaluation**

Initial laboratory evaluation includes a complete blood count (including ANC), platelet count, liver and renal function tests. Chest radiographs should be done for all patients but may have no (or minimal) findings at presentation even in patients with pulmonary infection. Conversely, patients with a normal clinical examination may have abnormal chest radiographs. Concomitant blood cultures obtained from peripheral veins and the catheter if present also should be performed. Properly collected blood cultures maximize the chances of isolating a pathogen. More than one culture should preferably be drawn, to increase the yield as well as to help distinguish from contaminants. Culture samples must be of adequate volume (based on body weight) and should preferably be plated in continuously monitored enriched aerobic liquid media (such as BACTEC) which can detect 90% to 100% of bacterial pathogens within 48 hours. Culture of stool, urine and lumbar puncture samples should be performed when clinically indicated. High-resolution chest computed tomography (CT) will demonstrate early signs of lung infection even in patients with a normal chest radiograph and is strongly encouraged at presentation. Repeat CT may show increasing features of lung infection as the neutropenia resolves.

**Risk assessment**

All patients with fever and neutropenia are not at the same risk for life-threatening complications or death. Risk assessment of febrile neutropenic patients is an integral part of initial evaluation. It also allows for the identification of patients who are suitable for outpatient treatment. Risk-stratification models in adults have been developed by Talcott, et al. and the Multinational Association of Supportive Care in Cancer (MASCC). Some pediatric groups have also proposed risk prediction models for children. Santolaya, et al found serum CRP more than 90 mg/L, hypotension, relapsed leukemia, platelet count less than 50,000/mm³ and recent chemotherapy to be useful predictors of serious bacterial infection. Klaassen et al found an absolute monocyte count less than 100 cell/mm³, co-morbidity and abnormal chest radiograph to correlate with high risk for significant bacterial infection. These models have been shown to have a reasonably high sensitivity but are limited by low specificity. Absence of sufficient data on low-risk outpatient management in pediatrics precludes its use in routine oncologic practice and is an unmet need.

**Management of febrile neutropenia**

**Essentials of management**

1. Administer empiric high-dose, broad-spectrum antibiotics promptly in patients with fever and neutropenia. Empirical treatment should begin as soon as possible, even before the results of cultures are available. Antibiotics should be given in maximal therapeutic doses adjusted to renal/hepatic function. This is necessary because of the limited sensitivity, specificity and rapidity of current diagnostic tests and high mortality rates associated with inappropriately treated gram-negative sepsis.
2. If the cultures yield a specific pathogen, the regimen should be modified accordingly. However, it should still provide broad-spectrum coverage for the possible presence of copathogens. Select the drugs in such a way so as to prevent bacterial superinfection. It is important to note that the infecting organism is confirmed microbiologically only in one-third of neutropenic patients even in the best of centers.

3. The selection of initial antimicrobial therapy should also take into consideration many factors, which are depicted in Table 2. Clinicians should be aware of the common pathogens and their susceptibility patterns in their own institution. This should guide them in formulating appropriate empirical therapy.

4. Discontinuation rules should always be kept in mind to minimize development of bacterial resistance, optimise cost of therapy and minimize the occurrence of drug-related toxicities. For example, vancomycin continuation should be based on available clinical and culture evidence after 48-72 hours.

**Starting empirical therapy in children with febrile neutropenia**

All children should be admitted and administered broad-spectrum antibiotics given either as monotherapy or combination therapy. Monotherapy with antibiotics with an extended antimicrobial spectrum such as ceftazidime, cefepime, meropenem, imipenem, or piperacillin/tazobactam are as effective as conventional beta-lactam/aminoglycoside combinations. Efficacy of quinolones and aminoglycosides as monotherapy is unproven and these should not be used alone. The limitations of monotherapy include the possibility of developing resistance among gram-negative pathogens and occurrence of breakthrough gram-positive infections. Combination therapy has the disadvantages of increased possibility of drug related toxicity, need for drug level monitoring in many instances and high cost of care. In India, high prevalence of ESBL isolates as well as available susceptibility data demands use of beta-lactam/β-lactamase inhibitor combinations such as cefoperazone-sulbactam and piperacillin-tazobactam or carbapenems for initial therapy. Vancomycin should be included upfront only at institutions that have a high rate of infections due to MRSA

**Table 2. Important considerations during initial empirical therapy**

<table>
<thead>
<tr>
<th>Risk stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any focal signs and symptoms, site of infection (e.g., lung)</td>
</tr>
<tr>
<td>Local ecology and antimicrobial susceptibilities of local pathogens</td>
</tr>
<tr>
<td>Recent hospitalization, recent antibiotic exposure or prophylactic drugs</td>
</tr>
<tr>
<td>Past history of infection (especially fungal or resistant bacterial such as ESBL or MRSA infection)</td>
</tr>
<tr>
<td>Most common potentially infecting organism based on type of immune defect</td>
</tr>
<tr>
<td>Co-morbid conditions</td>
</tr>
<tr>
<td>Organ dysfunction, drug allergy</td>
</tr>
<tr>
<td>Exposure to infections from other household members.</td>
</tr>
</tbody>
</table>
or S. viridans, documented infections due to gram-positive organisms resistant to the initial therapy, suspected serious catheter related infections, known colonization with MRSA, and hypotension.^

**Outpatient therapy in low-risk febrile neutropenic patients**

Outpatient treatment with oral antibiotics has many advantages (low cost, avoidance of catheter, good quality of life and low risk of superinfection with resistant nosocomial organisms). However such children still have the potential risk of life-threatening complications (such as septic shock) away from the hospital. Outpatient therapy may be considered in highly selected patients after careful consideration of the risk status, availability of a broad-spectrum oral antibiotic and ability of the patient to promptly access a suitable medical facility.

**Follow-up evaluation**

Daily evaluation is essential with focus on site-specific assessment. After appropriate initial antibiotic therapy, time to defervescence usually ranges from 2 to 7 days (median, 5 days). Hence, it is advisable not to change the antibiotic regimen for the first 3-5 days. This should be done even if the patient remains febrile as long as the child is otherwise stable and there are no new symptoms or signs. Needless to say, if the patient’s condition deteriorates or if a pathogen resistant to initial antibiotics is isolated, treatment should be modified promptly.

**What to do if patient has persistent fever**

A challenging scenario is the persistence of fever after 3-5 days of empirical antibiotic therapy without clinical or microbiologic documentation of infection. A number of factors may cause nonresponsiveness to antibiotics, which are shown in Table 3. Careful re-evaluation of the patient is crucial and may reveal new signs, symptoms and clues regarding possible cause of infection. Laboratory work-up should consist of fresh blood cultures, special cultures, serology for specific pathogens and imaging studies (including high-resolution chest computed tomography and upper abdomen imaging). If the re-evaluation of a persistently febrile neutropenic patient reveals a specific cause, then treatment should be modified accordingly.

If reassessment of the patient yields no new information, antimicrobial therapy requires reconsideration. The need for a change in therapy should be based on the patient’s clinical status and likelihood of early bone marrow recovery. In a clinically stable patient with no organism identified; patient could have a non-bacterial infection or slow treatment response of an infection such as viridans streptococcal infection. The antibiotic regimen should not be changed if patient is anticipated to recover neutrophil counts soon (except for discontinuation of vancomycin if there is no evidence warranting its continuing use). In a patient with progressive clinical disease; possibilities include a serious non-bacterial infection, bacterial resistance to current antibiotics and most importantly possibility of invasive fungal disease (Table 3). Consideration should be given to adding vancomycin (especially in patients with lung infiltrates, septic shock and clinically documented gram-positive bacterial infection) and/or a second agent active against Gram-negative organisms (based on clinical clues and local ecology). Empiric antifungal agents should be added in the high risk host with persistent fever for 5 days (earlier in the setting of appropriate and adequately dosed antibiotics). The choice of agents includes conventional amphotericin B, voriconazole and lipid formulations of amphotericin B. The latter two drugs are equally efficacious, less toxic but are costly compared to conventional amphotericin B. Although rare, the possibility
of infections such as malaria and tuberculosis should always be considered in India.

**Duration of the antibiotic therapy**

The duration of antimicrobial therapy is dictated by the underlying site of infection, causative organism(s), the patient’s condition along with response to treatment and recovery of neutrophils. Antimicrobial therapy for documented infections should be continued not only till patient shows neutrophil recovery (ANC 500/mm³) but also using a defined course of therapy appropriate for the specific infection. If a patient has a clinically or microbiologically documented specific infection (e.g. pneumonia, cellulitis), then antibiotics should be administered until all symptoms and signs are resolved and cultures become sterile. In general, most uncomplicated skin and alimentary tract mucosal infections require 4 to 7 days of therapy. For most bacterial bloodstream infections, 7 to 14 days of therapy is usually adequate with longer durations (10-14 days) recommended for gram-negative bacteremias. A duration of 14-21 days is usually indicated for infections of the lungs, sinuses and bacteremias complicated by major organ infection. The duration of treatment for HSV and VZV infections has become standardized at 7 to 10 days.

For the majority of febrile neutropenic patients without clinical or microbiologic documented infection, decisions about the duration of treatment after defervescence is based on persistence and depth of neutropenia, patient’s risk group, presence of mucositis, need for further chemotherapy and clinical stability of the patient. If the patient is afebrile and stable for more than 48 hours, has no focus of infection and neutropenia is resolved antibiotics can be stopped with confidence. If the same patient still remains neutropenic, discontinuation can be considered after 5-7 afebrile days provided the patient remains under close monitoring. For patients with profound neutropenia and mucositis, treatment should be continued for at least 2 weeks despite defervescence of fever.

Discontinuation of antibiotics in persistently febrile neutropenic patients is not without risk. The ideal strategy is to continue antibiotics until the neutropenia is resolved or for at least 2 weeks. If the fever persists 5 days after the resolution of neutropenia, treatment can be discontinued after

**Table 3. Important causes of persistent fever**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow response to initial infection</td>
</tr>
<tr>
<td>Resistant bacterial infection (e.g., ESBL, VRE)</td>
</tr>
<tr>
<td>Bacterial infection associated with cryptic foci (abcess, endocarditis)</td>
</tr>
<tr>
<td>Nonbacterial infection (virus, AFB, malaria, mycoplasma, toxoplasmosis)</td>
</tr>
<tr>
<td>Occult fungal infection</td>
</tr>
<tr>
<td>Drug or transfusion fever</td>
</tr>
<tr>
<td>Suboptimal serum concentration of antibiotics</td>
</tr>
<tr>
<td>Phlebitis, catheter related infection</td>
</tr>
<tr>
<td>Malignancy related fever</td>
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</tbody>
</table>
ruling out cryptic bacterial, fungal, or viral infections.

The length of therapy with antifungal agents is not well defined. When an invasive fungal infection is identified, antifungal therapy is typically continued till the complete clinico-radiological resolution of such infection. Treatment should be stopped in patients without any signs or symptoms of fungal infection after resolution of neutropenia. In the clinically well, persistent neutropenic patient with no evidence of fungal infection, antifungal therapy can be discontinued after 2 weeks. In hemodynamically unstable patients who have persistent fever and neutropenia, antifungal treatment should be continued until resolution of both fever and neutropenia\(^1\).

**Adjunctive therapy**

Colony stimulating factors are recommended only in complicated febrile neutropenia (cases associated with pneumonia, hypotensive episodes, severe cellulitis, sinusitis, systemic fungal infections, multiorgan dysfunction and unresponsive infections with expected delay in recovery of the marrow). Granulocyte transfusions are not routinely recommended but may be considered in uncontrolled gram negative bacterial infection or invasive fungal infection in patients expected to recover from neutropenia soon\(^{1,12}\).

**Conclusions**

Substantial progress made over the past few decades has reduced morbidity as well as mortality of febrile neutropenia. However, major challenges still remain in the treatment of febrile neutropenia in children with cancer. The objectives for the future include: a) the development of new, effective antimicrobials for the emerging resistant pathogens; b) the refinement of the existing models of risk stratification to reliably identify low-risk patients; c) the development of algorithms for safe ambulatory treatment with oral antibiotics in selected patients and d) the introduction of novel nonculture-based tools for early detection of infections (especially fungal infections). The ultimate aim is replacement of empirical therapy with pathogen-directed, preemptive therapy to make treatment specific and cost-effective.

**Points to Remember**

- **Fever in a neutropenic patient is the most common oncologic emergency and demands urgent medical intervention**

- **Signs and symptoms of infection are often absent or muted in the presence of neutropenia with fever remaining the only consistent early sign. Approximately 48 to 60% of febrile neutropenic patients have an established or occult infection.**

- **Promptly administer empiric high-dose, broad-spectrum antibiotics in maximal therapeutic doses based on local culture sensitivity pattern in patients with fever and neutropenia, even before the results of cultures are available in view of high mortality rates associated with inappropriately treated gram-negative sepsis.**

- **Good initial and continued clinico-laboratory evaluation with properly taken blood cultures, early imaging and timely use of antibiotics, antifungals and other adjunctive measures is key to good outcome.**

**References**


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**NEWS AND NOTES**

**PG TRAINING COURSE, NEW DELHI**

**18-20 July, 2008**

**July 20, 2008 NALS (NRP) Workshop**

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HEMATOLOGY

DISSEMINATED INTRAVASCULAR COAGULATION

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* Yadav SP

Abstract: Disseminated intravascular coagulation is a complex disorder with activation of multiple factors leading to thrombosis and hemorrhage leading to multiple organ system damage. Though there are many causes, sepsis is one of the common causes. Clinical presentation includes the features of primary disease, bleeding tendency and multiorgan involvement. Usual laboratory findings are thrombocytopenia, prolonged clotting times, increased levels of fibrin related markers and low levels of coagulation inhibitors. A scoring system for the diagnosis of DIC has also been developed. Management of DIC is based on the treatment of underlying disease, replacement therapy, supportive measures and control of coagulation mechanism. Recent understanding has resulted in some novel therapeutic agents such as Activated Protein C which as shown some difference in the mortality.

Keywords: Disseminated intravascular coagulation, Consumption coagulopathy, Multiorgan dysfunction.

Disseminated intravascular coagulation (DIC) is a highly complex pathophysiological disorder secondary to varied triggers or etiological factors, which lead to both thrombosis and hemorrhage. It is also known as consumption coagulopathy since the coagulation factors in the plasma are consumed during the clotting process and as a result of plasmin degradation. Even though hemorrhagic manifestations are the most obvious, yet it is the diffuse thrombosis that leads to end organ damage and is responsible for most of its associated morbidity and mortality. Disseminated intravascular coagulation may thus be defined as a systemic thrombohemorrhagic disorder seen in association with well-defined clinical conditions and laboratory evidence of:

(a) Procoagulant activation
(b) Fibrinolytic activation
(c) Inhibitor consumption
(d) Biochemical evidence of end organ damage or failure.

As we all know that sepsis is one of the common causes of DIC but not the only cause. One should exclude the other possible causes of DIC with the help of history, clinical examination and laboratory investigations. The gram-negative organisms cause DIC primarily because of the endotoxemia where as gram-positive organisms cause DIC because of mucopolysaccharide of the bacterial cell wall. In a child with DIC in shock and active bleeding, an aggressive and systematic approach reduces the mortality and morbidity.

Epidemiology

Precise incidence of DIC is not known. In general it is estimated that out of every 1000 admitted patients to a community hospital, only one patient will develop DIC. The frequency
of DIC should be seen in relation to the underlying disease. The most frequent diseases, which lead to DIC are infections and SIRS (Systemic Inflammatory Response Syndrome). The incidence of overt DIC is equal in gram positive and gram-negative infections. Severe trauma with inflammatory response was associated with DIC in 50%-70% of cases. Giant hemangioma is associated with clinically significant DIC in up to 25% cases.

**Etiology**

Clinical conditions that may be associated with disseminated intravascular coagulation are given in Table 1.

**Pathophysiology**

It was thought earlier that the process of hemostasis starts either with extrinsic or intrinsic pathway and after few steps a common pathway starts which ends up making the normal hemostatic plug. However recent literature supports that it’s a combination of many biochemical reactions which occurs simultaneously rather than a cascade. Usually all the reactions are happening in a single time frame but the rate of the different reactions may vary and hence their outcome.

Once thrombin is generated it leads to thrombin burst. Thrombin burst is the primary reason for piling up of a huge amount of thrombin which by different mechanisms affects the hemostasis. Thrombin has different actions on the process of hemostasis by means of 1) Procoagulant effect a) Converts fibrinogen to fibrin, b) Activates factor XIII, V and VIII and c) Activates platelets and 2) Anticoagulant effects a) Activates protein C, b) Stimulates fibrinolysis.

Once the hemostatic plug sets in, the regulation pathways start working, via the protein C and S, Antithrombin III, thrombomodulin, tissue factor pathway inhibitor and the fibrinolytic system (Fig.1). These factors keep the cascade in check and don’t allow the diffuse microvascular thrombosis to set-in.

**Regulation of coagulation pathway**

The regulatory mechanisms of the coagulation reactions serve two main functions. a) Limit the amount of fibrin clot formed to avoid ischemia of tissues and b) Localize clot formation to the site of tissue or vessel injury, thereby preventing widespread thrombosis.

Tissue factor pathway inhibitor (TFPI) is a protein that mediates the feedback inhibition of the Tissue Factor-Factor VIIa complex, resulting in decreased activation of both Factor IX and X. Small amounts of Factor Xa are required for TFPI to achieve its inhibition of Factor VIIa-Tissue Factor complex. Of importance, heparin increases action of TFPI 2-4 fold.

**Antithrombin III (AT):** This is a protein synthesized by liver and endothelial cells which binds and directly inactivates thrombin and the other serine proteases (Factors IXa, Xa, and XIa). The uncatalyzed reaction between the serine proteases and AT is relatively slow. However, in the presence of heparin or similar sulfated glycosaminoglycans, the reaction between AT and the serine proteases is virtually instantaneous resulting in the immediate blockage of fibrin formation. Normal endothelial cells express heparan sulfate (a sulfated glycosaminoglycan). AT binds to this and then is able to inactivate any nearby serine proteases, thus preventing the formation of fibrin clot in undamaged areas. Note, in the presence of heparin, the primary target of AT is thrombin.

**Activated Protein C and Protein S:** Proteins C and S are both vitamin K dependent inhibitors of the procoagulant system. Protein S markedly enhances the activity of Protein C. By inactivating Factors Va and VIIa, Proteins C
and S significantly decrease the tempo of thrombin generation, thereby dampening the cascade significantly.

**Thrombomodulin:** This is an endothelial cell receptor, which binds thrombin. When thrombomodulin and thrombin form a complex, the conformation of the thrombin molecule is changed. This altered thrombin molecule now readily activates Protein C and loses its platelet activating and protease activities thus converting thrombin from a potent procoagulant into an anticoagulant.

**The fibrinolytic system:** The fibrinolytic system helps to keep clot formation in check by actually degrading the fibrin strands. Plasmin has this ability to degrade fibrin strands, preventing the

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**Table 1. Conditions associated with disseminated intravascular coagulation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sepsis</td>
<td>Gram positive or Gram negative infections, Viral hemorrhagic fevers, Severe infection (any microorganism)</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>Myeloproliferative/lymphoproliferative malignancies (acute promyelocytic leukemia), Solid tumors</td>
</tr>
<tr>
<td>• Intravascular hemolysis</td>
<td>Transfusion reactions, Paroxysmal nocturnal hemoglobinuria, Sickle cell anemia</td>
</tr>
<tr>
<td>• Vascular abnormalities</td>
<td>Kassabach-Merritt syndrome, Large vascular aneurysms, Hereditary hemorrhagic telangiectasia</td>
</tr>
<tr>
<td>• Trauma</td>
<td>Polytrauma, Neurotrauma, Fat embolism, Burns</td>
</tr>
<tr>
<td>• Obstetrical calamities</td>
<td>Amniotic fluid embolism, Abruptio placenta, Retained fetus syndrome</td>
</tr>
<tr>
<td>• Organ destruction</td>
<td>Severe pancreatitis</td>
</tr>
<tr>
<td>• Severe toxic or immunologic reactions</td>
<td>Snake bites, Recreational drugs, Transplant rejection</td>
</tr>
<tr>
<td>• Severe hepatic failure</td>
<td></td>
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<tr>
<td>• Cyanotic congenital heart disease</td>
<td></td>
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<tr>
<td>• Collagen vascular disease and allergic vasculitides</td>
<td>Polyarteritis nodosa, Systemic lupus erythematosis, Henoch Schonlein purpura</td>
</tr>
<tr>
<td>• Vascular abnormalities</td>
<td></td>
</tr>
<tr>
<td>• Miscellaneous</td>
<td></td>
</tr>
</tbody>
</table>

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2008; 10(2) : 117
build-up of excess clot.

The process of DIC is initiated when there is a triggering stimulus for thrombin generation that occurs usually via the extrinsic pathway due to release or increased expression of tissue factor as in sepsis and obstetrical accidents, and occasionally via the intrinsic pathway due to endothelial damage as in vascular disorders. Activated factor X generates thrombin from prothrombin by cleaving its N-terminal end and forms prothrombin fragments 1 and 2 (F1+2) (Fig. 1). Thrombin cleaves fibrinogen into fibrinopeptide A and B (FPA and FPB), and generates fibrin monomers. Thrombin also releases interleukin-1 (IL-1) and tumor necrosis factor (TNF) from the monocytes and macrophages, and this process is enhanced in the presence of gram-negative lipopolysaccharide endotoxemia.\textsuperscript{3,4} In addition, thrombin induces vascular endothelium to release endothelin and selectin.\textsuperscript{5}

In DIC, the fibrinolytic system also gets activated and plasmin is generated. Plasmin cleaves the carboxy terminal end of fibrinogen and forms X, Y, D and E fragments.\textsuperscript{6} These fragments form the fibrinogen degradation products (FDPs). The X and Y fragments combine with the fibrin monomer and form soluble fibrin monomer,\textsuperscript{7} which cannot get polymerized and hence this would aggravate bleeding.

Plasmin cleaves the complex fibrin polymer and forms D-dimer, which is a more specific fibrin degradation product.\textsuperscript{8} The complement system also gets activated by plasmin, which results in aggravation of many of the clinical manifestations of DIC as discussed later. Plasmin activation would lead to enhanced bleeding. However, the FDP’s and D-dimer releases Plasminogen activator inhibitor type I (PAI-1) from the monocytes and macrophages that would decrease fibrinolysis and enhance fibrin polymer precipitation.\textsuperscript{9} The increased levels of PAI-1 are especially seen in sepsis that explains why in sepsis-induced DIC, thrombosis is predominant and further contributes to the end organ damage.

**Cytokines:** Recently the role of various cytokines and vasoactive peptides has been elucidated which may be contributing to the end organ damage seen with disseminated intravascular coagulation and also in potentiation of the entire process. Thrombin induced release of TNF from the monocytes activates the complement. The FDPs and D-dimer releases IL-1, IL-6 and tissue factor (TF) from the monocytes and macrophages.\textsuperscript{10} IL-1 and IL-6 damage, disrupt the vascular endothelium, and enhance thrombosis along with tissue factor.\textsuperscript{11} Thrombin induces release of selectin and endothelin from the vascular endothelium. The released selectin E (ELASM-1) binds to granulocytes, lymphocytes, monocytes and macrophages, and induces more cytokine release as well as platelet activating factor (PAF). The PAF induces further thrombocytopenia and so aggravates the bleeding.\textsuperscript{12} The endothelin causes vasoconstriction and vasospasm that induces thrombosis.\textsuperscript{13} The granulocytes bind to the endothelium and release proteolytic enzymes such as elastase and cathepsin that directly damages tissues and degrades many of the procoagulant and profibrinolytic factors.\textsuperscript{14}

**Complement:** In DIC, the complement is activated by plasmin and TNF.\textsuperscript{3,6} This results in hemolysis and thrombocytopenia. Complement induced platelet lysis provides more procoagulant material further accentuating the coagulation process. The complement increases vascular permeability leading to hypotension and shock.

**Kinins:** The activation of factor XII converts prekallikrein to kallikrein that in turn converts high molecular weight kininogen to kinins. The kinins also increase vascular permeability and so induce hypotension and shock.
Significant tissue injury and activation of extrinsic pathway e.g., Sepsis

Endothelial injury leads to activation of intrinsic pathway. e.g. Vascular accidents

Plasmin

Cleaves carboxy terminal of Fibrinogen

X, Y, D, E fragments (FDPs) & D-dimer

D-dimers and FDPs

Stimulates Monocytes and Macrophages (Enhanced in Sepsis)

Release of IL 1, 6, Tissue Factor & PAI-1

* IL-1, 6 and TF causes endothelial damage and there by Thrombosis

* PAI-1 decreases Fibrinolysis and increases fibrin polymerization → Thrombosis

Other associated pathway in DIC:

Activated factor XII a

Prekallikrein → Kallikrein

Kininogen to Kinin → Increases capillary permeability → Hypotension & Shock

More procoagulant material

Accentuation of Coagulation

Thrombosis

Fig. 1. Pathophysiology of disseminated intravascular coagulation
During the process of DIC, the inhibitors such as protein C, protein S and antithrombin also get consumed along with other coagulation factors.

The following paragraph will summarize the important factors in pathogenesis of sepsis.

1. **Increased thrombin generation** - Mediated predominantly by tissue factor/factor VIIa pathway.

2. **Impaired function of physiological anticoagulant pathway**
   a) **Reduction of antithrombin levels**: The result of a combination of increased consumption, enzyme degradation, impaired liver synthesis and vascular leakage.
   b) **Depression of protein C system**: The result of a combination of increased consumption, impaired liver synthesis, vascular leakage and down-regulation of thrombomodulin.
   c) **Insufficient tissue factor pathway inhibitor (TFPI)**

3. **Impaired fibrinolysis** - Mediated by release of plasminogen activators from endothelial cells immediately followed by an increase in the plasma levels of plasminogen activator inhibitor type 1 (PAI-1).

4. **Activation of inflammatory pathway** - Mediated by activated coagulation proteins and by depression of the protein C system.

**Clinical features**

Disseminated intravascular coagulation is an intermediary mechanism of disease, an epiphenomenon and as such the signs and symptoms will also depend on the antecedent disease. Thus it is difficult to make generalization with regard to the clinical presentation as the primary disease frequently clouds these. The clinical presentation may vary in relationship to the primary condition.

Along with the obvious signs of DIC on the general physical examination (sick looking child, bleeding, shock, etc.) one should always look for the signs of thrombosis in large vessels, such as deep venous thrombosis (DVT), and of microvascular thrombosis, such as renal failure. Bleeding from at least three unrelated sites is particularly suggestive of DIC. Bleeding can be skin bleeds, epistaxis, gingival bleeding or mucosal bleeding. The important physical signs, which are suggestive of DIC, should be sought for systematically.

**Circulation**: Signs of spontaneous and life-threatening hemorrhage, shock, signs of sub-acute bleeding and signs of diffuse or localized thrombosis.

**Central nervous system**: Nonspecific features like altered consciousness are present. Focal deficits are not usually present.

**Cardiovascular system**: Hypotension, tachycardia or circulatory collapse.

**Respiratory system**: Pleural friction rub and signs of acute respiratory distress syndrome (ARDS).

**Gastrointestinal system**: Hematemesis and hematochezia.

**Genitourinary system**: Signs of azotemia and renal failure, acidosis, hematuria, oliguria, metrorrhagia or uterine hemorrhage.

**Skin and subcutaneous tissue**: Petechiae, purpura, hemorrhagic bullae, acral cyanosis, skin necrosis of lower limbs (purpura fulminans), localized infarction and gangrene, wound bleeding and deep subcutaneous hematomas and thrombosis.
Because DIC is a continuously progressing process, it can be subdivided into three phases that might be helpful in making the diagnosis and treating them.

**Phase 1: Compensated activation of the hemostatic system**

Clinical finding: No symptoms
Laboratory parameters: PT, APTT, Thrombin time within normal limits; platelet count normal, prothrombin fragment 1+2 and thrombin antithrombin complex are elevated and antithrombin levels are slightly decreased

**Phase 2: Decompensated activation of the hemostatic system**

Clinical finding: Bleeding from injuries and venipuncture sites as well as decreased organ functions (e.g., kidney, lung, liver)
Laboratory parameters: Platelet counts are low, PT, APTT are constantly prolonged. Thrombin time mostly within normal limits but may be prolonged, fibrinogen levels, coagulation factors activities and antithrombin levels are decreased, prothrombin fragment 1+2 and thrombin antithrombin (TAT) complex and FDPs are clearly elevated and soluble fibrin levels are increased

**Phase 3: Full blown DIC**

Clinical finding: Skin bleed of different sizes and multiorgan failure.
Laboratory parameters: Platelet counts are severely low (usually less than 40% of initial value), PT, APTT are constantly prolonged or unclottable, Thrombin time prolonged severely or unclottable, fibrinogen levels, coagulation factors activities and antithrombin levels are decreased (less than 50% of initial values), prothrombin fragment 1+2 and Thrombin antithrombin (TAT) complex and FDP’s are clearly elevated and soluble fibrin levels are increased.

**Diagnosis**

The most common clinical manifestations of DIC are bleeding, thrombosis or both, often resulting in dysfunction of one or more organs.\(^{15,16}\) Since no single laboratory test or set of tests is sensitive or specific enough to allow a definite diagnosis of DIC, in most cases the diagnosis is based on the combination of results of laboratory investigations in a patient with a clinical condition known to be associated with DIC.\(^{17,18}\)

The classical characteristic laboratory findings include prolonged clotting times (prothrombin time, activated partial thromboplastin time, thrombin time), increased levels of fibrin-related markers (fibrin degradation products [FDP], D-dimers), low platelet count and fibrinogen levels and low plasma levels of coagulation factors (such as factors V and VII) and coagulation inhibitors (such as antithrombin and protein C).\(^{19,20}\) However, the sensitivity of plasma fibrinogen levels for the diagnosis of DIC is low, since fibrinogen acts as an acute-phase reactant and its levels are often within the normal range for a long period of time. Thus, hypofibrinogenemia is frequently detected only in very severe cases of DIC.\(^{17,21}\) On the other hand, FDP and D-dimer levels have a low specificity since many other conditions, such as trauma, recent surgery, inflammation or venous thromboembolism, are associated with elevated levels of these fibrin-related markers.

Other more specialized and useful tests, not available in all laboratories, include the measurement of soluble fibrin and assays of thrombin generation; such as those to detect prothrombin activation fragments F1+2 or thrombin-antithrombin complexes.\(^{22,23}\) However, serial coagulation tests may be more helpful than single laboratory results in establishing the diagnosis of DIC. A scoring system for the
diagnosis of DIC, developed from a previously described set of diagnostic criteria\textsuperscript{24}, has been proposed by the Scientific subcommittee on DIC of the International Society on Thrombosis and hemostasis (ISTHSSC).\textsuperscript{25,26} This system consists of a five-step diagnostic algorithm (Fig. 2), in which a specific score, reflecting the severity of the abnormality found. A total score of 5 or more is considered to be compatible with overt DIC.

According to recent observations, the sensitivity and specificity of this scoring system are high (more than 90\%).\textsuperscript{26} However, an essential condition for the use of this algorithm is the presence of an underlying disorder known to be associated with DIC.\textsuperscript{27} Finally, a scoring system for diagnosing non-overt DIC (Fig. 3) has recently been proposed by the ISTH Scientific Subcommittee and validated by Toh and Downey who demonstrated its feasibility and prognostic relevance.\textsuperscript{28}

Two most important observations noted by Toh and Downey while validating the score for non-overt DIC were:

- First, the demonstration that non-overt DIC itself carries a poor prognosis independent of developing overt DIC. A more probable explanation would be that overt coagulopathy, only one mechanistic pathway that can lead towards death. In others, the more commonly encountered sub clinical coagulopathy could indicate underlying activation in critical endothelial processes that have been indirectly captured via the proposed non-overt DIC diagnosis. This observation therefore appears consistent

\begin{table}[h!]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Step 1} & Does the patient have an \textbf{underlying disorder known} to be associated with DIC, If yes-2 score; If no 0 score & \textbf{Total score} \\
\hline
\textbf{Step 2} & \textbf{Major criteria} & \\
\hline
\textbf{Platelet count;} & If $> 1 \text{ lac}$ - 0 score & Minus 1 if counts rising \\
If $< 1 \text{ lac}$ - 1 score & Zero if counts stable & Plus one if counts falling \\
\textbf{PT prolongation;} & If $< 3 \text{ seconds}$ - 0 score & Minus 1 if counts rising \\
If $> 3 \text{ seconds}$ - 1 score & Zero if counts stable & Plus one if counts falling \\
\textbf{Fibrin related markers} & If normal - 0 score & Minus 1 if counts rising \\
If raised - 1 score & Zero if counts stable & Plus one if counts falling \\
\hline
\textbf{Step 3} & \textbf{Specific criteria} & \\
\hline
\textbf{Antithrombin;} & Normal levels = Minus 1 score, Low levels = Plus 1 score & \\
\textbf{Protein C;} & Normal levels = Minus 1 score, Low levels = Plus 1 score & \\
\hline
\textbf{Step 4} & Calculate final score & \\
\hline
\end{tabular}
\caption{Fig. 2. Approach for the diagnosis of overt DIC}
\end{table}

\begin{table}[h!]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Coagulation tests:} & \\
(Platelet count, PT, Fibrinogen, soluble Fibrin monomers and Fibrin degradation product) & \\
Platelet counts ($\times 10^9$/L): $> 100 = 0$; $< 100 = 1$; $< 50 = 2$ \\
PT (sec.): $< 3 = 0$; $> 3$ but $> 6 = 1$; $> 6 = 2$ \\
Fibrinogen (g/L): $> 1 = 0$; $< 1 = 1$ \\
Fibrin-related markers: No increase = 0; Moderate increase = 2; Strong increase = 3 & \\
\hline
\end{tabular}
\caption{Fig. 3. Scoring for the diagnosis of non-overt DIC}
\end{table}
with the concept as proposed by the ISTH SSC, of considering the vascular endothelial system as a physiological organ in its own right and that DIC represents failure or dysfunction in this vast organ.

- A second observation of significance is the equivalence in mortality rates between non-overt and overt forms of DIC. The pathophysiological implications are that non-overt DIC could be indicating that host responses have changed from being adaptive and overall protective to becoming maladaptive, with potentially lethal consequences. As such, recognition that this adaptive threshold has been crossed could have therapeutic relevance in better timing targeted intervention, especially as it has been shown the mean interval between non-overt and consequent overt DIC and death to be 24 h and 5 days, respectively. In addition, this tends to happen around days 3–5 into admission. A non-overt DIC diagnosis could therefore present a therapeutic window of opportunity for targeting treatment.

Finally, it is worthwhile re-emphasizing that overt DIC has its own scoring system. The separate non-overt DIC scoring system, as proposed by the ISTH SSC, now has a defining score of 5 and greater. While the non-overt DIC scoring system does capture some patients that evolve onto overt DIC, it also defines those who do not, but whose coagulopathy nonetheless forewarns of a potentially lethal outcome.

Investigations and their relevance in the diagnosis of DIC

Thrombocytopenia: Low platelet count is a primary feature of the vast majority of the patients and around 50% will be having counts less than 50,000/mm³. If done accurately this is the most useful screening test available except in the conditions like leukemia where other factors are involved.

Peripheral smear: Microangiopathic blood picture with associated anemia have been described as hallmarks for DIC but are relatively non specific as they can also be seen in conditions associated with risk of developing DIC, e.g., Kassabach Meritt Syndrome and vascular prosthesis.

Indicators of activation of coagulation: FPA [Fibrinopeptide A], F1+2, soluble fibrin and thrombin antithrombin complexes]. FPA and F1+2 are not specific parameters for diagnosing DIC as the coagulation can take place extravascularly also e.g., Pneumonia and peritonitis. In contrast soluble fibrin in plasma can only be generated intravascularly, thus represents a specific test for hypercoagulability. A reliable FPA, F1+2 and soluble fibrin estimation depends upon optimal venous puncture, so it’s a drawback for these tests. A simple test will be estimation of thrombin-antithrombin complex estimation, which indirectly indicates thrombin generation.

Indicators of fibrinolysis activation: [Fibrinogen degradation products (FDPs), D-dimers, α₂ antiplasmin and plasmin-antiplasmin complexes]. In the recent years it has been found that D-dimer is more sensitive than FDPs assay and a normal D-dimer has a high negative predictive value for the presence of intravascular fibrin degradation. Since fibrinogen is also degraded extravascularly, an elevated FDP or D-dimer level does not prove intravascular fibrinolysis. Since FDPs are metabolized by liver and excreted by kidney its levels are dependent on liver and kidney functions. Demonstration of fibrinogen degradation products (FDP) has been an essential prerequisite for a diagnosis of DIC. However negative FDPs do not rule out DIC. FDPs are named X, Y, D and E and appear in this sequence. During FDP assay, when thrombin
clot tubes are used with the idea of removing fibrinogen, fragments X and Y are also removed. Newer methods, which assay D and E, have evolved but if secondary fibrinolytic response is minimal then fibrinolysis may stop at X, which is not measured. Or else DIC may be formidable and degradation may occur past the stage of D and E. It is also possible that overwhelming release of granulocyte enzymes degrades FDPs. In the cascade, extreme hyperfibrinolysis is prevented by α2-antiplasmin and does not happen until α2-antiplasmin is depleted. So, α2-antiplasmin is helpful in judging the dynamics of fibrinolysis. The dynamics of activation, exhaustion or inhibition of fibrinolysis can be better judged by measuring plasmin antiplasmin complexes.

The best initial investigations for screening of DIC would be APTT, PT, TT, Platelet counts, D-dimer and peripheral smear and reserve the more specific tests for patients showing abnormalities in these tests.

**Treatment**

The heterogeneity of the underlying disorders and of the clinical presentations makes the therapeutic approach to DIC particularly difficult. Thus, the management of DIC is based on the treatment of the underlying disease, supportive and replacement therapies and the control of coagulation mechanisms. The recent understanding of important pathogenetic mechanisms that may lead to DIC has resulted in novel preventive and therapeutic approaches to patients with DIC. However, in spite of this progress, the therapeutic decisions are still controversial and should be individualized on the basis of the nature of DIC and the severity of the clinical symptoms. Over the years, replacement therapy has been an integral part of the treatment for patients with DIC. The aim of replacement therapy in DIC is to replace the deficiency due to the consumption of platelets, coagulation factors and inhibitors in order to prevent or arrest the hemorrhagic episodes. Platelet concentrates and fresh frozen plasma (FFP) were, in the past, used very cautiously because of the fear that they might “feed the fire” and worsen thrombosis in patients with active DIC. However, this fear was not confirmed by clinical practice and now a days replacement therapy is a mainstay of the treatment of patients with significant bleeding and coagulation parameters compatible with DIC.

**Treatment modalities for disseminated intravascular coagulation**

1. **Replacement therapy:** Fresh-frozen plasma


3. **Restoration of anticoagulant pathways:** a) Antithrombin, b) Recombinant human activated protein C.


**1. Replacement therapy**

The treatment for DIC includes replacement therapy, anticoagulants, restoration of anticoagulant pathways and other agents. Summary of the treatment modalities for DIC is given below.
fibrinogen concentrates (total dose 2–3 g) or Cryoprecipitate (1U/10Kg body weight) may be administered. However, FFP should be preferred to specific coagulation factor concentrates since the former contains all coagulation factors and inhibitors deficient during active DIC and lacks traces of activated coagulation factors, which may instead contaminate the concentrates and exacerbate the coagulation disorder.

2. Anticoagulants

The role of heparin in the treatment of DIC remains controversial. However, on the basis of the few data available in the literature, heparin treatment is probably useful in patients with acute DIC and predominant thromboembolism, such as those with purpura fulminans. The use of heparin in chronic DIC is better established and it has been successfully employed in patients with chronic DIC associated with those diseases in which recurrent thrombosis predominates, such as solid tumors, hemangiomas, and dead fetus syndrome. The role of heparin in the treatment of DIC associated with acute promyelocytic leukemia (APL) is another controversy, since some authors support its use whereas other studies failed to demonstrate its efficacy. Heparin is given at relatively low doses (5–10U/Kg of body weight per hour) by continuous intravenous infusion and may be switched to subcutaneous injection for long-term outpatient therapy (i.e., for those patients with chronic DIC associated with solid tumors). Alternatively, low-molecular-weight heparin may be used, as supported by the positive results in both experimental and clinical DIC studies. Heparin is given at relatively low doses (5–10U/Kg of body weight per hour) by continuous intravenous infusion and may be switched to subcutaneous injection for long-term outpatient therapy (i.e., for those patients with chronic DIC associated with solid tumors). Alternatively, low-molecular-weight heparin may be used, as supported by the positive results in both experimental and clinical DIC studies. Heparin is given at relatively low doses (5–10U/Kg of body weight per hour) by continuous intravenous infusion and may be switched to subcutaneous injection for long-term outpatient therapy (i.e., for those patients with chronic DIC associated with solid tumors). Alternatively, low-molecular-weight heparin may be used, as supported by the positive results in both experimental and clinical DIC studies.

Inhibition of the tissue factor and factor VIIa pathway is another strategy that has been explored. Moons and colleagues demonstrated the efficacy of recombinant nematode anticoagulant protein C₂ (NAPC₂), a potent and specific inhibitor of the ternary complex between tissue factor/factor VIIa and factor Xa, in inhibiting coagulation activation in a primate model of sepsis and shown promising results.

3. Restoration of anticoagulant pathways

Since patients with active DIC have an acquired deficiency of coagulation inhibitors, restoration of the physiologic anticoagulation pathways seems to be an appropriate aim of the treatment of DIC. Considering that antithrombin (AT) is the primary inhibitor of circulating thrombin, its use in DIC is certainly rational. Recent studies in animals and humans with severe sepsis have demonstrated that
antithrombin also has anti-inflammatory properties (reduction of C-reactive protein and IL-6 levels), which may further justify its utilization during DIC.\textsuperscript{52,53} The administration of antithrombin concentrates infused at supraphysiologic concentrations was shown to reduce sepsis-related mortality in animal models.\textsuperscript{54}

Based on the fact that the protein C system is impaired during DIC some authors have investigated the therapeutic efficacy of exogenous administration of this protein in patients with DIC.\textsuperscript{55,56} A dose-ranging clinical trial, patients were given recombinant human activated protein C (APC) by continuous infusion at doses ranging from 12ìg/Kg/hour to 30 ìg/Kg/hour or placebo.\textsuperscript{57} A 40 percent reduction in mortality was observed in those patients who received the higher doses of activated protein C. On comparing the safety and efficacy of APC and unfractionated heparin in the treatment of DIC it was concluded that the former improved DIC, and finally the survival, more efficiently than did heparin.\textsuperscript{58} A very recent trial on 2640 patients with severe sepsis and a low risk of death (defined by an Acute Physiology and Chronic Health Evaluation [APACHE II] score <25 or single organ failure) did not find a statistically significant difference in 28-day mortality rate between the placebo and APC-treated groups\textsuperscript{59}, suggesting that APC is of benefit only in patients at high risk of death from sepsis. Ongoing studies are focusing on the concomitant use of heparin in patients with DIC who receive activated protein C.\textsuperscript{18}

4. Other agents

Recombinant factor VII activated (rFVIIa) may be used in patients with severe bleeding who are not responsive to other treatment options. Bolus doses of 60–120 ìg/Kg (after the reconstitution of substrate), possibly repeated after 2–6 hours, have been found to be effective in controlling refractory hemorrhagic episodes associated with DIC.\textsuperscript{60,61}

**Antifibrinolytic agents**, such as epsilonaminocaproic acid or tranexamic acid, given intravenously at a dose of 10–15 mg/Kg/h, are occasionally used in patients resistant to replacement therapy who are bleeding profusely or in patients with disease states associated with intense fibrinolysis (prostate cancer, Kassabach-Meritt syndrome, acute promyelocytic leukemia).\textsuperscript{62} However, since these agents are very effective in blocking fibrinolysis, they should not be administered unless heparin has been previously infused in order to block the prothrombotic component of DIC. The use of these drugs in acute promyelocytic leukemia (APL) has declined in the last few years, given the efficacy of all-trans-retinoic-acid in preventing the majority of the hemorrhagic complications of this malignancy.\textsuperscript{18}

The advances in the understanding of the pathophysiology of DIC have resulted in novel preventive and therapeutic approaches to this disease. Based on the fact that tissue inflammation is a fundamental mechanism in DIC associated with sepsis or major trauma, some researchers have successfully employed the combined blockade of leukocyte/platelet adhesion and coagulation in a murine model by using antiselectin antibodies and heparin and have suggested the potential clinical use of such a strategy.\textsuperscript{63} Based on the same rationale, other researchers have demonstrated that the administration of recombinant IL-10, an anti-inflammatory cytokine which may modulate the activation of coagulation, completely abrogated endotoxin-induced effects on coagulation in humans.\textsuperscript{64} By contrast, the use of monoclonal antibodies against tumor necrosis factor has shown disappointing or at best modest results in septic patients.\textsuperscript{65-67} More recently, Branger and
colleagues found that an inhibitor of p38 Mitogen-activated protein kinase (MAPK), an important component of intracellular signaling cascades that mediates the inflammatory response to infectious and noninfectious stimuli, attenuated the activation of coagulation, fibrinolysis and endothelial cells during human endotoxemia. Finally, although studies using antibodies against the receptor for bacterial endotoxins (CD14) produced positive results, other studies using endotoxin antibodies failed to improve outcome.

**Points to Remember**

- **DIC is a syndrome characterized by systemic intravascular activation of coagulation, leading to widespread (micro) vascular deposition of fibrin, thereby contributing to multiple organ dysfunction.**

- The ongoing activation of coagulation may result in exhaustion of platelets and coagulation factors, which may cause bleeding.

- **DIC is invariably seen as a complication of a variety of disorders, most commonly, severe infection or inflammation, cancer, or trauma.**

- A diagnosis of DIC can be made by a combination of routinely available laboratory tests for which diagnostic algorithms have become available.

- **Recent knowledge on important pathogenetic mechanisms that may lead to DIC has resulted in novel supportive therapeutic approaches to patients with DIC. Strategies aimed at the inhibition of coagulation activation may theoretically be justified and are being evaluated in clinical studies. These strategies comprise anticoagulant agents or agents that may restore physiologic anticoagulant pathways.**

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**NEWS AND NOTES**

### MADURAI PEDICON 2008

**33rd ANNUAL STATE CONFERENCE OF IAP – TAMILNADU STATE CHAPTER**

**Date:** 8th – 10th August 2008

**Venue:** Lakshmi Sundaram Hall, Madurai

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### EIGHTH COURSE OF MEDICAL GENETICS AND GENETIC COUNSELING, LUCKNOW, UP

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HEMATOLOGY

THROMBOTIC DISORDERS IN CHILDREN

*Nitin K. Shah

Abstract: Thromboembolic episodes (TEs) are on the rise in pediatric age group due to improved survival of sick children admitted in PICUs, liberal use of central venous and arterial catheters, increased survival of cancer patients and increased recognition of TE due to availability of better diagnostic facilities. This article gives an overview of thrombotic disorders in children with special reference to management of venous thrombosis in children.

Key words: Thromboembolism, Central venous Catheter.

Thromboembolism in children is being increasingly recognised nowadays. The incidence of thromboembolism is estimated to be 14.5 per 10,000 in babies < 28 days of age and 0.05 per 10,000 in children between 1 month to 18 years of age.¹ This is much less than the estimated incidence of 2.5 to 5% in adults. Thromboembolism can be venous or arterial; associated with a specific organ and due to a specific cause. Most of the central venous catheter related TEs are in the upper body venous system whereas idiopathic deep vein thrombosis often involves the deep leg veins.

Clinical presentation

Clinical presentation will depend on the organ involved and whether it is venous or arterial TE. The incidence of TE depends on the depth to which the investigations are carried out as many of the TEs are asymptomatic and detected only on detailed radiological investigations. Deep vein thrombosis in leg presents with pain, swelling and discoloration of the affected limb and occasionally associated with fever and abdominal pain. Homan’s sign will be positive. Upper system venous TE presents with swelling, edema, discoloration of the affected limb. There may be collateral circulation in chest, arm, face or neck. There may be flushing of face with headache. Arterial TE presents as ischemia of the affected organ; e.g. cerebral stroke presenting with focal neurological deficit in case of carotid artery involvement. Acute pulmonary TE presents with sudden onset of respiratory distress, incessant cough, rusty sputum, right sided cardiac failure, pleuritic pain, cyanosis, increasing oxygen requirements, fever, arrhythmias etc. Chronic pulmonary embolism will result in pulmonary hypertension and congestive cardiac failure (CCF).

Underlying disorders

Only 2 to 5% of TEs are idiopathic in children as compared to 40% in adults. Most TEs have underlying serious cause as shown in Table 1.¹² Incidence of various underlying disorders varies depending on how aggressively one looks for the etiology. Congenital prothrombotic disorders of TE are uncommon in children and hence it is not cost effective to screen each and every patient with TE for congenital cause.
**Congenital prothrombotic disorders:** Various congenital disorders are now known to promote thromboembolism in children and adults. These are listed in Table 2. Heterozygotes are usually asymptomatic till later age and develop TEs spontaneously or following another prothrombotic insult. Homozygotes present with severe TEs very early in life as purpura fulminans. Patients with anti-thrombin III (AT III) deficiency will be relatively resistant to effect of initial heparinization. They are a common cause of spontaneous TEs in adults, whereas in children they are rare and they contribute to less than 2-15% of total patients. Hence in pediatric patients one should investigate for a congenital cause only if there are spontaneous, idiopathic, recurrent TEs, especially in young patients with familial history for similar TEs. These tests are not easily available at all the centers. In any case the priority while managing such patients is to start heparinization and not wait till one can collect samples for all these tests, or still worse await till reports become available. Besides, at the time of initial TE, the level of AT III and some of the other natural anticoagulants may be lower due to consumption in the thromboembolic process while the level of Protein C may be falsely higher than normal. Hence the best time to test for these congenital causes is after 3-6 months when the anticoagulation therapy is stopped.

**Central Venous Line (CVL) induced TE:** The incidence of TE is on the rise due to increasing use of CVL in neonatal intensive care units, pediatric intensive care units and oncology units. Nearly 80% of TEs in newborn and 60% of TEs in children involve upper venous system as they are all related to placement of CVL in upper body veins. CVL related TEs are often linked to catheter blockage and catheter related sepsis. The incidence of CVL related TEs varies from 1-80% depending on the depth of investigations carried out to detect TEs as most of the CVL related TEs are asymptomatic. Blocked catheter is best diagnosed by linograms, however it will not detect TEs in the concerned vein for which venogram is the best tool. Radiologically diagnosed CVL TEs are clinically significant and should be treated with anticoagulation.

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**Table 1. Underlying disorders leading to TE**

<table>
<thead>
<tr>
<th>Catheters: Central venous and arterial catheters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies: Acute leukemia</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Hematological conditions like sickle cell disease</td>
</tr>
<tr>
<td>Hepatic diseases</td>
</tr>
<tr>
<td>Renal diseases</td>
</tr>
<tr>
<td>Drugs like L-asparaginase, birth control pills</td>
</tr>
<tr>
<td>Congenital prothrombotic diseases like Protein C deficiency</td>
</tr>
<tr>
<td>Trauma, Surgery</td>
</tr>
<tr>
<td>Cardiac illnesses</td>
</tr>
<tr>
<td>Autoimmune disorders: SLE, APLA</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

**Table 2. Congenital prothrombotic disorders**

| Anti-thrombin III deficiency                   |
| Protein C deficiency                          |
| Protein S deficiency                          |
| Factor V leiden mutation and APC resistance   |
| Prothrombin G20210A mutation                  |
| Hyper homocysteinemia                         |
| Dysfibrinogenemias                            |
| Inherited abnormalities of fibrinolytic pathways like plasminogen deficiency |
Prophylactic use of heparin in a patient with CVL is known to reduce chances of catheter blockage by 67%, bacterial colonization of the catheter by 82% and catheter induced bacteremia by 74%. CVL related TEs can lead to postphlebitic syndrome with loss of venous vasculature due to non-canalisation which may lead to difficult venous access later in the life for some of these patients.

**Diagnosis**

The ultimate diagnosis of TEs is based on high index of clinical suspicion followed by radiological demonstration of the thrombus. For jugular or deep vein thrombosis of the leg ultrasound doppler study is quite sensitive. However for upper venous system doppler may not detect 80% of the TEs.\(^4,5\) Bilateral upper limb venography remains the investigation of choice in such cases. Echocardiography may help detect case of pulmonary embolism (PE), however ventilation perfusion scan is the most sensitive test to prove PE. One can perform linogram for central venous catheter; however it will only demonstrate catheter patency or thrombosis and not the patency of the vein as such for which venography is the only answer.

**Management**

The immediate aim of the management of TEs is to prevent spread of the thrombus; prevent embolism, especially PE; and subsequently to allow natural dissolution of the clot. This is achieved by use of antithrombotic agents. Initially intravenous heparin is used to achieve immediate antithrombosis which is then maintained by using either oral anticoagulation or low molecular heparin. Normally anticoagulation is maintained for 3-6 months following first episode of TE. In case of recurrent TEs, consider life long anticoagulation. Thrombolytic agents can be used to lyse clots if there is danger of losing a limb or incur severe organ damage due to TE.

**Initial heparin therapy:** Dose of unfractionated heparin used depends on the age of the child. Newborn and infants require larger doses as compared to adolescents and adults. Usual loading dose of heparin is 75 mg/kg given as intra

<table>
<thead>
<tr>
<th>APTT (Sec)</th>
<th>Bolus (units/kg)</th>
<th>Hold (min)</th>
<th>Rate Change (%)</th>
<th>Repeat aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>50</td>
<td>0</td>
<td>+ 10%</td>
<td>4 hr</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+ 10%</td>
<td>4 hr</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next day</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>- 10%</td>
<td>4 hr</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>- 10%</td>
<td>4 hr</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0</td>
<td>60</td>
<td>- 15%</td>
<td>4 hr</td>
</tr>
</tbody>
</table>

IV. Obtain blood for aPTT 4 hours after administration of the heparin loading dose and 4 hours after every change in the infusion rate

V. When aPTT is in therapeutic range, a daily CBC and aPTT should be done
venous infusion over 10 minutes. This is then followed by continuous intravenous infusion of heparin in the dose of 24 mg/kg/hr in newborn, 20 mg/kg/hr in infants or 18 mg/kg/hr for adolescents and continued for 5-10 days depending on the severity of the disease and delay in starting the therapy. The anti-thrombotic effect is monitored based on the aPTT which is maintained at 60-85 seconds. This roughly corresponds to heparin level of 0.2 to 0.4 units/mL based on the protamine titration assay or anti-FXa level of 0.3 to 0.7 units/mL. The dose of heparin is modified based on the aPTT as shown in the Table 3.

Use of low molecular weight heparin (LMWH): Fractionated heparin has many advantages as compared to unfractionated heparin, which makes it a drug of choice for initial heparinization and also for long term anticoagulation when compared to oral anticoagulation. Monitoring is needed much less frequently with LMWH. It is given by subcutaneous route which is helpful in small babies with difficult intra venous access and is given once a day. Complications like heparin induced thrombocytopenia and osteoporosis on chronic use are much less with LMWH. Enoxaparine is the most frequently used drug. The dose required is more per kg than adults. However it is an expensive drug which makes it out of reach for most patients in developing countries.

Side effects of heparin: Heparin can lead to clinical bleeding which can be managed by using protamine sulphate or FFP. The risk of bleeding is much less with LMWH than unfractionated heparin. Long term use of heparin is associated with osteoporosis though it is less common in children as compared to adults. Heparin can also lead to heparin induced thrombocytopenia (HIT), the incidence of which is lesser with LMWH than with unfractionated heparin.

Maintenance with oral anticoagulation: After initial heparinization, oral anticoagulant is added on day 2-3 while continuing intravenous heparin infusion. After 5-7 days heparin is stopped and oral anticoagulation is continued. After first episode of TE oral anticoagulation is continued for at least 3-6 months after which it is stopped. In case the patient has recurrent TEs or has presence of congenital prothrombotic tendency or has family history of similar congenital disorders, one has to use oral anticoagulation life long. One may use LMWH for maintenance; but is expensive.

The most common drug used for maintenance anticoagulation is oral coumadin group of drugs.

Table 4. Schedule for oral anticoagulation therapy using coumarin

| I. Day 1: If the baseline INR is 1 to 1.3 – | Action |
| Give 0.2 mg/kg of orally | |
| II. Days 2-4: If the INR is: | |
| INR | Action |
| 1.1 – 1.3 | Repeat initial loading dose |
| 1.4 – 1.9 | 50% of initial loading dose |
| 2.0 – 3.0 | 50% of initial loading dose |
| 3.1 – 3.5 | 25% of initial loading dose |
| > 3.5 | Hold until INR < 3.5 and then restart at 50% less than previous dose |
| III. Maintenance oral anticoagulation dose | |
| INR | Action |
| 1.1 – 1.4 | Increase by 20% of dose |
| 1.5 – 1.9 | Increase by 10% of dose |
| 2.0 – 3.0 | No change |
| 3.1 – 3.5 | Decrease by 10% of dose |
| > 3.5 | Hold until INR < 3.5 and then restart at 20% less than previous dose |
like coumarin. The oral route makes it the most preferred drug for this purpose. Besides, it is also cost effective as compared to LMWH, the other choice for maintenance therapy. The initial loading dose used is 0.2 mg/kg orally on day 1.\textsuperscript{6,9} This is then adjusted on subsequent days to achieve INR of 2 to 3 as shown in Table 4. Normally it takes 3-5 days to achieve INR of 2-3. For next 3 months dose is adjusted to keep INR at 2-3 and the dose required per day is usually 0.1 mg to 0.3 mg per kg. Older children need lesser dose. In children, where risk of recurrent TEs is lower or where monitoring using INR is difficult, one can use lower dose of coumarin to keep INR at 1.5-2.5.

**Side effects:** Oral coumarin can lead to 20\% risk of minor bleeding and 2-3\% chances of serious bleeding.\textsuperscript{10} It can be easily reversed by using vitamin K. In case of severe bleeding one may have to use FFP infusions as vitamin K will take 12-24 hours to revert INR to normal. Other side effects seen with coumarin include tracheal calcification or hair loss. It can also lead to fetal warfarin syndrome if given to pregnant women.

**Thrombolytic therapy:** Thrombolytic therapy is indicated in patients with significant effects on end organ due to TEs or as a resort to salvage a blocked catheter due to thrombosis. Tissue plasminogen activator (tPA), urokinase (UK) or streptokinase (SK) are the drugs used.\textsuperscript{11,12} tPA is more safer and more effective than UK or SK, at least in vitro tests. Local tPA is the best therapy for blocked catheter in the dose of 0.5 mg diluted in normal saline to volume enough to fill the line for less than 10 kg weight child and 1.0 mg for more than 10 kg weight child. For systemic thrombolytic therapy one can use tPA in the dose of 0.1-0.6 mg/kg/hr for 6 hours or UK in the dose of 4400 U/kg/hr for 6-12 hours or SK in the dose of 2000 U/kg/hr for 6-12 hours. Monitoring for the effect is done by monitoring FDP level and fibrinogen levels and kept at more than 100 mg/dL. 20\% of children treated with thrombolytic therapy develop bleeding and 1-2\% of patients develop intracranial bleeding.

**Complications of venous TEs:** Complications of TE can be immediate or late. Immediate complications include death due to extension of thrombus into heart or fatal pulmonary embolism; non-fatal PE, superior vena cava syndrome or chylothorax. Late complications can be due to TE itself like post-phlebitic syndrome (PPS), recurrence or blocked catheter leading to repeated insertion of CVL, or due to anticoagulation used like bleeding, osteoporosis, HIT etc. as discussed before. Mortality in pediatric TE is reported as 2-3\%. 7-8\% of children with TE have recurrence.\textsuperscript{12,13}

**Pulmonary embolism (PE):** Incidence of PE in pediatric patients varies depending on the depth of investigations carried out to detect one. Estimated incidence reported is 8.6/100,000 hospitalization in children of 1 month to 18 years of age.\textsuperscript{14} 50\% of the PEs are asymptomatic and only 15\% are considered for diagnosis.\textsuperscript{15} PE carries nearly 50\% mortality.\textsuperscript{2} Patient usually presents with sudden onset of unexplained breathlessness, cough, rusty sputum, chest pain, cyanosis and increasing requirements of oxygen. Often PE is confused as pneumonia or sepsis and it should be kept in mind as a differential diagnosis in a critically ill child. The best tool to diagnose PE is ventilation perfusion scan. Even pulmonary angiography can be used for diagnosis.

**Postphlebitic syndrome (PPS):** It occurs due to imperfectly performing venous valves permitting backflow of blood from central to peripheral venous system leading to damage to subcutaneous tissues. It presents as edema, pain, pigmentation, induration of the involved skin and chronic non-healing ulcerations. It can occur up to 5-10 years after the occurrence of TE.
The incidence is estimated to be 30% in pediatric patients.\(^2\) This means loss of peripheral venous system forever leading to difficulties in venous access.

**Points to Remember**

- **Pediatric TEs are increasingly recognised due to better awareness and improved diagnostic facilities.**
- **Congenital prothrombotic disorders contribute only to a small percentage.**
- **Unfractionated heparin or LMWH remain the drug of choice for initial rapid anticoagulation.**
- **Recurrent TE may require life long anticoagulation.**
- **Monitoring of small children on long term anticoagulants is difficult and needs careful management.**

**References**

HEMATOLOGY

CHRONIC IMMUNE THROMBOCYTOPENIC PURPURA IN CHILDREN

* Lalitha Kailas, ** Abhilash TG

Abstract: About 20% of children with acute immune thrombocytopenic purpura (ITP) progress to chronic ITP, which could be due to underlying conditions like autoimmune disorders, lymphoproliferative disorders or persistent infections like HIV. Children with chronic ITP can tolerate low platelet counts; hence the goal is to treat the symptoms and not to achieve a normal platelet count. Therapies like steroids, IVIG and IV anti-D are to be tried before considering splenectomy in children with chronic ITP.

Key words: Chronic ITP, Steroids, IVIG, IV anti-D, Immunosuppressants

Immune thrombocytopenic purpura (ITP) in children is a bleeding disorder which occurs either as an acute self-limiting condition or as a recurrent or chronic auto immune disorder. Chronic ITP is defined arbitrarily as the persistence of thrombocytopenia (i.e. platelet count <1,50,000/µl) for longer than 6 months after the acute presentation. 20% of children with acute ITP progress to chronic ITP. In adults and adolescents, chronic ITP is more common in women in the ratio of 3:1. Table 1 shows the conditions associated with chronic ITP of childhood.

In up to one third of patients with chronic ITP, spontaneous remissions will occur months or years later and an estimated five percent have recurrent ITP characterized by intermittent episodes of thrombocytopenia (at intervals of 3 months) followed by lengthy periods of remissions. This is presumed to reflect a chronic compensated state of ITP. During periods of remission, increased platelet production balances the increased rate of platelet destruction. During exacerbations, platelet production by the marrow is suppressed by viral infections or other factors and is unable to offset the rate of destruction.

Table 1. Conditions associated with chronic ITP of childhood

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Collagen vascular disorders</td>
</tr>
<tr>
<td>o SLE</td>
</tr>
<tr>
<td>o Auto immune hepatitis</td>
</tr>
<tr>
<td>o Autoimmune thyroiditis</td>
</tr>
<tr>
<td>o Anti phospholipid syndrome</td>
</tr>
<tr>
<td>• Lymphoproliferative disorders</td>
</tr>
<tr>
<td>o Autoimmune lymphoproliferative syndrome (ALPS)</td>
</tr>
<tr>
<td>o Hodgkins lymphoma</td>
</tr>
<tr>
<td>• Immune deficiency states</td>
</tr>
<tr>
<td>o Hypogammaglobulinemia</td>
</tr>
<tr>
<td>o Ig A deficiency</td>
</tr>
<tr>
<td>o Common variable immunodeficiency</td>
</tr>
<tr>
<td>• Infections</td>
</tr>
<tr>
<td>o HIV</td>
</tr>
<tr>
<td>o Hepatitis C</td>
</tr>
<tr>
<td>o Helicobacter pylori</td>
</tr>
</tbody>
</table>

* Professor and Head of the Department
** Junior Resident
Department of Pediatrics, SAT Hospital, Medical College, Thiruvananthapuram, Kerala.
Clinical features of chronic ITP

The onset is usually insidious: antecedent infections or fever and splenic enlargement are uncommon. Patients with chronic ITP usually have a fluctuating clinical course. Episodes of bleeding of mild to moderate severity may last few days or few weeks and may be intermittent. Spontaneous remissions are uncommon and are likely to be incomplete. Relapses in some cases appear to be associated with vaccination, for e.g., MMR. The differences between acute and chronic ITP are given in Table 2.

Lab findings

Complete blood count

Platelet counts: In chronic ITP platelet count at the time of presentation is usually higher [30,000-75,000/µl] compared to acute ITP. In the peripheral smear, platelets are often large and reveal more than normal variation in size and shape. Mean platelet volume [MPV] and platelet distribution width are increased in chronic ITP. If anemia present, it is proportional to the extent of blood loss and usually normocytic. Iron deficiency anemia may occur if bleeding has been severe and long standing. Patients may also have a positive Coomb’s test and autoimmune hemolytic anemia, the combination is known as Evan’s syndrome.

Total leukocyte count: is usually normal except for those changes resulting from acute bleeding such as mild to moderate neutrophilia with some increase in immature forms. Mild peripheral eosinophilia may be seen but is by no means consistent.

Bone marrow examination: This should be done in cases of persistent thrombocytopenia if not already done. Megakaryocytes are usually increased in size and are numerous. Examination of the bone marrow is helpful, particularly in ruling out other conditions with which ITP may be confused. Panel of American Society of Hematology Practical Guidelines recommend bone marrow biopsy in children with ITP who have persistent thrombocytopenia (more than 6 months) or are unresponsive to IVIG.

ESR: helps to suspect autoimmune disorder.

Coombs test: helps to differentiate Evan’s syndrome.

Autoimmune profile: to exclude autoimmune diseases (ANA, anti ds-DNA etc.).

Table 2. Differentiating features between acute and chronic ITP

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>Younger, 2-4 years</td>
<td>Older, above 10 years</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>None</td>
<td>More in females</td>
</tr>
<tr>
<td>Antecedent infection</td>
<td>Common, 1-3 weeks before bleeding</td>
<td>Unusual</td>
</tr>
<tr>
<td>Onset of bleeding</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt; 20,000/µl</td>
<td>30,000-80,000/µl</td>
</tr>
<tr>
<td>Eosinophilia and lymphocytosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Duration</td>
<td>2-6 weeks</td>
<td>Months or years</td>
</tr>
<tr>
<td>Spontaneous remissions</td>
<td>Occurs in 80% of cases</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Serology for HIV and Hepatitis C.

Blood grouping: Before giving anti-D

Antiplatelet antibodies: Although these tests are highly sensitive they have very low specificity as the patients with both immune and nonimmune thrombocytopenia have elevated PAIgG (platelet associated IgG). As per the recommendations of American society of hematology (ASH) guidelines testing for platelet antibody is not necessary for the diagnosis of ITP.

Treatment of chronic ITP

The primary goal of treatment in chronic ITP is to prevent the bleeding episodes and not to cure the disease. As with acute ITP decision should be based on symptoms than on platelet count.

Because the goal of treatment is a safe platelet count and not necessarily a normal platelet count observation alone is an appropriate approach for many patients especially with minimal symptoms. This conservative approach is based on the fact that spontaneous remissions may occur in one third of children, even as late as fifteen years.

Steroids: patients who had initial response to steroids can be treated with one to two courses of steroids (prednisolone 1-2mg/kg for 2-3 weeks, with tapering in one week). In some patients a safe platelet count (above 20000 - 30000/µl) may be maintained with low doses of prednisolone.

Mega dose steroid therapy

Methyl prednisolone 30mg/kg/day IV or orally for 3 days is effective in increasing platelet count to a safe level.

Pulse oral dexamethasone (20mg/m²/day for four sequential days/month for 6 months) has been tried with a response rate of 17 % in children.

IVIG: A dose of 0.8g/kg elevates the platelet count in most children with chronic ITP. Periodic doses of IVIG may be used as a maintenance therapy to defer splenectomy in young children with chronic ITP. About 25% of children with ITP will become refractory to maintenance therapy with IVIG. Low dose alternate day prednisolone therapy can be used as adjunct to maintenance IVIG therapy

Intravenous Anti-D can also be used as an effective maintenance therapy in Rh positive, Coomb’s test negative nonsplenectomised patients. Anti D is preferred over IVIG because of ease of administration (shorter 5-30 minutes infusion time), comparable efficacy and lower cost. Anti D binds Rh positive erythrocytes and leads to their destruction in the spleen blocking the splenic Fc receptors thus more antibody coated platelets survive in the circulation. A single dose of 50-100µg/kg is recommended by IV infusion over 3-5 minutes.

Splenectomy

Splenectomy is deferred longer in children with ITP than in adults, because of delayed remissions and significant post-splenectomy sepsis.

American Society of Hematology (ASH) guidelines for splenectomy (Table 3)

Splenectomy can often be deferred through the use of maintenance therapy with corticosteroid, IVIG or anti-D, although there is no evidence that any of these medical treatments alters the natural history of chronic ITP in children.

Splenectomy is effective because in most patients the spleen is the major site of platelet destruction and auto antibody production. At least 2-4 weeks before surgery, patients should
be immunized with pneumococcal vaccine, H.influenzae b vaccine and meningococcal vaccine as they are susceptible to overwhelming sepsis especially from bacterial infections.

Laparoscopic splenectomy is preferred in children with chronic ITP in view of the shorter hospitalization and more rapid normalization of activities.

A complete remission rate of 72% has been reported with splenectomy. Relapse after splenectomy may be due to transient viral suppression of thrombopoiesis. If thrombocytopenia persists, an accessory spleen should be considered.

**Table 3. Splenectomy-ASH guidelines**

<table>
<thead>
<tr>
<th>Children with ITP persisting for more than one year and</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those who have symptoms of bleeding and a platelet count</td>
</tr>
<tr>
<td>&lt; 10,000/µl (3-12 years) or 10-30,000/µl (8-12 years)</td>
</tr>
</tbody>
</table>

**Second line therapies**

In approximately 10-15% patients ITP cannot be controlled with splenectomy or frontline medical therapy. ASH practice guidelines recommend alternate treatment for children with symptomatic thrombocytopenia (less than 30,000/µl) that has failed to respond to splenectomy and primary drugs such as corticosteroids, IVIG, and Anti-D. No regimen is universally effective though several drugs have been tried.

**Danazol**

Danazol, an attenuated androgen with mild virilising effect has been shown to increase the platelet counts in patients with refractory ITP. The dose is 300-400mg/m²/day orally. In general, 2 months of therapy is required before a response is seen.

**Vinca alkaloids**

The vinca alkaloids, vincristine and vinblastine may induce a response in some patients with chronic refractory ITP. The usual dose of vincristine is 1.5mg/m² and vinblastine is 6mg/m² weekly IV for 4-8 weeks.

**Azathioprine**

Azathioprine, a potent immunosuppressive agent is also effective in the treatment of refractory ITP. The dose is 1-4mg/kg/day for 3-6 months.

**Cyclophosphamide**

Cyclophosphamide has also been used in ITP with variable success rates given orally 1-2mg/kg/day or intermittent IV in dose of 750-1000mg/m² every 3 weeks.

**Cyclosporine**

Cyclosporine has been recently tried in refractory ITP in the dose of 5mg/kg/day for 4 weeks.

**Other therapies**

Many other therapies including interferon, dapsone, ascorbic acid, colchicine and plasmapheresis have been studied for refractory ITP cases but none has been clearly found to be effective. Several investigators have reported that Rituximab, a monoclonal antibody against CD20, presumably by depleting the auto reactive B cell clone is effective in the treatment of refractory ITP. Agents designed to reduce bleeding without necessarily affecting the platelet count like aminocaproic acid can be used for excessive menstrual bleeding in young women and may reduce blood loss.
Points to Remember

- About 10-20% of children with acute ITP progress to chronic ITP.
- In chronic ITP, treat the child and not the platelet count. The goal of treatment is to prevent bleeding episodes, not to cure the disease.
- Achieve a safe platelet count as patients with chronic ITP can tolerate very low platelet counts.
- Children with significant mucosal bleeds may be treated with steroids, IVIG or intravenous anti-D. Immune suppressive drugs may have a role in refractory cases.
- Though splenectomy is the definite treatment, it is to be deferred longer in children in view of the overwhelming post splenectomy sepsis.

Bibliography


NEWS AND NOTES

APLS: THE PEDIATRIC EMERGENCY MEDICINE COURSE

6th-7th December 2008

Organizer: IAP, Delhi and Center for Child Health, Sir Ganga Ram Hospital, Delhi

Venue: Auditorium, Working Women Hostel, Sir Ganga Ram Hospital, Delhi

Registration: Limited to 40 delegates, Registration Fee: Rs 2000/- in favor of “Ambulatory Pediatrics”.

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

* Revathi Raj

**Abstract:** Hemophagocytic lymphohistiocytosis is not uncommon in children. It is due to dysregulation of the normal immunological downregulation, occurring usually after viral infections like EBV, CMV. The hyper cytokinemia secondary to this is responsible for the symptoms like fever, pallor and splenomegaly.

**Key words:** Hemophagocytosis, Children

Histiocytosis is a group of disorders characterised by abnormal proliferation of cells of the mononuclear phagocytic system with the histiocyte being the central cell. These cells could be Langerhan cells or macrophages. Histiocytosis is now classified based on their cell of origin (Table 1).

**Classification of histiocytic disorders**

**Class I - Dendritic cell histiocytosis**
(arise from dendritic cells)
  - Langerhans cell histiocytosis

**Class II - Non dendritic cell histiocytosis**
(arise from macrophages)
  - Familial hemophagocytic lymphohistiocytosis
  - Secondary hemophagocytic lymphohistiocytosis
  - Rosai-Dorfman disease

**Class III – Malignant histiocytosis**
(arise from monocytes)

**Hemophagocytic lymphohistiocytosis (HLH)**

HLH can be familial or acquired.

**Familial HLH:** An autosomal recessive condition that results in reduced apoptosis triggering. This leads to reduced natural killer (NK) cell activity and T cell cytotoxicity. Mutations have been identified in pertorin gene, munic gene and syntaxin gene that are essential in cytolysis. The incidence is 1 in 1 million and generally presents in infancy after a minor viral trigger. The condition is fatal if left untreated. Children can also present with central nervous system manifestations such as seizures, ataxia, meningeal signs or regression of developmental milestones. A family history of consanguinity and age less than 2 years at presentation are highly suggestive of familial HLH.

**Secondary or acquired HLH:** Increased macrophage activity is seen in the following conditions. 1) Viral associated HLH (VAHS) seen after viral infections, 2) Macrophage activation syndrome (MAS) seen in connective tissue disorders and 3) Malignancy associated HLH which is seen in T cell lymphomas.

Familial and secondary forms need therapy and carry a high mortality.

**Diagnostic criteria**

1. Molecular diagnosis consistent with HLH or 2. Clinical features: 5 out of 8 of these following criteria:

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Treatment includes steroids in the form of dexamethasone (since it has better penetration into the central nervous system), cyclosporin and etoposide. All three drugs have specific action against T lymphocytes and result in profound immunosuppression. The treatment of HLH with immunosuppression is one of the most heroic therapies that a hemato-oncologist can embark on (Figs. 2 and 3). The children are often very ill with fever and pancytopenia and commencing etoposide under such circumstances increases their susceptibility to infections. Prophylactic antifungals, antivirals and intravenous immunoglobulins in infants are used in supportive care.

Children with neurological involvement need repeated intrathecal chemotherapy and this is often seen in the familial form of the disease. Hematopoietic stem cell transplantation has increased the survival in this group to 60%, as chemotherapy alone is not enough to achieve durable remission.

Viral associated HLH is most often seen with Ebstein Barr virus infection. In India, HLH associated with Dengue fever and malaria with a high parasite index has been documented. Children with primary immune deficiencies can also present with HLH following viral infections and the distinction can often be difficult. Systemic lupus erythematosus or juvenile idiopathic arthritis can present with a stormy picture and HLH. Therapy is the same as the familial form and early etoposide has been shown to make a difference between life and death.

HLH is underrecognized and undertreated in pediatric practice. Awareness should be created to make early diagnosis and start specific therapy to reduce mortality.

**Points to Remember**

- A high index of suspicion is required to suspect and diagnose this condition.
* If there is a treatable infection it should be treated but be aware that this may not be sufficient and the patient may need HLH-treatment in addition. All severe forms should start HLH-treatment. If HLH is persistent or recurring consider that the patient may have an undiagnosed inherited disease. HLH may also develop secondary to a number of other diseases as malignancies, rheumatic diseases and metabolic disorders, requiring a different treatment.

# Start therapy if the patient has a genetically verified disease, a familial form of HLH, or if the disease is severe, persistent, or recurrent.

SCT : Stem Cell Therapy

**Fig. 2. Flow-sheet for children with hemophagocytic lymphohistiocytosis (HLH-2004)**
Fig. 3. Treatment protocol overview for hemophagocytic lymphohistiocytosis (HLH-2004)

Go to SCT during continuation therapy as soon as an acceptable donor is available with - HLA-identical related donor or - Matched unrelated donor or - Mismatched unrelated donor or - Family haploidentical donor (further SCT information: see text)

A donor search as soon as possible is suggested in familial patients and poorly responding patients, and is to be considered in infants.

Doses calculated per m² also if BW <10kg

*= EVALUATION, see Table 1
§See Fig 1 for info on start of Continuation

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Dexa = Dexamethasone daily with 10 mg/m² for 2 weeks, 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week; and taper then discontinue during 8th week.

# Pulses every second week with 10 mg/m² for 3 days during the continuation therapy.

VP-16 = Etoposide 150 mg/m² i.v., twice weekly for the first two weeks, then weekly during the initial therapy. Every second week during the continuation therapy. Only in certain conditions, such as if ANC <0.5 x10⁹/L and the bone marrow is hypocellular (which only rarely is the case), can the first two doses be omitted.

CSA = Cyclosporin A aiming at levels around 200 microg/L (monoclonal, trough value). Start with 6 mg/kg daily orally (divide in 2 daily doses), if normal kidney function.

I.T. therapy : = Methotrexate doses by age: <1 year 6 mg, 1-2 years 8 mg, 2-3 years 10 mg, >3 years 12 mg each dose.
Prednisolon doses by age: <1 year 4 mg, 1-2 years 6 mg, 2-3 years 8 mg, >3 years 10 mg each dose.
Maximum four doses are suggested, but start only if progressive neurological symptoms or if an abnormal CSF has not improved.

Supportive therapy: Cotrimoxazole, eq 5 mg/kg of trimethoprim, 2-3 times weekly (week 1 and onwards). An oral antimycotic from week 1 to week 9.
IVIG (0.5 g/kg iv) q 4 weeks. Gastroprotection suggested week 1-9.

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← INITIAL THERAPY → SCT / CONTINUATION THERAPY →

(dexamethasone daily)
(dexamethasone in pulses #)

Dexa (mg/m²)

| 10 mg | 5 mg | 2.5 mg | 1.25 mg |

VP-16

↑↑↑↑

CSA

I.T. therapy

(↑ ↑ ↑ ↑)

1 2 3* 4 5* 6 7 8 9*§ 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

weeks

25 26 27* 28 29 30 31 32 33 34 35 36 37 38 39 40*

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• **Suspect HLH in any child with prolonged fever, progressive splenomegaly with more than 2 cell lineage depression of the peripheral blood count.**

• **Early initiation of treatment improves outcome.**

**Bibliography**


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NEWS AND NOTES

IAP-AAP CME 2008
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HEMATOLOGY

PRENATAL DIAGNOSIS OF HEMATOLOGICAL CONDITIONS

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Abstract: With the rapid advances in prenatal diagnosis it is important to know about the methods available for early detection of various hematological disorders. This article deals with various methods that are available for prenatal diagnosis of hematological disorders.

Key words: Prenatal diagnosis, Hematological disorders.

What is prenatal diagnosis (PND)?

Prenatal diagnosis is a process of performing tests on the unborn fetus, for specific problems. The process involves detailed examination of the fetus using non invasive methods such as ultrasound and doppler studies and invasive methods such as chorionic villous and fetal blood sampling.

Indications for PND

Fetus may be affected with conditions that may manifest during pregnancy or after birth. Prenatal diagnosis for hematological conditions may be attempted in the following scenarios:

1. To rule out inherited disorders in babies with positive family history. In certain conditions the fetus generally does not show evidence of a hematological problem, but prenatal diagnosis is offered because the fetus is considered to be at a risk of being affected with an inherited blood disorder. The carrier status of the parents has to be ascertained in the following situations:
   - Previous child with a diagnosed inherited hematological problem such as thalassemia, hemophilia – the parents are obligate carriers in this situation
   - Family history of hematological problems, as in males on the maternal side being affected with hemophilia
   - In high risk communities where known genetic disorders are considered to be more prevalent – for eg. Sindhis and Bengalis have a high prevalence of thalassemia trait in their communities.

In these conditions and in asymptomatic parents with incidentally diagnosed recessive problems (for example thalassemia trait) diagnosed in routine tests, the fetus is tested to assess if the baby is likely to manifest the hematological condition after birth.

2. Abnormality in antenatal ultrasonogram in the fetus such as evidence of anemia on ultrasound and evidence of bleed, usually intracranial.

Steps in PND (Fig. 1)

Establishing the diagnosis

Detailed history and examination: Establishing diagnosis in the affected individual (index case) is the single most important step in PND. The elicitation of general history in the affected person is useful in arriving at a reasonable
conclusion. The age of onset of symptoms, the nature of problems such as anemia or unexplained bleeding and progression of disease have to be elicited. Detailed clinical examination including anthropometry of the affected child is the next step in diagnosis. Clinical examination may reveal clues like limb anomalies seen in TAR syndrome (Thrombocytopenia absent radius), organomegaly as in hemolytic anemias and storage disorders and history of repeated packed cells and specific concentrate transfusions in thalassemia and hemophilia respectively.

**Investigations:** Perusal of reports helps in arriving at a conclusion at times. When the reports are inconclusive, careful ordering of tests is an essential step to identify the exact diagnosis. For eg. Xrays are diagnostic of osteopetrosis.

**Expert opinion:** If a condition does not fit into any particular category, help may be obtained from experts in the field to arrive at a conclusion.

When the affected child is not alive, information has to be obtained from available records, reports, notes of the primary physician who had looked after the child and by reviewing the photographs.

**Identifying the mutation**

Molecular diagnosis is an essential prerequisite for PND. Molecular diagnosis varies from condition to condition. For example blood sent for molecular diagnosis of hemophilia can establish only that condition and not all or other related coagulation abnormalities such as Von Willebrand disease. Identifying the mutations in the affected individual is essential, because the mutation responsible for the same condition may vary in different families.

**Family pedigree as an aid in diagnosis and counselling**

A detailed pedigree charting will not only help in identifying the mode of inheritance of the condition but will also help in identifying

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**Fig. 1. Algorithm for PND**

**Fig. 2. Autosomal recessive inheritance**
the members of the family who are at risk of transmitting the condition. In Fig 2, the pedigree is that of an autosomal recessive (AR) condition such as thalassemia and Fig. 3 shows the pedigree of an X-linked recessive (XLR) condition such as hemophilia.

Fig. 3. X-Linked inheritance
Squares represent males and circles females. Fully shaded figures represent affected individuals; Carriers are represented by half shaded figures in AR conditions. Circles with central spot represent female carriers in XLR conditions.

Carrier testing
Once the mutation is identified in the affected child, the blood samples of parents of the affected child are sent to screen for carrier status. The samples of the child and the parents may all be sent at the same time for work up. The lab has to be contacted prior to sending the samples to identify the type of sample required for testing. Where the affected child is not alive, carrier testing may be attempted for the parents, after contacting the concerned lab. However a small percentage of lab-based errors may be anticipated, as confirmation with the affected child is not possible.

Prenatal diagnosis
Once the mutation has been identified, prenatal diagnosis may be offered to the couple in each of their pregnancies. Fetal tissue is collected and sent for molecular analysis. Chorionic villous sampling (CVS) is ideal as it can be collected early between 12 – 13 weeks of gestation. Under local anesthesia and ultrasound guidance, a needle is passed transabdominally and a small amount of placental tissue is aspirated. (Fig. 4). This tissue is then sent to the lab for further studies. Simultaneously a maternal EDTA sample is also sent to rule out maternal contamination.

Some important facts
1. The specific diagnosis for which the prenatal test is being attempted should be known. For example PND can not be offered for a nonspecific condition such as ‘hemolytic anemia’.
2. Tests that may be used after birth may not always be useful in prenatal diagnosis. For example hemoglobin electrophoresis will help in diagnosis of β thalassemia postnatally, however in fetal life presence

Fig. 4. Diagrammatic representation of chorionic villus sampling - under ultrasound guidance placental tissue is aspirated transabdominally
of foetal hemoglobin (HbF) is normal and hence diagnosis of β thalassemia will be missed when only hemoglobin electrophoresis is used prenatally.

3. The mutation in the affected family should be known; the affected child and / or the parents should have been tested and the molecular abnormality should be identified before planning PND.

4. PND may be attempted in early pregnancy. As the gestational age advances, the reports may not be available even until delivery! Late information is of no use.

5. PND carries a small risk of fetal loss and lab based errors.

6. Prenatal treatment for most fetal conditions (except immune anemia, thrombocytopenia) is not available.

7. Prenatal diagnosis is offered in conditions where the mortality or morbidity in affected children is high. In conditions where the morbidity is low, such as hereditary spherocytosis, PND is generally not offered.

8. Parents may opt for termination of pregnancy if fetus is found to be affected.

9. Carrier status of a fetus is generally not revealed due to ethical reasons. They are reported as “unaffected”.

Prenatal diagnosis and management of a fetus with anemia

Rh isoimmunisation

It is a condition that occurs in an Rh negative mother, usually after her first pregnancy. The red cells of an Rh negative mother do not bear the D antigen on them. When such a system is suddenly exposed to the D antigen present in an Rh positive blood, there is a response in the maternal system by production of anti-D antibodies. This exposure generally occurs after delivery or termination of pregnancy with an Rh positive fetus. These antibodies are then present in the maternal circulation eternally. When the mother bears an Rh positive fetus again, these antibodies enter the fetal circulation through the placenta causing hemolysis in the fetus resulting in fetal anemia.

Detection of fetal anemia

Rh isoimmunisation should be anticipated in an Rh negative mother whose indirect Coomb’s test (ICT) is positive. In such cases, serial monitoring with scan and doppler is recommended from early pregnancy. Early pick up and appropriate intervention help in preventing fetal and neonatal morbidity and mortality.

Evidence of fetal hemolysis may be seen in the form of hepatosplenomegaly, placentomegaly and cardiomegaly with or without hydrops due to anemia. Doppler changes of fetal middle cerebral artery (MCA) is a sensitive, reliable and non invasive method of detecting fetal anemia.

Fig. 5. Showing fetal middle cerebral artery - peak systolic velocity (MCA PSV) values for corresponding gestational age and the follow up plan.
(Fig.5). It is used to plan timing of fetal sampling and therapy

**Intervention**

When fetal anemia is suspected, fetal blood sampling is done to assess blood counts and a direct Coomb’s test is also done to confirm if it is immune hemolytic anemia. Discretion is used in fetal blood transfusion\(^1\). When there is evidence of anemia with a low hematocrit of 30% or less, intrauterine transfusion may be done with O negative packed cells cross matched with maternal serum, under strict aseptic precautions. Umbilical vein or portal vein is catheterized and fetal transfusion is done. The volume of transfusion will depend upon the initial fetal hematocrit, hematocrit of the donor packed cells unit, gestational age of the fetus and the transfusion volume is calculated using standard nomograms.

(Figs. 6a & 6b). The mother is given low dose antibiotics and tocolytics 24 hours before and 48 hours after the procedure.

**Monitoring**

The fetus is monitored every 2 – 4 weeks for evidence of anemia. Most fetuses require transfusions 4 weekly, however there are individual variations. The decision for transfusion is based on fetal age and the neonatal facilities available. Timing of delivery and place of delivery have to be planned so that the newborn is neither too sick nor too premature or anemic and is in a centre where neonatal interventions may be performed if necessary. These neonates have to be monitored for anemia and hyperbilirubinemia. They may require postnatal exchange transfusions. However antenatal therapy helps in reducing mortality and morbidity of these neonates as they are less anemic and hence are able to withstand

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**Fig. 6a. Fetoplacental blood volume for fetuses of varying ages.** For example 28 weeks old fetus has a volume of about 100 ml. (Nicolaides et al)

**Fig. 6b. Conversion factor.** [This is multiplied with fetoplacental volume and the volume to be transfused is decided (Nicolaides, et al)
procedures better. Long term outcome of well managed cases of Rh isoimmunisation have shown encouraging results.

**Other causes of fetal anemia**

When there is fetal anemia and the maternal ICT is positive but mother is Rh positive, minor group incompatibility is to be ruled out. Finding suitable donors for fetal transfusions is difficult and outcome in these situations will depend on the availability of compatible blood for transfusion.

When there is fetal anemia and the maternal ICT is negative, the condition is generally secondary to a nonimmune process. The causes could be varied. Some of them are:

1. Transplacental infections: Parvovirus and CMV, are common. Parvovirus has a classical feature of pure red cell hypoplasia or aplasia which can be seen on the peripheral smear.
2. Other rare hemoglobinopathies—such as alpha thalassemia that can be detected in hemoglobin electrophoresis.
3. Storage disorders—such as Gaucher’s disease can also have features of anemia.

**Diagnosis**

These conditions when suspected can be confirmed by fetal sampling. The amniotic fluid or fetal blood sample may be collected, depending on the period of gestation. Fetal blood sample is beneficial as more information may be obtained. However the procedure itself may be performed after 22 weeks when the umbilical cord size is good enough to be accessed. Amniocentesis may be done after 16 weeks. The procedure guidelines are the same as for CVS. Under local anesthesia, through a transabdominal approach, amniotic fluid is aspirated or fetal blood sample is collected from the umbilical cord. Fetal blood may be sent for peripheral smear, hemoglobin electrophoresis and antibody estimation for specific investigations. Baseline liver function tests may be done. Amniotic fluid or fetal blood may be used for PCR studies for fetal infections.

Simultaneously maternal samples may be collected wherever necessary for corresponding estimation of hemogram, smear studies and infection screen.

**Prenatal diagnosis and management of bleeding diathesis in a fetus / neonate**

At times it may be possible to identify neonates with intracranial bleed on the scan. There are many causes that can result in intracranial bleed. It could arise secondary to a combination of local and systemic factors. Systemic factors associated with intracranial bleed include thrombophilic conditions that produce infarcts which may then get lodged in the systemic circulation resulting in vascular catastrophes. It may also result from neonatal allo immune thrombocytopenia. This is an immune mediated condition the mechanism of which is similar to Rh isoimmunisation. However it may manifest even in the first pregnancy. Platelets also express specific antigens. Problems occur when the fetus inherits platelet antigens from the father, which is absent in the maternal platelets. When the maternal system produces antibodies against the paternally derived platelet antigen, they enter the fetal circulation and produce fetal thrombocytopenia. When this value is critically low, it manifests as bleeding in the fetus. Diagnosis and management may be difficult in primi, however when there is a history of bleeding in a fetus / neonate, this condition has to be suspected and the parental blood may be sent to a special lab for further work up. In subsequent pregnancies, management options such as fetal platelet transfusions and immunoglobulin therapy may be attempted.
Other conditions requiring prenatal diagnosis

Immunity and infection related conditions are more complex. These conditions (such as Interleukin deficiencies) are now being diagnosed, though the task is not very easy. As already explained, once the genetic tests are made, prenatal diagnosis may be offered on the same lines.

Points to Remember

- **In fetus with anemia on the scan**
  a) confirm maternal blood group Rh type,
  b) Repeat ICT for mother. *Rh isoimmunisation is the single most important condition to be identified by PND because it is treatable.*
- **Diagnosis of other conditions requires more extensive investigations on the fetus and can be done by invasive tests only.**

- **Specific diagnosis in the affected child is essential to predict recurrence risk and to offer prenatal diagnosis.**

- **Prepregnancy period is the best time to offer genetic counseling for the couple. They need the time and frame of mind to accept the information given.**

References

ACUTE MYOCARDITIS

* Shakuntala Prabhu
** Sumitra Venkatesh

Abstract: Most common aetiology of acute myocarditis is viral. The true incidence of myocarditis is unknown. Myocarditis should be ruled out in any child presenting with cardiac failure, unexplained shock, disproportionate tachycardia or with respiratory distress with cardiomegaly. Differential diagnosis, investigating approach and management in detail are outlined.

Keywords: Acute Myocarditis, Aetiology, Management, Children.

Acute myocarditis is an inflammatory disease of the myocardium and is diagnosed by an established histological, immunologic, and immunochemical criteria. It is an elusive illness to study, diagnose and treat, as the clinical presentation may range from nearly no symptoms to overt heart failure or sudden death. A myriad of etiological causes have been reported, with viral being the most common and almost synonymous with the disease.1,2

Pathophysiology

Myocarditis is caused by a wide variety of infectious organisms, autoimmune disorders and exogenous agents in hosts with genetic and environmental predisposition (Table 1). Viruses are the most common cause of myocarditis with adenovirus (55-60%) and coxsackievirus (30-35%) being the most common. Others like influenza A and B, herpes simplex, Ebstein Barr virus, and cytomegalovirus contribute to less than 15% of cases. The cardiac tropism of the two most common viruses (Coxsackie virus and Adeno virus) is explained from the isolation of the coxsackie virus-adenovirus receptor (CAR), a protein mapped to chromosome 2q11. The CAR, a member of the immunoglobulin helps in internalization of the coxsackie virus and adenovirus genome. This genomic theory helps one to speculate that the expression of these receptors could play a major role in determining the individual susceptibility and to developing viral myocarditis. Myocardial damage occurs in three phases, one evolving into another with transient period of distinctness. (Fig.1).

Phase I, Acute (0-4 days) - A period of viral multiplication and replication leads to further disruption of metabolism and perturbation of inflammation and its response. Diagnosis is by virus isolation and treatment seems promising with antiviral agents and CAR receptor blockers during this phase.

Phase II, Sub acute phase (4-14 days): This phase is marked by cell-mediated cytotoxicity, cytokine release and autoimmune mediated myocardial damage and dysfunction. Detection of the causal agent is uncommon during this stage. Myocardial biopsy could reveal necrosis of myocyte and inflammatory infiltrate as defined by Dallas criteria, which helps in diagnosis. Immunomodulation or immunosuppression has
Table 1. Major causes of myocarditis

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helped to down tone the antibody damage to the myocardium during this stage.\(^3,4\)

Phase III, Chronic phase- (14 days – 3 months): Remodeling, fibrosis, cytokine induced transformation and apoptosis leading to dilated cardiomyopathy is the hallmark of this phase. Diagnosis is usually by endomyocardial biopsy. Treatment is mainly supportive. Immune modulation has been tried with mixed response.

The resultant injury to the myocardium, whatever be the inciting agent, leads to a decrease in myocardial function with concomitant enlargement of the heart and an increase in the end-diastolic volume due to increased preload. Due to the damaged myocardial muscle, cardiac decompensation occurs, resulting in increase in left atrial, pulmonary venous and arterial pressures, resulting in increasing hydrostatic forces. These increased forces lead to both pulmonary edema and congestive heart failure. Without treatment, this process may progress to end-stage cardiac failure and death.

**Epidemiology**

The true incidence of myocarditis is unknown because the majority of cases are asymptomatic or at times is the cause of
unexplained death and studies give a wide spectrum of mortality and morbidity statistics. No racial or sex predilection exists. Younger patients, especially newborns and infants may have increased susceptibility and mortality rate (75%) than older infants and children (10-25%). Complete recovery of ventricular function has been reported in as many as 50% of patients. Some patients develop chronic myocarditis (ongoing or resolving) and/or dilated cardiomyopathy and may eventually require cardiac transplantation.\textsuperscript{5}

**Clinical manifestations**

Acute myocarditis should be suspected in any child presenting in cardiac failure with a structurally normal heart without a history of heart disease.

In fact, one should rule out an underlying myocarditis in any infant with unexplained shock, disproportionate tachycardia or with respiratory distress with cardiomegaly without murmur.

Generally, children present with vague complaints, often coincident with a history of a viral prodrome. In the myocarditis treatment trial, 89% of patients reported a viral-like prodrome with infectious symptoms which at times predominate. The cardiovascular symptoms may be entirely missed initially. The cardio respiratory complaints of dyspnea, orthopnea, pedal edema, palpitations, syncope, CHF and dysrhythmias are noted usually 7-10 days later.

**Physical examination often reveals**

- Signs of diminished cardiac output such as tachycardia, weak pulse, cool extremities, decreased capillary refill and pale or mottled skin. Mild hypotension, unexplained metabolic acidosis and occasionally syncope (due to heart block or other arrhythmias) may be seen.
- Heart sounds may be muffled, especially in the presence of pericarditis. An S\textsubscript{3} may be present and a heart murmur caused by atrioventricular valve regurgitation may be heard.
Hepatomegaly may be present in younger children.

- Rales due to pulmonary edema may be heard in older children.
- Jugular venous distention and edema of the lower extremities may be present.

Neonates may seem irritable with respiratory distress and exhibit signs of sepsis. Somnolence, hypotonia and seizures can be associated if the CNS is involved. Hypothermia or hyperthermia, oliguria, elevated liver enzymes and elevated blood urea nitrogen and creatinine caused by direct viral damage and/or low cardiac output may be present.\(^6\),\(^7\)

If the presentation is more fulminant and severe, the course may be either death or complete recovery (Fig 2).

### Diagnosis

A diagnosis of acute myocarditis must be made based on clinical history, physical examination, imaging studies and laboratory tests. The following are the diagnostic modalities available or reported in literature with their relative strength and weaknesses.\(^8\)

**Chest radiograph**: The cardiac silhouette is generally enlarged with acute myocarditis but occasionally may be normal in size and configuration. Pulmonary congestion may be present along with pleural effusion and interstitial infiltrates.

**Electrocardiography**: The diagnostic triad of sinus tachycardia, ST–T wave changes and low voltage QRS complexes (< 5 mm) in standard and precordial leads has been popularly

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**Fig.2. Natural history based on clinical presentation**
described. However, it is important to remember that the diagnostic triad may not be present in all. Other findings include, arrhythmias like supraventricular tachycardia, atrial ectopic tachycardia, ventricular premature beats, ventricular tachycardia and ventricular fibrillation. Variable degrees of atrioventricular blocks including complete heart block have also been reported.

Other laboratory values: Elevated C-reactive protein and white blood cell count with lymphocyte predominance may be seen in acute myocarditis. Serum LDH (lactic dehydrogenase), SGOT, SGPT may be elevated but are non specific. Positive viral titers, especially a fourfold rise in acute and convalescent IgM antibody titers establishes a diagnosis of viral myocarditis. However it is not routinely available and reporting takes time thus, when available the diagnosis is postdated.

There is limited data on myocardial muscle creatine kinase isoenzyme (CPK-MB) in diagnosis of myocarditis and is found elevated in only 25% of the cases. Soongswang et al. demonstrated that CPK-MB and cardiac troponin-T were significantly higher in myocarditis as compared to dilated cardiomyopathy and left to right shunts with congestive heart failure.9-11

Echocardiography: This is the most useful investigation in an appropriate clinical setting. Echocardiography often shows globally reduced ventricular systolic functions, although this finding is certainly not specific for myocarditis. Other common echocardiographic findings include, increased ventricular cavity dimensions (a dilated left ventricle) with or without ventricular wall thinning, atrio-ventricular (AV) valve regurgitation, segmental wall motion abnormalities and pericardial effusion. Occasionally, diastolic functions are also affected.

Endomyocardial biopsy

Endomyocardial biopsy remains theoretically, the standard for diagnosing acute myocarditis despite its known limitations such as sampling error, procedural complications, variability of pathological interpretation and low negative predictive value. The standard histological criteria for establishing the diagnosis in adult population (the Dallas criteria) have been widely used in children (Table 2). Recent advances in molecular biology, especially the polymerase chain reaction and ribonucleic acid hybridization to detect viral genetic material have improved the yield and sensitivity of endomyocardial biopsy. Myocardial biopsy is

<table>
<thead>
<tr>
<th>Table 2. Dallas criteria for diagnosis of myocarditis</th>
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<tbody>
<tr>
<td><strong>General definition</strong></td>
</tr>
<tr>
<td><strong>Active myocarditis</strong></td>
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<tr>
<td><strong>Borderline myocarditis</strong></td>
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<tr>
<td><strong>Persistent myocarditis</strong></td>
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<tr>
<td><strong>Resolving /Resolved myocarditis</strong></td>
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</table>
always not feasible in children and is available only at selected centers. Since its introduction in the early 1980s, it has highly variable results with a reported incidence of myocarditis ranging from 0 to 80%. A second clinicopathological classification system was proposed in 1991, but has received only limited acceptance.\textsuperscript{12-14}

**Magnetic resonance imaging:** Several imaging techniques are emerging as adjunct diagnostic tests. Antimyosin scintigraphy to judge the degree of myocardial necrosis, contrast enhanced cardiovascular magnetic resonance imaging and echocardiographic digital image processing help in localization and assessment of the extent of inflammation in patients with presumed viral myocarditis. These non-invasive modalities in diagnosis of acute myocarditis seem promising in future.\textsuperscript{15}

**Differential diagnosis**

Viral infections are responsible for the majority of cases of acute myocarditis. These are difficult to prove as viral particles are rarely seen in myocardium either on biopsy or autopsy. Most viral cultures or serology are also not consistently supportive. Hence the diagnosis of acute viral myocarditis starts with ruling out other causes of myocardial dysfunction.\textsuperscript{16}

Structural cardiac lesions with left sided outflow tract obstruction like coarctation of aorta, aortic stenosis and anomalous coronary artery can cause congestive cardiac failure and myocardial dysfunction.

Arrhythmias which are incessant like supraventricular tachycardia and junctional reciprocating tachycardia should be ruled out using an electrocardiogram.

Systemic hypertension can present with congestive heart failure and dysfunction.

Inherited metabolic causes (like glycogen storage disorders, carnitine deficiency) could present with myocardial dysfunction and has to be ruled out especially in neonates and infants. A positive family history of cardiomyopathy, failure to thrive, significant metabolic acidosis and/or hypotonia may give clue to the diagnosis.

Occasionally, hypocalcemia and vitamin D deficiency in infants have been reported to cause left ventricular failure and dysfunction.

**Treatment**

Supportive care is the first line of treatment in acute myocarditis. A minority of patients who present with fulminant or acute myocarditis will require an intensive level of hemodynamic support, fluid and electrolyte monitoring and aggressive pharmacological intervention, including vasopressors and positive inotropic agents. The goal of treatment is to support the blood pressure and cardiac output, keeping in mind that an increase in oxygen consumption may be harmful to the injured myocardium. In children with acute heart failure and clinical signs of low cardiac output or oxygen delivery, inotropic support with beta agonists such as dobutamine and phosphodiesterase inhibitors such as milrinone is indicated. More severe cardiogenic shock states would need low dose epinephrine and presence of hypotension may merit use of inotropic agents with alpha adrenergic activity such as dopamine or higher dose of epinephrine (Table 3). Non-invasive ventilation may be effective in treating pulmonary edema which also helps to reduce left ventricular after load\textsuperscript{8}.

Several drugs used for chronic heart failure are also useful in cardiac failure due to acute myocarditis with less severe presentation. Diuretics (particularly loop diuretics), should be used to decrease pulmonary edema and total body water, and addition of spironolactone may be complementary. Angiotensin converting enzyme inhibitors (ACEI) should be started early after
establishing adequate renal perfusion. The use of digoxin is controversial and traditionally has been avoided, although clinical data neither support nor refute this and the present recommendation is that digoxin should probably be used with caution and in low doses in these patients.

Use of anticoagulation is common and antiarrhythmic drugs are frequently used to treat arrhythmias in acute myocarditis.

Levosimendan, a novel inotropic agent that increases the sensitivity of myofilaments to calcium have been tried in 15 children with either end stage or acute myocarditis. However results were interpreted with caution due to the small number of study group and a lack of control group.

Studies using beta agonists and antagonists in severe heart failure have concluded that overall survival is better with latter as opposed to former. Carvedilol, metoprolol, and bisoprolol have all been subject to at least one large scale trial and shown to be effective in reducing mortality in adults.17,18

Immunotherapy for acute myocarditis – Despite a common practice of immune globulin administration in acute myocarditis, there are no randomized, controlled studies in children to definitely support its use. There is no class I evidence in pediatric literature and no meaningful meta-analysis of available studies. Likewise, there is also a lack of evidence based data to conclude whether the use of immunosuppressive agents benefit children with acute myocarditis. Similarly, early trials of antiviral therapies, such as interferon suggest a potential therapeutic role but require further investigation.19-22

A ventricular assist device or extracorporeal membrane oxygenation may rarely be required to sustain patients with refractory cardiogenic shock. These devices favorably alter ventricular geometry, reduce wall stress, decrease cytokine activation and improve myocyte contractile function. Although the data on survival after ventricular assist device or extracorporeal membrane oxygenation implantation are largely observational, the high likelihood of spontaneous

<table>
<thead>
<tr>
<th>Inotropic support</th>
<th>Afterload reduction</th>
<th>Diuresis</th>
</tr>
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<tbody>
<tr>
<td>Dobutamine 5–20 µg/kg/min</td>
<td>Milrinone 0.5–0.75 µg/kg/min</td>
<td>Frusemide 1 mg/kg IV</td>
</tr>
<tr>
<td>Milrinone 0.5–0.75 µg/kg/min</td>
<td>Nitroprusside 0.5–3.0 µg/kg/min</td>
<td>Chlorothiazide 20 mg/kg/day orally divided BID</td>
</tr>
<tr>
<td>Dopamine 5–10 µg/kg/min</td>
<td>Enalaprilat 5–10 µg/kg/dose IV every 8–24 hours</td>
<td>4 mg/kg/day IV divided every 6–12 hours</td>
</tr>
<tr>
<td>Epinephrine 0.05–0.1 µg/kg/min</td>
<td>Enalapril 0.1–0.5 mg/kg/day orally divided BID</td>
<td>Spironolactone 1–3 mg/kg/day orally divided every 6–12 hours</td>
</tr>
<tr>
<td></td>
<td>Captopril 0.15–0.5 mg/kg/dose orally every 8 hours</td>
<td></td>
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</tbody>
</table>
recovery of ventricular function argues for aggressive short-term hemodynamic support.

Natural history and prognosis

The myocarditis treatment trial reported mortality rates for biopsy-verified myocarditis as 20% and 56% at 1 year and 4.3 years, respectively. These outcomes are similar to the Mayo clinic’s observational data of 5-year survival rates that approximate 50%. Survival with giant cell myocarditis is lower with less than 20% of patients surviving for 5 years.

Poor prognostic markers have been reported in viral myocarditis. In fulminant myocarditis, cardiac arrest and ventricular tachycardia during acute phase have poor prognosis while those with chest pain at presentation, younger age group (except neonates) and those with atrioventricular block have good prognosis on a long term follow up with complete recovery of left ventricular functions. Most cases of asymptomatic myocarditis and those presenting in congestive heart failure with insidious onset, either have sudden cardiac death during acute stage or may have complete recovery or develop into dilated cardiomyopathy on long term follow up. (Fig 2)23

Points to Remember

- *Acute myocarditis is a major cause of acquired cardiac problem in infancy and childhood. Most of them are caused by viruses.*

- *It is an important contributor to left ventricular dysfunction and dilated cardiomyopathy in children.*

- *Age and mode of presentation are two important factors in determining the long term natural history and prognosis.*

- *Treatment of myocarditis, still remains largely supportive.*

References


A CLINICAL APPROACH TO SKELETAL DYSPLASIA

* Elizabeth KE
** Binoy Thomas

Abstract: Skeletal dysplasia (SD) is one of the major causes of pathological short stature. It represents a heterogeneous group of genetic disorders with variable presentation, severity and associated morbidities. In the diagnosis of short stature, a systematic approach is necessary for proper early diagnosis. Radiological findings are characteristic in most of these conditions. A brief account of the common skeletal dysplasias is presented. In the management, multidisciplinary team approach and genetic counselling are recommended.

Key words: Skeletal dysplasia, Constitutional bone disorders, Short stature.

Skeletal dysplasia (SD) is a group of genetic conditions with inherent or constitutional disorders of bone formation and modeling due to genetic mutations. These are also called constitutional bone disorders. There are several hundred conditions in this group. These may present at birth or later in life. One fourth of these disorders are lethal or lead to still birth and one third may result in postnatal death. Those who survive will present with pathological short stature and associated orthopedic problems, neurological problems, deafness, blindness etc.

Definitions

When bone alone is affected, the condition is called ‘skeletal dysplasia’ and when cartilage is also affected, it is called ‘osteo-chondrodysplasia’. The term ‘dysostosis’ is used exclusively for bone malformations. Disorders of bone density include inherited osteopenias like ‘osteogenesis imperfecta (OI)’ and inherited osteosclerosis like ‘osteopetrosis’. Non genetic conditions that mimic genetic SD are fetal warfarin syndrome and vitamin D deficiency syndrome.

Hemimelia refers to the absence of part of a limb, e.g., forearm, hand, foot etc. Phocomelia is used to denote marked reduction in the size of limb, e.g., hand close to trunk. Syndactyly is fusion of fingers/toes. Polydactyly is extra fingers/toes. Pre-axial polydactyly is on the radial side and post axial on the ulnar side.

The classification of skeletal dysplasia depends on the prognosis, associated anomalies, site of involvement, etc.

Classifications

1. Based on outcome - lethal or non lethal

Some of the mutations are severe or homozygous and are florid at birth and often lethal leading to miscarriage or still birth, e.g. rhizomelic-thanatophoric dysplasia, homozygous achondroplasia and acromelic-achondrogenesis.
2. Based on associated anomalies

SD may be purely bone disorders like achondroplasia or may be associated with multiple congenital anomalies (MCA), SD-MCA syndrome, e.g. Ellis van Creveld syndrome. Sometimes, it may also be associated with mental retardation (MR) like SD-MCA-MR syndrome, e.g. camptomelic dysplasia. The usual associated anomalies are cleft palate, polydactyly, syndactyly, myopia/cataract, congenital heart disease, club foot, cystic ears, short rib, long narrow thorax, kypho-scoliosis, large head, prominent forehead, flat face, platybasia, cranio-vertebral anomalies, peg shaped teeth, hitchhiker thumb, etc.

3. Based on physis involvement

SDs usually affect long bones and may be confined to epiphysis, metaphysis or diaphysis, e.g. epiphyseal dysplasia, diaphyseal dysplasia (Multiple diaphyseal dysplasia) or metaphyseal dysplasia or may be overlap syndromes like meta-epiphyseal dysplasia. Sometimes it may also be ‘expanded syndromes’ involving spine and cranium, e.g., spondylo epiphyseal dysplasia, cranio metaphyseal dysplasia, fronto epiphyseal dysplasia and so on. Spondylo-meta-epiphyseal dysplasia is referred to as pseudoachondroplasia.

4. Based on limb shortening

When the proximal segment of the limb, e.g., humerus/femur is short, it is called ‘rhizomelic short stature’. When the mid segment, e.g., radius-ulna/tibia-fibula is short, it is ‘mesomelic short stature’ and when the distal segment, e.g., hands/feet are short, it is ‘acromelic short stature’. Examples of rhizomelic dwarfing are achondroplasia, spondylo-epiphyseal dysplasia and metaphyseal dysplasias. Example of mesomelic dwarfing is mesomelic dysplasia and examples of acromelic dwarfing are Ellis van Creveld syndrome (chondro-ectodermal dysplasia), asphyxiating thoracic dysplasia (Jeune syndrome) and diastrophic dysplasia.

Most of the skeletal dysplasias present as short stature. Short stature may or may not be evident at birth. In the severe forms, it is recognizable at birth, but in some, it becomes evident only during follow up. Short stature may also be classified as normal variant (physiological) or pathological (Fig. 1).

Normal variant versus pathological short stature

Short stature may also be a normal variant. Genetic short stature (GST) and constitutional/maturational growth delay (CGD/ MGD) are included in this group. The term MGD is preferred than CGD as the condition is due to delayed maturation and correctable, unlike other constitutional disorders.

When the stature is abnormally short, e.g. less than 3rd centile or less than 3 standard deviation of the normal, it is referred to as pathological short stature or dwarfing. In this condition, the adult height is often less than 145 cm. Hypochondroplasia is an exception to this rule, in which the adult height may be more than 145 cm. Usually, in pathological short stature, the limbs are shorter and the upper limbs stop above mid pelvis in infants and above upper thigh after infancy.

More insight regarding “Stature” is now available. “Short stature homeobox containing gene (SHOX gene)” located on the pseudoautosomal region of p arm of X and Y chromosomes is in highlight now. It is interesting to note that it is active on both XX and XY. This explains short stature in Turner syndrome. Deletion of SHOX gene is said to be the cause for idiopathic short stature (ISS).
The infancy, childhood and puberty (ICP) concept of growth is yet another break through model. In infants, nutrition is the prime influence on growth. In children, growth hormone, thyroxine, IGF 1 and IGF binding protein (IGFBP 3) have major influences. In puberty, sex steroids exert major influence on growth.

The mid point of the body is umbilicus in the newborn and it is pubic symphysis in the adult. The upper segment is up to the hip socket and lower segment is below that. The upper segment to lower segment ratio should be calculated and compared with that for the chronological age (CA) of the child. It is roughly 1.7:1 at birth, 1.6:1 at 6 months, 1.5:1 at 1 year, 1.4:1 at 2 years, 1.2:1 at 4 years and 1:1 by 10 years of age.

In proportionate dwarfing, body proportions are comparable to that for the chronological age, but in disproportionate dwarfing, it does not correspond to that for the chronological age. It is usually infantile in conditions with limb shortening, i.e. lower segment will be shorter than upper segment. In those with trunk shortening, the upper segment will be shorter. If upper and lower segments are equally affected, proportionate dwarfing can occur. Thus the short stature may be short limbed, short trunked or proportionate.

**Dysostosis multiplex**

This term refers to the various bone manifestations in diseases with involvement of other systems as well. The exact diagnosis of the underlying condition will need other laboratory evidences, for eg, the bone changes in mucopolysaccharidosis and mucolipidosis are the same. The differentiation is possible only by urine studies and enzyme studies. The bone changes in this category includes osteoporosis with coarse laced trabeculations, thick calveria, J shaped sella, wide clavicle, ‘oar’ shaped ribs, ‘oval and hook’ shaped vertebrae, wide ileum, coxa valga.
irregular diaphysis, metaphyseal widening, epiphyseal dysplasia and proximally tapered bullet nosed 2nd to 5th metacarpals.

**Diagnosis**

SD are a heterogeneous group of genetic conditions that result in abnormal short stature and handicaps. A proper history, thorough clinical examination, anthropometric, biochemical and radiological evaluation are helpful in diagnosis and management. Special disease specific growth curves are now available for evaluation of common conditions like achondroplasia.

Based on the chronologic age (CA), height age (HA) and bone age (BA) by ossification in X-ray, a working classification can be arrived:

- BA=CA - genetic short stature
- BA=HA - but < CA, constitutional maturational delay
- BA<HA - pathologic short stature

Apart from proper history, clinical, anthropometric, radiological and other tests like karyotyping, metabolic screen, etc are important in the diagnosis. Rickets, mucopolysaccharidosis, chromosomal anomalies, sporadic syndromes, etc. come in the differential diagnosis. Many of these disorders may be fresh mutations without any family history. The causes of short stature are given in Table 1. The diagnostic clues from history and physical examination are given in Table 2. The diagnostic approach for skeletal dysplasias and the categorization are given in Tables 3 and 4. Table 5 summarizes the associated medical conditions, that need special attention in the evaluation and management.

**Common skeletal dysplasias**

1. **Achondroplasia**

It is the commonest SD with an autosomal dominant inheritance. It may be a fresh mutation in many cases. The fibroblast growth factor receptor (FGFR3) gene on chromosome 4 p16.3 is defective. It is a spondylo-metaphyseal dysplasia with disproportionate rhizomelic short limbs and characteristic cranio-facial features like large head, prominent forehead, depressed nasal bridge, mid facial hypoplasia and trident like hands, kyphosis and cranio-vertebral anomalies. Intelligence is normal. The radiological features are metaphyseal flare with ball and socket arrangement of metaphysis with epiphysis, cuboid vertebra with L1 and L2 anterior beaking and flat pelvis with rounded tomb stone like ileum (Fig.2). Hydrocephalus may occur due to narrow foramen magnum. The adult height is around 131 cm in male and 124 cm in female. Homozygous achondroplasia is lethal.

2. **Pseudoachondroplasia**

It is spondylo-meta epiphyseal dysplasia with normal cranium and face. Epiphyseal ossification is severely affected and there are abnormally short limbs.

**Table 1. Causes of short stature**

| 1. | Racial or genetic : e.g. Pygmies |
| 2. | Maturational/Constitutional growth delay: e.g. delayed puberty |
| 3. | Low birth weight / intra uterine growth retardation/primordial dwarfining : e.g. Syndromic and non-syndromic malformations, Hypoplastic babies |
| 4. | Chromosomal : e.g. Down, Turner |
| 5. | Metabolic : e.g. Morquio |
| 6. | Skeletal : e.g. Achondroplasia |
| 7. | Nutritional : e.g. Chronic PEM |
| 8. | Emotional deprivation |
| 9. | Endocrine : e.g. Hypopituitarism |
| 10. | Chronic diseases : e.g. Congenital heart disease and Chronic asthma |
Table 2. Clues in history and clinical signs leading to diagnosis

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>DIAGNOSIS</th>
</tr>
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<tbody>
<tr>
<td>Antenatal substance abuse, medications,</td>
<td>Intrauterine growth retardation</td>
</tr>
<tr>
<td>low birth weight, breech delivery,</td>
<td></td>
</tr>
<tr>
<td>neonatal hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia, jaundice, hepatomegaly</td>
<td>Glycogen storage disease</td>
</tr>
<tr>
<td>Micropenis</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Edema hands and feet</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Shortness of breath, cyanosis, cough, fever</td>
<td>Congenital heart disease, asthma, tuberculosis</td>
</tr>
<tr>
<td>Diarrhea, steatorrhea, abdominal pain</td>
<td>Malabsorption</td>
</tr>
<tr>
<td>Constipation, weight gain,</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Inadequate growth</td>
<td>Pituitary-hypothalamic region mass</td>
</tr>
<tr>
<td>Social history</td>
<td>Psychosocial dwarfism</td>
</tr>
<tr>
<td>Inadequate dietary intake, sunlight exposure</td>
<td>Familial short stature and maturational delay of growth and puberty</td>
</tr>
<tr>
<td>Family history for height, timing of puberty</td>
<td></td>
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<tr>
<td>in parents</td>
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<table>
<thead>
<tr>
<th>CLINICAL SIGN</th>
<th>DIAGNOSIS</th>
</tr>
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<tbody>
<tr>
<td>Disproportion</td>
<td>Skeletal dysplasia, rickets, hypothyroidism</td>
</tr>
<tr>
<td>Dysmorphism, midline defect</td>
<td>Chromosomal anomalies, sporadic syndromes, hypopituitarism,</td>
</tr>
<tr>
<td></td>
<td>septo-optic dysplasia</td>
</tr>
<tr>
<td>Pallor</td>
<td>Chronic anemia, chronic renal failure, hypothyroidism</td>
</tr>
<tr>
<td>Vitamin deficiency signs</td>
<td>Undernutrition, malabsorbtion</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Jaundice, clubbing</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Frontal bossing, depressed nasal bridge,</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>crowded teeth, small penis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Goitre, impalpable thyroid, coarse skin,</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>delayed return of tendon jerks</td>
<td>Pseudohypoparathyroidism</td>
</tr>
<tr>
<td>Central obesity, striae, proximal weakness</td>
<td>Pituitary/hypothalamic tumor</td>
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<tr>
<td>Round face, short 4th metacarpal, mental</td>
<td></td>
</tr>
<tr>
<td>retardation</td>
<td></td>
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<tr>
<td>Visual field defect, optic atrophy, optic</td>
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<tr>
<td>nerve hypoplasia, papilledema</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3. Diagnostic approach for skeletal dysplasia

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I</td>
<td>Family history, pedigree, antenatal, natal/ neonatal events</td>
</tr>
<tr>
<td>Step II</td>
<td>Recognition of short stature, type, site, evolution / follow up and course</td>
</tr>
<tr>
<td>Step III</td>
<td>Clinical categorization- proportionate/ disproportionate,</td>
</tr>
<tr>
<td></td>
<td>rhizomelic/mesomelic/acromelic,</td>
</tr>
<tr>
<td>Step IV</td>
<td>Associated anomalies, multiple congenital anomalies/ MR</td>
</tr>
<tr>
<td>Step V</td>
<td>Radiolgical assessment, bone age, Epi/meta/diaphyseal</td>
</tr>
<tr>
<td>Step VI</td>
<td>Diagnosis, course, follow up,</td>
</tr>
<tr>
<td>Step VII</td>
<td>Genetic diagnosis, genetic counseling</td>
</tr>
</tbody>
</table>

3. Hypochondroplasia

It is a milder type compared to achondroplasia with the defect in the same gene, but a different mutation. Bow legs appearing in school age and vertebral involvement suggest the diagnosis. The adult height may be more than 145 cm. There may be mental subnormality, cataract, ptosis, post axial polydactyly in the lower limbs and brachycephaly. It may be mistaken as a case of maturational delay.

4. Spondylo epiphyseal dysplasia (SED)

The features are short neck, short spine, kyphoscoliosis, pectus carinatum, coxa vara and genu valgus. The other features are flat facies, wide set eyes, high myopia, club foot and cleft palate. The acetabular roofs are horizontal. It mimics Morquio disease, but without corneal opacity and keratin sulfaturia. There are 2 types, early onset congenital type and a late onset tarda type.

5. Spondylo metaphyseal dysplasia (SMD) – Koslowski type

The features are short trunk, waddling gait, kypho scoliosis, genu valgum, hyperopia, coxa vara and irregular metaphysis.
Table 4. Categorization of skeletal dysplasias

<table>
<thead>
<tr>
<th>Primary involvement</th>
<th>Category</th>
<th>Other areas involved</th>
<th>Expanded syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiphysis</td>
<td>Multiple epiphyseal dysplasia</td>
<td>Spine</td>
<td>Spondylo-epiphyseal dysplasia (Fairbank/Ribbing Types)</td>
</tr>
<tr>
<td>Metaphysis</td>
<td>Metaphyseal dysplasia</td>
<td>Spine</td>
<td>Spondylo- metaphyseal dysplasia (Achondroplasia,Kozlowski Type)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cranium</td>
<td>Cranio-metaphyseal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Forehead</td>
<td>Fronto- metaphyseal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>Multiple exostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enchondromatosis (Ollier)</td>
</tr>
<tr>
<td>Diaphysis</td>
<td>Diaphyseal dysplasia</td>
<td>Spine</td>
<td>Spondylo-epiphyseal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cranium</td>
<td>Cranio-epiphyseal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>Progressive diaphyseal dysplasia (Englemann)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Polyostotic fibrous dysplasia (McCune Albright)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infantile cortical hyperostosis (Caffey)</td>
</tr>
<tr>
<td>Mixed Types</td>
<td></td>
<td></td>
<td>Spondylo-epi-metaphyseal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spondylo-meta-epiphyseal dysplasia (Pseudo achondroplasia)</td>
</tr>
<tr>
<td>Special Types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td></td>
<td></td>
<td>Acro-facial dysostosis (Gene Wiedmann with postaxial defects and Nager type with preaxial defects)</td>
</tr>
<tr>
<td>Bowed limbs</td>
<td>Camptomelic dysplasia (SD+MCA+MR syndrome)</td>
<td>Diastrophic dysplasia (SD+MCA syndrome)</td>
<td></td>
</tr>
<tr>
<td>Cartilage+bone</td>
<td>Metaphyseal-chondro dysplasia/ chondro dystrophy (Schimid, Jansen Types)</td>
<td>Chondro-ectodermal dysplasia (Ellis van Creveld)</td>
<td></td>
</tr>
<tr>
<td>Ectoderm</td>
<td>Cartilage hair hypoplasia (metaphyseal+ectodermal)</td>
<td></td>
<td></td>
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<tr>
<td>Bone density disorders</td>
<td></td>
<td>Osteopenia</td>
<td>Osteogenesis Imperfecta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteosclerosis</td>
<td>Osteopetrosis, Pyknodysostosis</td>
</tr>
</tbody>
</table>

SD- Skeletal dysplasia,
MCA- Multiple congenital anomalies
MR- Mental retardation
6. Metaphyseal chondrodysplasia- Schmid type

Short limbs, bow legs, waddling gait, coxa vara and genu varus become evident by 2 years of age. It is an autosomal dominant condition that mimic rickets, but without any biochemical abnormalities. The Jansen type is associated with hypercalcemia.

7. Diastrophic dysplasia

The word, diastrophic means ‘twisted’. It is an autosomal recessive condition with meta epiphyseal dysplasia, platyspondyly, scoliosis, etc. The features are short bow legs, club foot, knee contractures, clino camptodactyly and low set hitchhiker thumb (Fig.3). They have ear cysts that become inflamed leading to ‘cauliflower ear’, that later become calcified and ossified. There may be cleft palate or high arched palate.

8. Camptomelic dysplasia

It is associated with camptomelic or bowed limbs. The inheritance may be dominant or recessive. Micrognathia and cleft palate are the other anomalies. Aspirations are common in this condition.

9. Asphyxiating thoracic dystrophy (Jeune syndrome)

It is associated with severe respiratory distress and early death.

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Table 5. Medical complications of skeletal dysplasias

<table>
<thead>
<tr>
<th>Category</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>dyspnea, hypoxia, pneumonia</td>
</tr>
<tr>
<td>CNS</td>
<td>hydrocephalus, cord compression, Cranio vertebral junction anomalies</td>
</tr>
<tr>
<td>Muscular</td>
<td>hypotonia, contractures</td>
</tr>
<tr>
<td>Dental</td>
<td>malocclusion, dentigenesis imperfecta</td>
</tr>
<tr>
<td>Eye</td>
<td>myopia, cataract, retinal detachment</td>
</tr>
<tr>
<td>Nutrition</td>
<td>obesity, short stature</td>
</tr>
<tr>
<td>Joint</td>
<td>arthropathy, deformity</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>difficult delivery and cesarian, cephalo pelvic disproportion</td>
</tr>
<tr>
<td>Psychological</td>
<td>emotional problems, lack of confidence</td>
</tr>
<tr>
<td>Others</td>
<td>various handicaps</td>
</tr>
</tbody>
</table>

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**Fig.3. Low set hitchhiker thumb in diastrophic dysplasia**
10. **Osteogenesis Imperfecta (OI)**

It is a heterogeneous group of conditions with inherited osteopenia and pathological fractures due to defective Type I collagen (Fig.4). Types I and IV of Sillence are milder types with autosomal dominant inheritance. Variable types of inheritance have been described in other types. Type I has persistent blue sclera and type IV has white sclera. Types II and III are severe types, type II has intrauterine presentation and early death and type III survive with severe deformities.

11. **Osteopetrosis**

It is a recessively inherited condition with osteosclerosis. The infantile variety presents early and is lethal in the first decade and the tarda type may survive longer. There is large head, blindness, deafness, hepatosplenomegaly and pancytopenia or leukoerythroblastic blood picture. Due to defective bone resorption and secondary hyperparathyroidism, there may be hypocalcemia and hypophosphatemia resulting in rickets and this condition is called ‘osteopetrorickets’ (Fig.5).

**Management**

A multidisciplinary team approach is warranted in the management. The team should consist of pediatrician, orthopedician, pediatric surgeon, neurosurgeon, geneticist, psychologist, special teachers and counselors. Evaluation for other medical conditions, cranio vertebral anomalies, multiple other anomalies and mental and learning disabilities should be undertaken.

Bone lengthening operations are expensive and very time consuming requiring dedication, commitment and multiple procedures. External fixator technique of Ilizarov is tried in achondroplasia. Growth hormone therapy is tried in hypochondroplasia⁶. Bone marrow stem cell transplant may be helpful in osteopetrosis and
certain metabolic bone disorders like mucopolysaccharidosis. Genetic counseling is the mainstay in the approach to most of these conditions.

**Points to Remember**

- **Skeletal dysplasia is an important cause of pathological short stature.**
- **It is a heterogeneous group of genetic conditions with variable severity.**
- **A systematic approach is needed for the diagnosis of short stature.**
- **Radiological findings are characteristic for most of the skeletal dysplasias.**
- **Multidisciplinary team work and genetic counseling are recommended for the management.**

**Acknowledgement**

We acknowledge the consent given by the individuals to publish their photos and X-rays.

**References**


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**NEWS AND NOTES**

**PALS Course, Andhra Pradesh**

**June 28-29, 2008**

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URTICARIA IN CHILDREN AND THE ROLE OF ANTIHISTAMINES IN PRURITUS

*Jayakar Thomas

Abstract: About 20% of the pediatric population experience episodes of urticaria at least once in their lifetime. Type I hypersensitivity reactions may be involved in acute conventional and contact urticaria, but uncommonly in chronic urticaria. The diagnosis of urticaria can often be made only from the history. Patients may not present with skin lesions. Drug intake and presence of an infective focus have to be assessed. Nearly 50% of chronic idiopathic urticaria is associated with histamine-releasing autoantibodies. Episodes of urticaria lasting for more than 24 hours need to be evaluated for vasculitis and systemic disease. Antihistamines are the mainstay of treatment. Caution is to be taken while combining antihistamines with drugs like erythromycin and ketoconazole, for risk of cardiac arrhythmia (torsade de pointes).

Key words: Urticaria, Children, Antihistamines, Pruritus.

The coining of the term urticaria is attributed to Johann Peter Frank of Vienna, and in the English literature, to William Cullen of Scotland. Angio-oedema was recognized by Donato in the sixteenth century but named so by Strubing only in the 1880s. Robert Willan first described the association of urticaria with factors such as certain foods. Urticaria, commonly known as ‘nettle rash’ or ‘hives’, presents with short-lived, itchy weals that may be pale or pink in the centre, surrounded by a red flare. Deeper swellings of the skin or submucosa are termed ‘angio-oedema’. They are usually seen in the mouth, over the eyelids or genitalia, but may occur anywhere on the skin.

Etiopathogenesis

Urticaria is caused by transient leakage of plasma through small blood vessels, usually as a result of release of histamine from skin mast cells. Histamine also causes itching by stimulating nerve receptors, and contributes to the axon reflex flare. Other mediators causing vasopermeability include kinins in hereditary angio-oedema, and leukotrienes in pseudoallergic reactions caused by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).

Immunologic and non-immunologic causes are recognized, but some cases remain idiopathic even after full evaluation.

Allergic urticaria is caused by type I hypersensitivity reactions. Mast cell degranulation is triggered by the binding of multivalent allergen to specific IgE on high-affinity IgE (FceRI) membrane receptors. Localized reactions at the site of contact with the allergen cause contact urticaria. Generalized urticarial reaction can also occur. Anaphylaxis is a severe systemic reaction caused by type I hypersensitivity reaction. It involves bronchospasm, a fall in blood pressure or both and is usually associated with widespread urticaria and itching.
Idiopathic urticaria comprises up to 70% of cases with chronic duration. Histamine-releasing autoantibodies are present in the blood during disease activity. IgG antibodies are directed against FceRI on mast cells or IgE bound to it. There is increasing evidence that a good number of this subgroup of idiopathic urticaria patients have an autoimmune disease.

Non-immunological urticaria can be as severe as immunologic disease. Anaphylactoid reactions to radiocontrast may be caused by direct release of mast cell contents without involvement of IgE. Pseudoallergic reactions to aspirin and NSAIDs may occur up to 20 hours after taking the drug, and are thought to involve the release of newly synthesized sulphonidopeptide leukotrienes in addition to histamine. Inhibition of kinin breakdown by angiotensin-converting enzyme inhibitors probably explains the rare occurrence of angio-oedema with this class of drugs.

**Types of urticaria**

Urticaria can be classified into five main groups on the basis of the history, appropriate challenge tests and simple laboratory investigations. However, it must be remembered that these groups are not mutually exclusive and fair amount of overlap exists. The duration of individual weals can be helpful in the history. Weals lasting less than 1 hour usually have a physical cause (the exception is delayed pressure urticaria, which characteristically develops several hours after exposure and lasts up to 24 hours). Contact urticaria usually resolves within 2 hours, conventional urticaria within 24 hours and urticarial vasculitis within 3 days. Angio-oedema may be present for days, but severe contact dermatitis should be suspected if the swelling lasts for several days and resolves with scaling.

**Conventional urticaria**

Recurrent urticaria is termed ‘conventional’ or ‘ordinary’ if there is no predominantly physical cause or underlying small vessel vasculitis. It is the most common pattern. Attacks may occur daily or less frequently. It is considered acute if symptoms last for less than 6 weeks and chronic if for a longer period. Attacks of shorter duration may go on for long periods of time, the so-called ‘acute on chronic urticaria’ (personal observation). Weals are often numerous, and may occur on any part of the skin, including the scalp, palms and soles, where they may be painful rather than itchy. They generally last 2 to 24 hours, vary in size from less than 1 cm to many centimetres across, and may coalesce. Nonspecific symptoms (e.g. lassitude, indigestion) may accompany severe attacks, but wheezing is not a feature. Onset is often abrupt and unexpected, but occasionally there is a history of streptococcal infection, immunization, consuming an unusual food (e.g. fish, eggs, and nuts) or drug therapy (e.g. aspirin, penicillin). Acute conventional urticaria caused by food or drug is often apparent from the history because it occurs within 2 hours of ingestion, but most cases remain unexplained (idiopathic).

Blood tests are almost always normal. Tests for specific IgE (fluoroimmunoassay, often misnamed ‘RAST’ because radioallergosorbent tests were used in the past) may be useful for confirming the cause of allergy. In specialist centres, skin testing with autologous serum is a useful *in vivo* test for histamine-releasing autoantibodies, for which there is no commercially available test. Intradermal skin testing with different antigens proves to be a futile exercise in most cases.

**Physical urticaria**

Physical urticarias are defined by the triggering stimulus. Immediate dermographism can be elicited by stroking the skin firmly with a blunt instrument, cholinergic urticaria by physical exercise to the point of sweating (sweat glands...
have cholinergic sympathetic innervations), and cold urticaria by contact with ice or generalized chilling. Cutaneous mast cells degranulate in response to these stimuli; the mechanism is not clear. More than one stimulus may be necessary to elicit urticaria (e.g. cholinergic dermographism). Simple physical challenge tests are useful to confirm the diagnosis.

**Contact urticaria**

Contact urticaria is not uncommon, but is seldom a reason for referral to the specialist. Immunologic contact urticaria involves binding of percutaneous allergen to specific IgE in previously sensitized individuals. Localized wealing occurs within 10 minutes. Atopic patients are particularly susceptible. Nonimmunologic contact urticaria from direct mast cell degranulation or eicasanoid release is probably more common; the mechanism is unclear and difficult to define. Preservatives and fragrances in cosmetics may cause stinging, itching and burning. Food preservatives (e.g. benzoic acid, sorbic acid) and flavourings (e.g. cinnamic aldehyde) may cause contact urticaria around the mouth.

**Urticarial vasculitis**

Urticarial vasculitis is an uncommon systemic disorder occurring in patients with underlying small-vessel vasculitis caused by immune complex deposition. The skin lesions may be indistinguishable from other forms of urticaria, or may resemble erythema multiforme. They last 2 to 3 days and resolve with a typical violaceous hue. They may burn rather than itch. Patients feel unwell with fever and joint pains, and associated renal, pulmonary or neurological disease must be excluded. The defining feature is venulitis as seen in skin biopsy; erythrocyte sedimentation rate is raised, and some individuals show hypocomplementaemia; this could be a sign of poor prognosis and is associated with renal disease.

**Angio-oedema**

Angio-oedema can occur in conventional, physical and vasculitic urticaria, but may also occur without weals. These cases need to be specially considered to rule out hereditary and acquired $C_1$ esterase inhibitor deficiency. Measurement of $C_4$ is a useful screening test. It is reduced in both type I hereditary disease (reduced absolute levels of $C_1$ inhibitor) and the less common type II hereditary disease (normal quantitative $C_1$ inhibitor on immunochemical assay but reduced function).

**Management**

The first step in the management involves the identification and removal of any specific causative factor. The next step is use of antihistamines. Over-the-counter products such as chlorpheniramine and diphenhydramine are usually adequate. Prescription products such as hydroxyzine and loratadine may be considered when over-the-counter drugs fail. One should initiate therapy with a dose that is within the upper recommended level. This dose can be gradually increased until either improvement occurs or side effects become troublesome. An amount twice the recommended dose should never be exceeded.

**General measures**

Detailed history-taking, careful explanation, written information and cooling lotions (e.g. Calamine lotion) can help patients cope with their disease, particularly when drug treatment is disappointing. Identifying the causes of physical or contact urticarias may help patients avoid them. Drugs that may aggravate the urticaria nonspecifically (e.g. aspirin) should be avoided. Stress, alcohol and overheating should be minimized. Exclusion diets (e.g. food colourings, preservatives, natural salicylates)
may be useful when indicated by the history, but are difficult to follow and are usually reserved until after first-line drug therapies have been tried.

First-line treatment

Antihistamines are the treatment of choice in all urticarias except C1 esterase inhibitor deficiency. Most patients prefer a low dose and non-sedating antihistamine by day (e.g. levocetirizine, 5 mg/day). Addition of a sedating antihistamine (e.g. hydroxyzine, 10 mg/day) in the night can help the patient sleep and relieve the pruritus. Caution is required while combining certain antihistamines with drugs like erythromycin and ketoconazole, for risk of cardiac arrhythmias (torsade de pointes). The tricyclic antidepressant doxepin, 10 mg thrice daily or as a single dose of 30 mg at night, has potent H1 and H2 antagonistic properties and is preferred for some patients. Alternatively, an H2 antagonist (e.g. ranitidine, 150 mg twice daily) or a mast cell stabilizer (e.g. nifedipine, 5 mg) can be added, but the results may be disappointing. H2 antagonists should never be used alone in urticaria, as there may be overreaction of H1 receptors resulting in worsening of lesions.

Second-line treatment

Prednisolone, usually 0.5 mg/Kg body weight initially followed by a tapering dosage schedule over a period of 1 to 2 weeks may be necessary in severe acute urticaria or angio-oedema. Prolonged treatment of chronic urticaria with oral corticosteroids should be avoided except in disabling delayed-pressure urticaria and urticarial vasculitis, which are usually unresponsive to antihistamines. Subcutaneous administration of 0.5 to 1.0 ml of 1:1000 adrenaline is useful in severe angio-oedema of the mouth, and can be life-saving in anaphylaxis.

Third-line treatment

Studies on immunosuppressive therapies in disabling chronic autoimmune urticaria, using plasmapheresis or intravenous immunoglobulins, have been encouraging. The efficacy of cyclosporin A in such cases has recently been confirmed.

Hereditary angio-oedema

Hereditary angio-oedema can often be prevented by low-dose anabolic steroids (e.g. stanozolol, 2.5 to 5 mg/day), which increase functional inhibitor levels. Virilizing effects are a disadvantage in women. Tranexamic acid, an antifibrinolytic agent is used for acute episodes, but is contraindicated in thromboembolic disease. Antihistamines are of no use.

Antihistamines and pruritus

No aspect of pruritus has evoked more debate than the use of antihistamines to relieve itching. To many non-dermatologists the presence of a patient with a dermatological disorder evokes a reflex desire to prescribe antihistamines.

The anaesthetic effect of topical antihistamines may be used to benefit the patient with pruritus. Topical antihistamines carry a significant risk of sensitization and hence must be used with caution. For the short term (up to 7 days) management of pruritus, 5% doxepine hydrochloride cream is effective. However, its systemic absorption causes sedation. Visible discontinuity on the skin is a definite contraindication.

Systemic therapy with antihistamines is used as a panacea for all itchy dermatoses. Where histamine plays the major role in causing itching, as in urticaria, antihistamines are absolutely indicated. But in the vast majority of itchy disorders where histamine is not the mediator,
antihistamines at best work by virtue of their sedative action. In such cases, the newer nonsedating antihistamines are never effective.

**Points to Remember**

- **About 20% of the pediatric population experience episodes of urticaria at least once in their lifetime.**
- **The diagnosis of urticaria can often be made only from the history. Patients may not present with skin lesions.**
- **Drug intake or an infective focus may be associated.**
- **Episodes of urticaria lasting for more than 24 hours need to be evaluated for vasculitis and systemic disease.**
- **Antihistamines are the mainstay of treatment in urticaria.**

**Bibliography**


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BOOK REVIEW

Title : Essentials of Pediatric Pulmonology (3rd edition)

Authors : Dr. L.Subramanyam, Dr. So. Shivbalan, Dr. N.C.Gowrishankar, Dr. D.Vijayasekaran, Dr. A.Balachandran

Foreword : Dr. (Capt) N. Somu

Publisher : Pediatric Pulmonology Foundation of India (PPFI), Chennai - 600 031.

Review : The third edition of this book “Essentials of Pediatric Pulmonology” which has come after a span of twelve long years after the second edition is worth the wait. All the sections in this book have been rewritten. New sections have been added in tune with the emerging fields in pediatrics like intensive care. The book covers almost the entire aspects in the field of pediatric pulmonology starting from the basics, applied anatomy and physiology to the most advanced ventilator therapy including loops and curves. The flow of language is simple and easy to understand. One interesting aspect is the addition of lot of figures for easy understanding. Another salient aspect is the separate chapters on newborn respiratory problems, radiology in newborn and sleep disorders. The radiology and bronchoscopy pictures have been printed clearly. After going through the book, it promises to provide complete satisfaction for not only those pediatricians in medical colleges and in practice, but also for all the pediatric postgraduates.

Price : Rs. 500/-
The use of radiological investigations for the evaluation of seizures continues to be controversial. No decision based on studies can replace clinical judgement that depends on each patient and each clinical setting. No algorithm can be total and exclusive. However it is useful to remember that radiation due to a CT scan of the head is equivalent to 200 chest x-rays and children are more sensitive to the harmful effects of radiation. The estimated lifetime risk of death from radiation – induced malignancy caused by a single CT scan of the head at one year of age is 0.07 percent.\(^1\) Caution is therefore necessary when you request for a CT scan. In view of this, CT with low dose radiation can be asked for and done. One point that everyone agrees on is that CT or MRI is not essential for the simple febrile seizure or even complex febrile seizures. Neuroimaging should however be considered when there is a postictal focal neurological defect or in children who take long time to return to normal neurological function. The CT brain (Fig.1) of a child who presented with seizures followed by hemiplegia, showed hypodensity in the right basal ganglia with white spots of hemorrhage. This is a hemorrhagic infarct.

Adults with an unprovoked seizure definitely need neuroimaging, but in children uncomplicated seizures and epilepsy are common where neuroimaging will be normal. Certain specific childhood epilepsy syndromes like benign rolandic epilepsy, absence seizures and juvenile myoclonic epilepsy do not require CT or MRI but have specific diagnostic EEG patterns.

In a study conducted in Institute of Child Health and Hospital for Childrne, Chennai, of 111 children with all types of seizures 53 (ie. 47% ) had an abnormality on CT. These 111 children (70 children had simple partial seizures) were not randomly chosen but referred by pediatricians on a suspicion of underlying abnormality. 37% had ring enhancing lesions, 13% had a chronic infarct and 11% had cerebral atrophy. Another 11% had hydrocephalus. Other conditions found were phakomatosis, neoplasm and intrauterine infection.

Mesial temporal sclerosis (MTS) or hippocampal sclerosis is a rare condition which manifests in late childhood or adolescence. It is interesting because it is a cause of temporal lobe epilepsy for which surgery offers a cure in almost ninety percent of patients. It is imperative to identify MTS as surgery has a high rate of eliminating seizures and is associated with a low incidence of new neurological impairments. Imaging techniques for diagnosing MTS include...
Fig. 1. Right basal ganglia infarct

Fig. 2. Mesial temporal sclerosis. Note the hyperintensity in left medial temporal area.

Fig. 3. Focal atrophy - right parietal area as evidenced by the adjacent wider subdural space. This patient had a history of head injury.

Fig. 4. Chronic infarct in left MCA territory in a 1 year old. The infarct area has liquefied and is of same density as CSF in the passively dilated left lateral ventricle.
MRI, ictal and interictal SPECT (single photon emission computerized tomography) and PET (Positron emission tomography). MRI is widely used and is more easily available.

The MRI features of hippocampal sclerosis include hippocampal atrophy, increased signal on T2-weighted images or fluid-attenuated inversion recovery (FLAIR) sequences, and decreased signal on inversion recovery sequences. The detection of these abnormalities should be carried out with optimized imaging techniques. Technique is important to make out subtle changes. If these primary features are not present the patient has a less than 50% likelihood of becoming seizure – free after surgery. Other secondary features are temporal lobe volume loss, temporal horn dilatation, narrow collateral white matter, smaller fornix and an atrophic mamillary body. These are considered secondary as mild asymmetries occur in normal people and also because volume loss alone might reveal only hippocampal gliosis on surgery. This group of patients have poor postoperative seizure control.

PET also shows hypometabolism in the temporal lobe in MTS. Another growing use of PET is in the identification of dysfunctional cortical regions of hypometabolism that correspond to epileptic foci. Children with intractable infantile spasms classified as cryptogenic can show hypometabolic foci of cortical dysplasia in PET. If the area is single, surgical removal of the epileptic focus can offer good seizure control. PET as an imaging modality is limited due to its use of tracers with a very short half-life that requires a cyclotron in close proximity. PET and SPECT are indicated when surgery is contemplated.

Seizures can also be due to developmental abnormalities like schizencephaly and hemihypertrophy. Hemorrhage should be considered when there is a history of trauma, increased blood pressure or bleeding disorders. CT is a useful modality to rule out neoplasms. In children with seizures CT is the primary modality while in young infants ultrasound is a good screening investigation. MRI is for intractable seizures with normal CT examination.

Reference

McCUNE ALBRIGHT SYNDROME

* Chitra Ayyappan
** Arun Prasath TS
* Meikandan D
*** Vasanthakumari ML

Abstract: Precocious puberty, presenting as premature thelarche or menarche in girls, as early as 2-3 years in association with polyostotic fibrous dysplasia, cafe-au-lait spots and other endocrinopathies should suggest the possibility of McCune Albright Syndrome (MAS). The precocious puberty associated with MAS typically is gonadotrophin independent. Fractures, malignancies and endocrine disorders are the modalities associated with this syndrome.

Key words: Precocious puberty, Polyostotic fibrous dysplasia, McCune Albright syndrome, Endocrinopathies.

Donavan McCune first described the classic triad and hyperthyroidism. MAS has been shown to be due to post zygotic mutation of the GS alpha gene in the affected tissues. Females have a greater risk of breast cancer probably due to their prolonged exposure to elevated estrogen levels.

Case Report

A 5 year old girl presented with bleeding per vaginum since six months of age, breast enlargement and facial asymmetry since 1 year (Fig.1). On examination, she was tall for her age. Height 125cms (> 97th percentile) and she weighed 23kg. Intelligence and dental age were normal for chronological age. She had facial asymmetry with right pseudo proptosis, multiple (7) cafe-au-lait spots over chest and abdomen. She had an SMR of 4 on Tanner staging. She also had a small goiter.

GnRH stimulation test showed low FSH of 2.09 mIU/ml (normal 11.8-18.6mIU/ml) and LH was 0.291 mIU/ml (normal 10.7-15.6mIU/ml). Estradiol 16.09 mIU/ml (normal 11.8-18.6mIU/ml) corresponding to Tanner staging II. Serum cortisol level 18µg/dL (7-24µg/dL) and TSH 5.6mlU/ml (0.7-6.4mlU/ml) were within normal limits. Serum and urinary phosphorus were normal. Imaging studies revealed

CASE STUDY

**Fig.1. Premature thelarche**
polyostotic fibrous dysplasia of skull, involving right orbital plate and lesser wing of sphenoid (Fig.2). Bone age was between 11 and 14 years of age. Ultrasound abdomen showed endometrial thickness and a cyst in ovary. Ultra sound thyroid showed cysts in the left lobe of thyroid.

A provisional diagnosis of McCune Albright Syndrome with GnRH independent precocious puberty was made. Child was started on Tamoxifen (40mg/1.73sq.m²). At the time of this report she had completed 8 weeks of tamoxifen and had no further episodes of vaginal bleeding.

**Discussion**

MAS is a very rare disorder, having no ethnic predisposition. The disease has been reported more frequently in girls than in boys, presumably due to the dramatic presentation characterized by the early onset of puberty, menarche and thelarche. In cases where polyostotic fibrous dysplasia is marked, multiple fractures are prominent early in the history. Symptoms begin in childhood. In some, the phenotypic features are mild and the onset of symptoms is considerably delayed, subtle findings such as mild asymmetry, dysmorphism and mild unequal limb length. Existing bone lesions may slowly worsen, remain stable or new lesions may develop. Spontaneous improvement or resolution of the bony lesions does not occur.

The worsening of the bone lesions is due to the trophic effect of estrogen on the fibrous dysplastic bone, which contain estrogen sensitive receptors.

Goiters with hyperthyroidism, diabetes mellitus, acromegaly, Cushing syndrome, herprolactinemia, painless myxomas, hypophosphatemic rickets, alopecia have also been found in association with MAS. Cafe-au-lait spots are often ipsilateral and predominant on the side with more bony lesions.

Management is often challenging and requires a multi disciplinary approach. Orthopedic surgical care for multiple bony fractures and deformities can be particularly frustrating. Endocrinopathies need to be identified and treated. Therapy for precocious puberty is available and should be tried, it is still largely experimental.

Because precocious puberty in patients with MAS is gonadotrophin-independent, continuous GnRH therapy has little utility. For female patients, the central theme is to block estrogen effects. Testolactone, a competitive aromatase inhibitor, is used for this purpose. Preliminary data from the testolactone therapeutic trials suggest that this medication causes reduction in estradiol and estrone levels, with reduced frequency of menses and reduction in growth and bone maturation. Other preliminary trials of other aromatase inhibitors, such as fadrozole and anastrazole, are underway with the goal of achieving better management of precocious puberty. Estrogen receptor antagonists, such as tamoxifen, have a therapeutic role. GnRH analogues may be added to testolactone as an adjunct for treatment of precocious puberty to suppress pituitary gonadotrophin production. Depot leuprolide acetate at a dose of 7.5mg (300-500mcg/kg) every 28 days is a typical regimen, the dose of which can be adjusted upwards or downwards based on clinical and laboratory

![Fig.2. CT skull showing thickening of orbital plate and lessor wing of sphenoid.](image)
findings. Other alternative treatment options include medroxyprogesterone acetate, which is particularly useful for controlling menstrual bleeding. The preferred agent is Depo-Provera in intramuscular doses of 4-15mg/kg monthly. Adequate medical therapy for precocious puberty in males consists of both antiandrogen and antiestrogen preparations. This typically consists of a combination of spironolactone and testolactone. Alternative antiandrogens, such as ketoconazole, also may be used in.

Some preliminary data suggest that bisphosphonates, pamidronate and alendronate may have beneficial effects on the bone disease.

Other identified co morbidities require to be treated. Oral phosphorus, Vit D, calcium replacement for hypophosphotemic rickets, bilateral adrenalectomy for Cushing, thyroidectomy (partial/total) for thyrotoxicosis are indicated. Ovariotomy or ovarian cystectomy may be used as the last resort for control of precocious puberty when medicl therapy fails.

Bibliography