



INDIAN JOURNAL OF PRACTICAL PEDIATRICS



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Dr. A. Balachandran
Editor-in-Chief

Dr. D.Vijayasekaran
Executive Editor

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E.mail : ijpp_iap@rediffmail.com

Address for registered/insured/speed post/courier letters/parcels and communication by various authors: Dr. A. Balachandran, Editor-in-chief, Indian Journal of Practical Pediatrics, "F" Block, No. 177, Plot No. 235, 4th Street, Anna Nagar East, Chennai - 600 102. Tamil Nadu, INDIA.

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- Editorial Board

FROM THE EDITOR'S DESK

I am very pleased to state that, Indian Journal of Practical Pediatrics has successfully completed 10 years from its inception, thanks to the excellent patronage by all the contributors, reviewers and our readers. We are now entering into 11th year of publication. We have grown from infancy to preadolescent age during this decade. This journal has been under the editorship of three eminent persons consecutively since 1993 viz., Dr. A. Parthasarathy (1993-1995), Dr. B.R. Nammalwar (1996-1998) and Dr. M. Vijayakumar (1999-2001). To recall, IAP Journal of Practical Pediatrics was launched in 1993 at the National Conference of IAP at Kolkatta. Since then the journal has been progressing each year with many newer topics and innovative ideas.

In 1999, with the concurrence of IAP Executive Committee, Dr. M. Vijayakumar, the immediate Past Editor-in-Chief, the journal's name was changed from IAP Journal of Practical Pediatrics to Indian Journal of Practical Pediatrics, for registering the journal with "Registrar of Newspapers in India".

The journal has become very popular among the practicing pediatricians and post graduates. Infact it has become a desktop reference for practitioners.

The editorial board is thankful to all the past and present IAP office bearers, executive committee and advisory board for their support and encouragement to the journal. We place on record with gratitude the yeoman service rendered by the previous editors-in-chief of IJPP, to popularise the journal.

The topic of interest for this issue is Hemato-oncology. We are thankful to Dr. Janani Shankar, consultant, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, who has helped us to formulate this issue. She has carefully chosen the topics which are more relevant to the clinical practice as well as to the post graduates. The authors with their vast experience and knowledge has contributed articles in this issue. The readers will definitely be benefitted by these articles.

The editorial board is planning to bring out practical guidelines in the management of common pediatric problems which will be of immense use to all the practising pediatricians of our country.

The recent hike in the postal tariff and escalation in the cost of printing and stationary has increased our overall expenditure. The steep fall in the interest rates of our fixed deposits has been causing huge deficit in our budget. In order to boost the revenue from the fixed deposits as interest, we are constrained to increase our corpus fund. So we sincerely request all our earlier subscribers who have enrolled with Rs. 500 to contribute Rs 1000/- and those who have initially paid Rs 1000 to pay Rs 500/- as an additional sum to increase our corpus fund. This will help to augment the drop in the bank interest from fixed deposits to meet our expenses. We also thank all our readers who have responded to our earlier appeal for thier generous contribution to our corpus fund, which we have already acknowledged in our journal.

Wishing all our readers a happy and prosperous New Year, 2003.

CHECK LIST

CHECKLIST FOR INDIAN JOURNAL OF PRACTICAL PEDIATRICS

The checklist must accompany the manuscript.

General

- Original articles which have not been published elsewhere are invited and should be sent to the Editor. They are considered for publication on the understanding that they are contributed to this journal solely.
- Four complete sets of the manuscript are submitted.
- Manuscript is typed double-space throughout with wide margin on one side of paper only including the list of references and tables.
- Manuscript is arranged as follows: Title page, text, acknowledgements, references, tables, figure legends, figures.
- All pages are numbered at the top of the right corner, beginning with the title page.
- The letter of submission has been signed by all authors.

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- Measurements must be in metric units with System international (SI) Equivalents given in parentheses.

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EDITORIAL

PEDIATRIC HEMATOLOGY AND ONCOLOGY: WHERE DO WE STAND?

Rapid strides in the diagnosis and management of childhood cancers and blood diseases have been made worldwide in the past two to three decades. Recently cure rates in some of the pediatric malignancies like childhood acute lymphoblastic leukemia, lymphomas and others have improved from almost negligible to more than seventy five percent. The same is true for a number of blood diseases in children like thalassemia, hemophilia and platelet disorders: through some are incurable, many can be well controlled and prevented. It is very heartening that some of this international success has definitely percolated to our country. This has benefitted a large number of children from both the public and the private hospitals for the diagnosis and management of these very specialized diseases.

Pediatric hematology-oncology does not as yet claim a separate existence in many medical colleges or private hospitals. Consequently most children with blood diseases and cancer are still being diagnosed and treated by adult hematologists and oncologists!

Recent advances

Like many other pediatric subspecialties the clinical practice in pediatric hematology oncology is being transformed by the application of genetic discovery to old and new problems alike¹. Modern pediatric oncology believes that "*Cure is not enough*". Hence pediatric oncologists are not satisfied with possibility of

cure but aim to apply the genetics of risk-based therapy to reduce therapy-related complications while retaining the potential for cure. Similarly, elucidating the genetic basis of many hematological disorders holds the promise of novel targets of pharmacological intervention and reducing the toxicity of treatment. More than ever, the integration of new knowledge in the day-to-day practice of general pediatrics will ensure timely and cost-effective evaluation of common hematological problems and promote the use of supportive care, thereby improving outcomes and, most importantly, ensuring adequate access to care in an universal era of shrinking resources.

Roadblocks in India

Pediatricians are usually very quick to suspect a hematological problem. They are good clinicians! But a reliable specialised advice and a good laboratory backup is essential for a quick hematological diagnosis. The delay and the hurdles start at this point. He thinks: To whom should I refer the child? Where are the tests that I need to do available in the city? How long will the results take? What treatment plan is to be followed? How should I monitor and the followup this child? - umpteen questions from the 'generalis' pediatrician still remain to be answered. This is due to several reasons, we have limited specialists in the country who are well-trained, the laboratory support is often not available or easily accessible or if available at a very high cost, facilities and services usually are not available under one roof resulting in patients running from pillar to post, lack of 'Day Care' centres leads to unacceptable and prolonged hospitalisations, treatment options are often so expensive that patients opt out; blood components

which are an essential constituent of the therapeutic armamentarium are perennially under short supply. These deficiencies lead to suboptimal management of these children. But I must add that despite these lacunae, we have continued to make significant progress.

The future: What should be done?

The demand for better care is increasing with regard to diagnosis, management and prevention of these specialized diseases. To meet this challenge, medical colleges and private hospitals in the country need to establish more specialized pediatric hematology and oncology units for catering to the increasing number of children with these problems. A number of hematological and oncological disorders are chronic in nature and require a long term treatment plan and follow-up, which can be carried out best by pediatricians with special interest in hematology-oncology. Therefore, there is an urgent need to establish dedicated units for this purpose. Establishment of more facilities would mean requirement of qualified specialists in pediatric hematology-oncology. We cannot shirk the onus of training them in house (in the country) !.

Secondly diagnostic facilities in some areas remain inadequate or sometimes inaccessible to the poor e.g. RBC enzyme studies (pyruvate-kinase etc) for diagnosis of hemolytic anemias, immunophenotyping for characterization of leukemias, pediatric histopathological review facilities, immunohistochemistry, immunodeficiency studies, etc. In the near future we have to take care of these requirements too. I can suggest centralization of resources in the country to efficiently carry out quality controlled laboratory analysis required for hematological diagnosis at nominal costs. Those who can pay should be charged for the tests, while the same service can be provided at a subsidized cost to the poor.

“Comprehensive care” for thalassemia, hemophilia, leukemia, and other diseases is the buzzword in pediatric hematology-oncology management. I can say that we do not yet have an ideal comprehensive care setup for any of these diseases. What would comprehensive care mean? Provision under one roof of services of a pediatric hematologist, pediatric surgeon, pediatric radiologist, pediatric pathologist, pediatric nurse, social worker, psychologist, etc. With regard to pediatric oncology, the participation and co-operation of pediatric surgeons is of utmost importance. I feel the lack of this co-ordination can be rectified right away.

The most relevant but crucial limitation to the progress of pediatric hematology-oncology care is the lack of resources and funds for growth and development. This situation has worsened over the last few years and might worsen further in the years to come due to the increasing costs of health care services. The most promising opportunity to tackle this resources crunch comes from the parents and volunteers and from their co-operation with the health professionals. Encouraging strong and viable parent organizations or support groups are essential from this point of view. Hence we will have to learn to harness the power of parent groups and associations to raise funds for our specialized efforts. We cannot and should not depend on the government alone to initiate and support all endeavours. Active support and involvement from the pediatricians can help in strengthening their activities and efforts for the wellbeing of all our own patients with these illnesses. The least we can contribute is by advising parents of children with these diseases to join hands in these various ‘self-help’ groups to minimize the financial, social and psychological burden of these chronic disorders.

I suppose we can and need to consolidate on the research front as well, considering more

than 1/3rd of country's population is below fifteen years of age i.e. approximately four hundred million children and the incidence of hematological and oncological diseases, like many other diseases, is enormous and there is ample opportunity for clinical and basic research. Cost-effective solutions need to be worked out for a number of our problems, in our own setting, by collaboration and cooperation.

Conclusion

"The truth is rarely pure and never simple"

- Oscar Wilde

We are taking slow, small, but purposeful steps towards expanding in the field of pediatric hematology/oncology. Provision of high standard

of patient care services, programme for training of fellow colleagues and continuing research for optimal low cost solutions should be our goals and the basis of our efforts for the future. Fulfillment of these ideas would be a dream come true.

Bharat R. Agarwal

Head of Department,

Pediatric Hematology Oncology Services,

B.J. Wadia Hospital for Children and

Institute of Child Health and Research Centre,

Parel, Mumbai - 400 012.

Reference

1. Vichinsky E, Walters MC, Feusner J. Pediatric Hematology Oncology. *Pediatr Clin N Am* 2002; 49(5): xiii-xvi

NEWS AND NOTES

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HEMATO-ONCOLOGY

ROLE OF PERIPHERAL SMEAR IN DIAGNOSING DIFFICULT CLINICAL SITUATIONS IN PEDIATRICS

* **Sarala Rajajee**

Examination of the peripheral smear and estimation of the full blood counts are the most basic and yet the most informative investigations performed in hematology.

The blood film

Morphology is best examined in the part of the peripheral blood film where red cells are closer to each other but not overlapping. Red cells are examined for abnormality of size (macrocytosis, microcytosis) by comparing them to small lymphocytes which are of similar size, abnormal shape (poikilocytosis eg, schistocytes, bite cells, burr cells) and staining characteristics (hypochromia, polychromasia). The morphology of the white cells and platelets are also examined. In a finger prick smear platelets are seen mainly in the tail end as aggregates.

Knowledge of normal variation is essential in the interpretation of blood films. Thus in the newborn, the presence of nucleated red cells (normoblasts) is physiological but they disappear from the peripheral blood by a few days of age.

The red cells

The most common abnormality seen in our

* Senior Consultant,
Kanchi Kamakoti CHILDS Trust Hospital
Chennai - 600 034.

population is hypochromic microcytic red cells (Fig.1) with anisopoikilocytosis due to iron deficiency. There is also associated thrombocytosis. This may be due hypoxic stimulus to the bone marrow or if iron deficiency is due to chronic blood loss.

Case I: A two year old girl presented with severe anemia. The blood smear was suggestive of iron deficiency. This was confirmed by low transferrin saturation. Her motion was however positive for occult blood and endoscopy revealed grade 3 oesophageal varices.

Key Point : In any case of iron deficiency anemia apart from diet history, examination for occult blood loss is essential.

The other often seen causes of hypochromic microcytic anemia is hereditary hemolytic anemia eg; β Thalassemia. The differentiating factors in the blood film is the presence of polychromasia and normoblasts (Note - This may be seen in iron deficiency due to blood loss and within 3-4 days after iron therapy due to reticulocyte response). Platelets are normal or low in thalassemia unlike the thrombocytosis seen in iron deficiency.

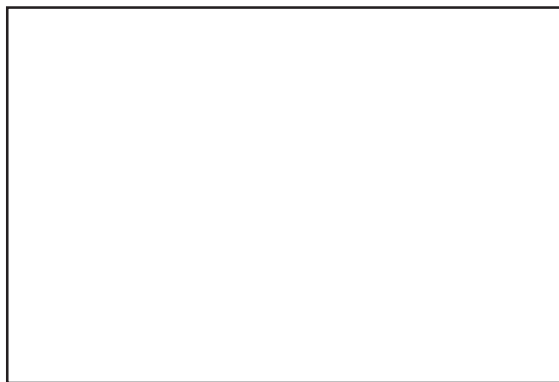


Fig. 1 Hypochromic microcytic anemia.

Congenital red cell disorders responsible for anemia may be spherocytosis or elliptocytosis.

Case 2: A twelve year old child presented with severe anemia, mild jaundice and splenomegaly following a febrile illness. She had been investigated for anemia earlier and was on hematinics. Her peripheral smear revealed more than 40% spherocytes with polychromasia. Her father's smear was positive for spherocytes.

Note: Malaria can cause acute hemolysis with micro spherocytes. Auto immune hemolytic anemia due to SLE may be associated with spherocytes. Examination of parents will give a clue to the hereditary nature of the problem.

Congenital hemoglobinopathy eg: sickle cell anemia and hemoglobin C can be picked up on the peripheral smear.

Case 3: A two year old girl presented with painful swelling of hands and feet. Her peripheral smear showed sickle cells. X-ray of hands revealed hypodense areas in the phalanges. This is veno occlusive problem in sickle cell disease presenting as Hand Foot disease. Peripheral smear in hemoglobin C shows many target cells.

Note: Target cells may be seen in other situations, eg; Thalassemia, iron deficiency, liver disorders etc.

G6PD deficiency though rare is seen particularly in some communities.

Case 4: A three year old boy was brought to emergency room with severe anemia and history of febrile illness treated with antimalarials and passage of red coloured urine. Peripheral smear showed red cell fragments (Fig 2), blister cells or ghost cells. In the absence of G6PD the oxygenated hemoglobin in red cell is removed by the spleen and these red cells take the appearance of blister cells. This is characteristic of G6PD deficiency and is an important pointer to avoid drugs which can aggravate the problem.

Malaria is the commonest infection associated with hemolysis. A skilled microscopist can pick up malarial parasite on smear at a parasite load of 10/ul. The other features on smear to suspect malaria are the evidence of hemolysis ie: polychromasia, microspherocytes, normoblasts with associated pigment in neutrophils and thrombocytopenia. A thick smear is warranted to pick up the presence of the parasite.

Presence of Howell-Jolly bodies in the red cells indicates absence of spleen or splenic dysfunction. Howell-Jolly bodies are ribosome remnants in the red cell appearing as a rounded red inclusion in the RBC.

Case 5: A one year old girl was admitted with pyogenic meningitis to the intensive care unit. The bacteria in the CSF was Pneumococcus. Ultrasound abdomen revealed absence of spleen and peripheral smear showed Howell - Jolly bodies. Asplenia in infants makes them susceptible to capsulated organisms like pneumococcus.

Red cell fragmentation syndrome can occur in a child with hemangioma where the peripheral smear shows red cell fragments (schistocytes) and anisopoikilocytosis.



Fig. 2 RBC fragmentation

Case 6: A three month old baby was diagnosed as hemangioma in the neck at birth which gradually increased in size. Prior to admission, there was sudden increase in size with signs of airway obstruction. Peripheral smear showed red cell fragments with thrombocytopenia. This is seen in Kasabach Merrit Syndrome, a complication of hemangioma where there is localized intravascular coagulation with consumption of platelets. Thrombocytopenia and prolonged PT, PTT leads to increased bleeds and increase in size of hemangioma.

Note: Red cell fragments can be seen in other situations like Hemolytic Uremic syndrome, prosthetic valves etc.

Leucocytes

Neutrophils: The commonest indicator of sepsis is neutrophilic leucocytosis in the peripheral smear. There is associated toxic granulation or vacuolation in the cytoplasm. In newborns and young infants with sepsis, there may be neutropenia and toxic changes are often seen in the neutrophils which may indicate sepsis.

Note: Neutrophilic leucocytosis may also occur due to acute stress eg: post-ictal and toxic granulation may be seen in inflammatory conditions eg: vasculitis, juvenile rheumatoid arthritis, Kawasaki disease.

In the initial phase of bacterial infections eg: enteric fever, there is often neutrophilic leucocytosis. There may be associated thrombocytopenia. After a course of appropriate antibiotics the fever may persist. At this stage the peripheral smear may show neutrophils with toxic changes, many reactive lymphocytes and thrombocytosis which indicate possible recovering infection. The fever often settles within a few days without change of drugs.

In immunocompromised children on chemotherapy with fever an absolute neutrophil

count of less than 500 indicates febrile neutropenia and warrants further investigation and treatment.

Hypersegmented neutrophils or neutrophils with scanty or no granules in the presence of recurrent infections indicates neutrophil function disorder.

Eosinophils: Eosinophilia (absolute eosinophil count more than 400) on the peripheral smear indicate underlying allergies or helminthiasis. Hypereosinophilia is seen in infections like filariasis, eosinophilic fasciitis, hypereosinophilic syndrome and eosinophilic leukemia.

Lymphocytes: Lymphocytic predominance is normal in infants. In the presence of viral fever there is lymphocytic response with reactive lymphocytes.

Case 7: A 8 year old boy presented with fever, generalized lymphadenopathy and hepatosplenomegaly. His peripheral smear revealed many atypical lymphocytes (Fig 3) i.e large lymphocytes with pale abundant cytoplasm with monocytoid, plasmacytoid or lymphocytoid nuclei. This is characteristic of infectious mononucleosis. Cytomegalovirus infections may also present in a similar manner.



Fig. 3 Atypical lymphocyte

Case 8: A three year old child presented with fever, generalized lymphadenopathy, hepatosplenomegaly and bony tenderness.

The peripheral smear showed numerous lymphoblasts. These cells has scanty cytoplasm with opened out nuclear chromatin and indistinct nucleoli suggestive of lymphoblastic leukemia.

Other types of leukemia indentifiable on peripheral smear are acute myeloid leukemia and chronic myeloid leukemia.

Platelets

Thrombocytopenia is seen in malaria, viral fevers like dengue haemorrhagic fever and bacterial infections. This is self limiting and recovers after treatment of infections. In DHF serial platelet count is useful in assessing the progress of the disease.

Case 9: A 2 year old girl presented with spontaneous skin and mucous membrane bleeds. A finger prick smear showed thrombocytosis but the platelets were all discrete with no aggregates. This is indicative of thrombasthenia, a inherited platelet function disorder where there is inability of the platelets of aggregate. A simple test like the finger prick peripheral smear will give the diagnosis avoiding further coagulation work up. Note: In any child presenting with problem of bleeding diathesis peripheral smear examination should be done before ordering further tests. Thrombocytosis in children is often benign and secondary to bleeds and inflammatory conditions. Only in conditions like Kawasaki disease does it warrant treatment with aspirin.

Case Scenarios

Abetalipoproteinemia: A 5 year old boy born to 2nd degree consanguinous parents presented with failure to thrive from infancy. There was a history of one sibling death due to similar problems and serial abortions in the mother. Routine examination of the peripheral smear revealed more than 50% acanthocytes. Based on this, tests were streamlined to doing lipid profile

and lipoprotein electrophoresis which revealed hypolipidemia and absent b lipoprotein band. Jejunal mucosal biopsy confirmed the diagnosis of abetalipoproteinemia which revealed lipid laden enterocytes. This case illustrates the importance of simple tests like peripheral smear examination in streamlining further tests in the diagnosis of major diseases.

Wiskott Aldrich Syndrome: A 2 year old boy was admitted with bronchopneumonia. He had a earlier history of recurrent infections with skin and mucous membrane bleeds. He had been diagnosed as dengue hemorrhagic fever the previous year as he had thrombocytopenia. Clinical examination revealed an undernourished child with atopic dermatitis, petechiae and hepatosplenomegaly. His peripheral smear revealed neutrophilic leucocytosis, moderate eosinophilia and thrombocytopenia. In view of earlier documented thrombocytopenia, eczema and recurrent infections, a diagnosis of Wiskott Aldrich Syndrome was made. The family later gave a history of similar problems in the elder sibling who died in infancy.

Chediak Higashi syndrome: 6 year old girl was referred for intermittent fever for 2 months, distention of abdomen, face and limbs for 1½ months and hematemesis of 2 days duration. She was pale, icteric with hypo and hyperpigmented generalized macular lesions, petechiae over the left foot with hepatosplenomegaly. Her peripheral smear showed predominant lymphocytes with many of them containing eosinophilic coarse granules. Bone marrow revealed a hypocellular marrow with occasional megakaryocytes with coarse brown inclusions in the cytoplasm of lymphocytes and few neutrophils. In view of the skin lesions, peripheral smear and bone marrow smear examination she was diagnosed to have Chediak Higashi Syndrome with a probable accelerated phase presenting as fever, pancytopenia, hepatosplenomegaly and lymphohistiocytosis.

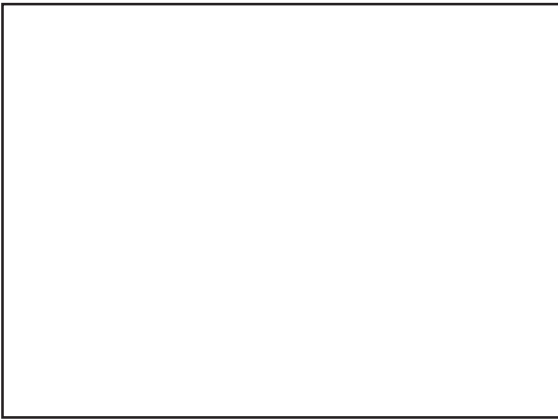


Fig. 4 Storage cell in Gaucher's disease

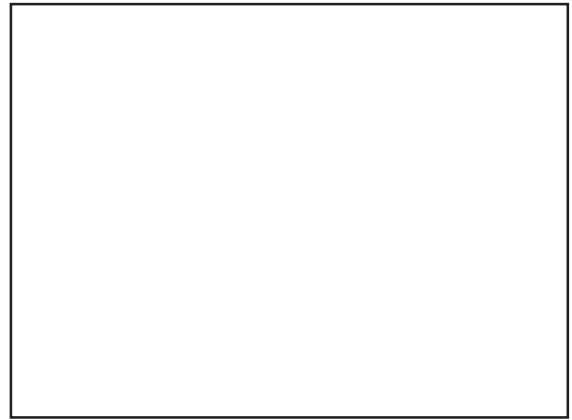


Fig. 5 Hypersegmented polymorph seen in megaloblastic Anemia

Hemolytic Uremic Syndrome: Serial peripheral smears are helpful in following the evolution of HUS. Initial smear in a child presenting with acute gastroenteritis reveals features of neutrophilic leucocytosis with toxic granulation and normal platelets. As the renal involvement due to HUS occurs thrombocytopenia evolves due to localized intravascular coagulation and platelet consumption. Later due to the stress effect on the red cells by fibrin strands there is red cell fragmentation and burr cells. During the recovery stage platelets return to normal with neutrophils showing decreasing toxic changes. Burr cells persist for a longer time. The triad of neutrophilic leucocytosis with toxic changes, burr cells and thrombocytopenia in a post diarrheal renal failure indicates possible HUS.

Lipid Storage Disorder: In lipid storage disorders presence of vacuoles in the cytoplasm of lymphocytes is an indication to do bone marrow to confirm presence of storage cells (Fig 4) like Gauchers or Niemann Pick disease.

Immerslund Grasbeck Syndrome: A six month old baby was referred as acute myeloid leukemia. Peripheral smear revealed macrocytes, hypersegmented polymorphs (Fig 5) and abnormal looking myeloid precursors with thrombocytopenia. Clinically the baby had pigmentation over hands and feet with associated

anemia. The peripheral smear was indicative of megaloblastic anemia which was confirmed by bone marrow aspiration. Urine protein-creatinine ratio was increased. The combination of megaloblastic anemia with proteinuria is indicative of Imerslund Grasbeck syndrome. With parenteral infections of vitamin B-12 the child is doing well on followup. Detailed examination of a peripheral smear can thus be an indicator of disease and can lead to proper streamlining of further investigations for diagnosis.

Osteopetrosis: A six month baby was referred for evaluation of anemia. The baby had prominent eyes with searching nystagmus, beaked nose and absence of filtrum of upper lip. There was associated hepatosplenomegaly. Peripheral smear revealed many red cells in the form of tear drop cells, normoblasts, myelocytes, metamyelocytes and thrombocytopenia. This is characteristic of leucoerythroblastic reaction in marrow infiltration disorders. Skeletal Xrays revealed dense bones which was suggestive of Osteopetrosis. Pancytopenia is usually due to excessive osteoid tissue in the marrow which suppresses the normal precursors.

Note: Other conditions causing myelothisic anemia include malignant infiltration or inflammatory granulomas in the marrow.

HEMATO-ONCOLOGY

UPDATE OF COMPONENT THERAPY IN PEDIATRICS

* **Nitin Shah**

Pediatric transfusions

Child is not a miniature adult and so a newborn is not a miniature child. The causes of anemia and bleeding vary at different ages. The indications, types and the dose of various components will accordingly vary depending upon the age. The compensatory physiological mechanisms also differ at different age. Hence decision as to when to transfuse, how much and how fast to transfuse and what to transfuse will depend upon the age and the weight of the child^{1,2}.

Why not whole blood and why components?

There are more than 6 important components in each unit of whole blood. Each component has a specialized function. All these functions are not deranged in all the patients and hence all the components are not required all the time. Blood is always in short supply and making components from one unit of whole blood will satisfy the needs of more than one patient from the same unit of blood. Besides, giving whole blood will lead to harmful effects because of the unnecessary components infused resulting in plasma overload; lymphocytes mediated toxicities or allosensitization etc. Some components can only be given effectively as

component e.g. platelets, which are otherwise destroyed in stored whole blood. Some components are better given as component e.g. clotting factors, the levels of which can be achieved at much higher level or even 100% by giving concentrates of such factors, than by giving whole blood or even FFP.

Which components?

From one unit of whole blood, one can make packed red blood cells, platelet pack (random donor platelets), granulocytes pack and fresh plasma. Fresh plasma can be frozen at -30°C and used as FFP in future or pooled plasma can be converted into components like cryoprecipitate, albumin, gamma globulins, anti-D globulins, plasma proteins etc. One can modify and manipulate these components and get neocyte packs, frozen red cells, washed red cells or platelets, filtered red cells or platelets, UV light or gamma irradiated red cells or platelets. One can select a specific donor and get CMV negative blood components, HLA matched blood components or blood products from specific minor blood group compatible donor. Lastly one can get stem cells from the umbilical cord blood of a newborn or peripheral blood of an older child for autologous or allogenic bone marrow transplant or rescue as the case may be.

Storage and shelf life

Whole blood is stored at 1-4°C. Shelf - life will depend upon the type of anticoagulant and additive used. ACD is no more used. Blood stored in CPDA1 - A2 (Citrate phosphate dextrose adenine) can be kept for 35 days. Packed red cells can be also stored up to 35 days with CPDA1.

* Consultant Pediatrician,
P.D. Hinduja National Hospital, Mumbai
Hon. Pediatrician, UHC,
LTM General Hospital, Mumbai

Only saline washed red cells should be transferred within 24 hours of preparation. If one uses additives like Nutrisol or Adsol, one can keep the blood for 42 days. Packed red blood cell is stored at 1-4°C and should be used within 24 hrs once packed. Platelets are stored at 20-22°C and that too on a constant agitator as resting platelets tend to aggregate. The shelf- life is 3 to 5 days. Granulocytes are kept at room temperature and should be used within 24 hours of collection. FFP and cryoprecipitate have shelf life of one year and should be kept at - 30°C. Frozen red blood cells (with cryoprotective agents added to it) can be kept at - 70°C and have shelf life of 5-7 years.

Whole blood

Whole blood is stored at 1-4°C and has a shelf life of 35 to 42 days as discussed before. In first 4-6 hrs of collection it has 100% of all the components. As the time passes, changes occur in these constituents. Platelets fall to less than 1% by 4-48 hrs. Labile clotting factors V and VIII also disappear in same time. Other clotting factors like factor II, VII, IX, and X disappear thereafter. The potassium levels go up, ATP levels fall and so do the levels of 2-3 DPG and pH, especially after 5-7 days of storage. Hence for exchange transfusion, one should not use more than 5-7 days old blood. 2-3-DPG levels tend to return to normal within 24 hrs of transfusion.

Advantage of whole blood is that it contains all the components. Disadvantage is that it leads to side effects due to plasma and lymphocytes, as their level remains almost 100% till last date of storage. Besides, it is also a waste of other components which are not required by the recipient.

Indications: Whole blood is naturally required where all the components of blood are necessary to be replaced. This will occur during massive hemorrhage, cardiac surgery, exchange

transfusion especially in neonates and ECMO. For exchange transfusion it is better to use fresh whole blood as far as possible and definitely not more than 5-7 days old. One can use reconstituted whole blood by using PRBC suspended in AB-ve plasma used with platelets if required. 10 cc/kg blood weight of whole blood will raise HCT by 5% and Hb by 1 to 1.5 gm%^{1,2}.

Packed red blood cells (PRBC)

PRBC contains packed red cells in 22-50% of original plasma. It has nearly 100% of polymorphonuclear cells and lymphocytes as at the time of collection but has less than 10% platelets and clotting factors. Ideal HCT for PRBC is 70-75% and it should not be too tightly packed. For newborns, while doing exchange transfusion, HCT can be adjusted to 50-55% using additional FFP or albumin.

Advantage of PRBC is that it is low volume as compared to whole blood and hence does not lead to circulatory overload. It has less plasma and hence has less citrate related toxicity. It being viscous, flows with difficulty through pediatric IV lines. Other problem is that its shelf life is 24 hrs, once packed. Lastly it contains significant amount of plasma and leukocytes to lead to toxicities related to them like allergic reactions, Non Hemolytic Febrile Transfusion Reaction (NHFT), allosensitisation, GVHD, etc. 10cc/kg dosage body weight of PRBC will raise the HCT by 10% and Hb by 3-4 gm%.

Indications: It is used for replacement of volume as well as oxygen carrying capacity. It is used in acute hemorrhage where more than 20% blood volume is lost, monitoring vitals, blood pressure and CVP. The commonest indication of PRBC is chronic transfusion dependent anemia as seen in thalassemias, sickle cell disease, congenital dyserythropoietic anemia, Diamond Blackfan Syndrome, Fanconi's anemia, aplastic anemia, chronic renal failure, cancer patients,

sideroblastic anemia etc. It is also useful in episodic transfusions for acute hemolysis like in G6PD deficiency, malaria, autoimmune hemolytic anemia, etc. It is rarely, if at all, used in nutritional anemia, if patient has severe anemia with impending cardiac failure or has associated cardio-respiratory disease. Lastly it can be used before surgery, where patient is anemic with Hb less than 7 gm% and where moderate blood loss is expected during surgery. It is most often misused as “top-up” in patients with nutritional anemia, or before surgery to keep Hb above “10 gm%”. In such cases, it is counterproductive as it can lead to immunosuppression of the recipient and delay in healing.

In newborn it is required for hemorrhage seen in cases of severe hemorrhagic disease of newborn, or any other cause of bleeding. It is used to replace iatrogenic blood loss, especially in sick preterms where more than one blood volume can be let out over the hospital stay for various diagnostic tests. For exchange transfusion one can use whole blood or reconstituted whole blood as discussed before. PRBC is also useful in anemia of prematurity when the baby has poor sucking, apneic spells, poor weight gain and anemia or less than 7 gm%. Very sick neonates usually have associated sepsis, acidosis, DIC, bleeding and anemia and will need support with PRBC, platelets and FFP.

Precautions

In patients who have chronic anemia and are transfusion dependent, special precautions should be taken. Detailed blood grouping should be done before first transfusion to find out presence of minor blood group incompatibility. Always use Coomb's cross-matched blood to detect development of antibodies against minor blood group antigens. One should at least use washed PRBC and if affordable, WBC filtered PRBC to decrease leuko-contamination.

Meticulous records of pre and post-transfusion Hb should be kept to see for efficacy of transfusions and suspect hypersplenism. Chelation should be started once serum ferritin is more than 1000 ng/ml. Regular check up for plasma borne infections, serum ferritin levels and LFT should be done. Lastly, all these patients should receive hepatitis-B vaccine before their first transfusion ^{3,4}.

Platelet transfusions

Special requirements: Platelets have to be stored to 20 to 22°C on constant agitator. It should be transported quickly and infused rapidly over 20-30 minutes to prevent loss of platelets due to aggregation. No glassware should be used and only plastic ware should be used to collect, store and administer platelets. One should use ABO / Rh identical compatible donor. In emergency one can use incompatible donors though the efficacy may be less than expected.

Types of Platelets: One can use either random donor platelets (RDP) or single donor platelets (SDP). One can also use manipulated platelets like plasma-depleted platelets, washed platelets, WBC filtered platelets, UV or gamma irradiated platelets or platelets from a specific donor like CMV negative donor or HLA matched donor.

RDP: It is also called as platelet pack and is derived from a single unit of whole blood. It contains $5-6 \times 10^{10}$ platelets in 50-60 ml of plasma per pack. One unit / 10 kg body weight will raise the platelet count by 20,000 to 30,000/cmm. The advantage of RDP is that it is less costly and easily available from the blood bank shelf. The disadvantage of RDP is that it is less efficacious than SDP as it contains 6-7 times less number of platelets. Hence, more number of RDP packs are used exposing the recipient to more number of donors. Again one cannot use specific donors like CMV negative or HLA matches donor when required.

SDP: It is also called platelet concentrate and is obtained from a single donor by apheresis using cell separator like COBECSPECTRA. Compatible donor is selected and subjected to continuous or discontinuous apheresis and platelets are collected over 4-6 hrs. period. It contains $2-3 \times 10^{11}$ platelets in 50-70 cc of plasma. It has 6-7 times more platelets than RDP. The donor should be healthy, off medicines like aspirin and should have platelet count more than 1.5 lakhs/mm³. After apheresis donor's platelet count can drop but still will be above 1 lakh/mm³. Advantage of SDP is that it is more concentrated and hence more effective exposing recipient to only a single donor. One can use same donor again after 2-3 weeks. One can select specific donor like CMV negative or HLA matched donor. But it is extremely costly and needs sophisticated equipments. Donor has to wait for longer period in blood bank.

Criteria to transfuse: Platelet transfusions are usually given to those with thrombocytopenia due to decreased production than to those with increased destruction. Platelet transfusions are given when they have significant mucosal bleeds. Only skin bleeds do not warrant platelet transfusion, but such patients should be closely monitored for any further mucosal bleeds^{5,6,7}.

It is controversial as to when to give prophylactic platelet transfusion. Child with thrombocytopenia usually does not bleed spontaneously unless the platelet count falls less than 50,000/mm³. The chances of intracranial hemorrhage increase when the count drops to less than 10-20,000/mm³. Decision when to transfuse is hence based on basic disease, type of thrombocytopenia, platelet count, and presence of associated coagulation abnormalities. A well child is given prophylactic transfusion when the platelet count is less than 5,000-10,000/mm³. A sick child is given platelet transfusion when the count is less than 10-20,000/mm³. Before surgery

it is given when the count is less than 30,000/mm³ and for surgeries in dangerous areas like eye-ball, it should be given when the count falls to 50,000/mm³. In patients with massive hemorrhage it should be given when the count is less than 30,000/mm³. as most of the circulating platelets are likely to be non-functional platelets of the infused stored blood.

Indications: Platelet transfusions are given for thrombocytopenia or for platelet dysfunctional disorders.

1. Decreased platelet production: It occurs when bone marrow failure occurs like in aplastic anemia, Fanconi's anemia, TAR syndrome, and other constitutional hypoplastic anemia. It can occur due to bone marrow infiltration e.g. in leukemias and other metastatic cancers. It can occur following bone marrow suppression due to chemo-radio therapy or fulminant infections. Platelet transfusions have revolutionized the treatment and the outcome of pediatric cancers. The cause of mortality has shifted from bleeding to infections with better platelet support available now.

2. Increased consumption of platelets: This occurs in DIC, NEC, HUS, TTP and Kasalbach-Merritt syndrome. In these cases, there is good platelet recovery at one hour after transfusion, but not at 24 hours. suggesting consumption.

3. Increased platelet destruction: This occurs due to immune or non-immune mechanisms. Immune destruction can occur in post-transfusion purpura, autoimmune disease, ITP, and alloimmune disease of newborn. Non-immune destruction can occur following drugs or infections. Platelet transfusions are generally not effective in this group of diseases, as they will be immediately destroyed after transfusion. However, in life-threatening bleeding like intracranial hemorrhage one may give platelet

packs just to tide over crisis till splenectomy is done or IVIG is administered.

In alloimmune thrombocytopenia of newborn, mother is PLA-1 antigen negative and child is PLA-1 antigen positive. This leads to allosensitization of the mother with production of alloantibodies, which are passed to the baby transplacentally leading to immune destruction of baby's platelets. Washed mother's platelets are given to the baby in such cases.

4. Hypersplenism: Normally 1/3rd of platelets are pooled in the spleen. This proportion will increase in patients with hypersplenism due to any reason. Again platelet transfusions may not be effective in such cases, as they will be immediately removed from the circulation into the enlarged spleen.

5. Dilutional: In patients with massive hemorrhage or following exchange transfusions, dilutional thrombocytopenia can occur when massive amount of whole blood are used in such cases. Additional platelet transfusions may be required in such cases.

6. Platelet-dysfunction: Various congenital and acquired platelet functional disorders may present with significant bleeding. If local measures fail to control bleeding, platelet transfusions will be required. One should use platelets sparingly in such cases as allosensitization may prevent good recovery in future after a number of transfusions are given. One can use HLA matched platelets in such cases.

Platelet transfusion efficacy: One unit of RDP per 10 kg. body weight increases platelet count by 20,000 to 30,000/cmm. SDP is 5-7 times more efficacious than RDP. The efficacy of platelet transfusion depend upon various factors. Platelet factors like sources of platelets, type of platelets, storage, collection and administration will affect the efficacy. Smililarly, factors in receiptant that

affect the efficacy include pre-transfusion count, fever, sepsis, size of liver and spleen, presence of antibodies or consumption coagulopathy and drugs taken by the receiptant.

Clinically one can judge the efficacy by seeing the cessation of bleeding. One can look for the expected increments by calculating Consumption coagulopathy index (CCI) as follows by doing platelet count at one hour and 24 hrs. after transfusion.

$$\text{CCI} = \frac{\text{Post tr. pl. ct} - \text{Pre-tr.plat.ct}}{\text{Platelets infused} \times 10^{11}} \times \text{BSA m}^2$$

Post.tr.pl.ct : Post transfusion platelet Count

Pre-tr.pl.ct : Pre transfusion platelet Count

CCI = Corrected count increment

BSA = Body surface area in m2.

Normal CCI is atleast 10,000 at one hour, and 7,500 at 24 hrs. If CCI is normal at one hour, but less at 24 hrs, it suggests consumption coagulopathy. If CCI is less at 1 hour itself, it suggests immune destruction.

Granulocytes

People have logically tried giving granulocyte transfusion in patients with severe uncontrollable infection, in patients with congenital or acquired neutropenia or neutrophil dysfunction. It is usually reserved for neutropenic patients with fulminant sepsis not controlled by antibiotics and antifungal with ANC < 300 in newborn, < 100 in infants and < 500 in immune compromised host. It should always be used along with antibiotics and antifungals.

Granulocytes can be given by three ways. Granulocyte pack can be obtained from buffy coat. Though it is less costly, the cells become non-functional. It can be obtained by aphaeresis from a donor. The cells remain functional but it

is costly. In newborns one can do partial exchange with fresh whole blood to replace granulocytes.

The dose is 10^9 granulocytes/kg. body weight per dose. It can be repeated 12-24 hourly for 4-6 days. Each pack of granulocyte has 10^{11} granulocytes in 200 cc of plasma. It is to be stored at room temperature and used within 24 hrs. It obviously leads to all the side-effects related to plasma and lymphocytes. One should use ABO / Rh compatible donor.

Why leucodepletion?

Donor lymphocytes present in most of the blood components do not serve much purpose but can lead to major side effects. Antibodies can develop against lymphocytes and platelets and lead to non-hemolytic febrile transfusion reactions (NHFTR). Activated lymphocytes can release cytokines like IL2, TNF during storage, which can also cause NHFTR. NHFTR is especially a problem for patients needing recurrent blood transfusions. Lymphocytes lead to allosensitization and subsequent graft rejection in prospective candidates for bone marrow transplants. Lymphocytes bear intracellular pathogens and can transmit infections like HIV, HTVL, EBV, CMV etc. Lymphocytes can lead to pulmonary toxicities like ARDS. In surgical patients lymphocytes can lead to immune suppression and delay healing. Lastly, in immune - compromised patients and in transfusion from first degree relatives, it can lead to transfusion associated graft Versus host disease (TAGVHD). Dose required for NHFTR is $> 5 \times 10^6$ lymphocytes whereas for TAGVHD it is $> 10^7$ cells/kg body weight. One pack of PRBC has 10^9 WBC, RDP has $4-6 \times 10^7$ WBC, SDP has $2-4 \times 10^8$ WBC and granulocyte pack has 10^{11} WBCS. Hence all these components can lead to all the above-mentioned lymphocyte mediated toxicities^{8,9}. Ideally all the transfusion should be leuko-depleted especially in patients needing

recurrent transfusions and in immune-compromised hosts.

Methods of leucodepletion

There are various ways of leucodepletion. Each method has its own merits and demerits.

1. WBC filter: 3rd generation WBC filters are highly efficient. The efficacy is 99.5 %. They contain fiber mesh to which the WBC stick and get filtered. When used during collection itself they will remove lymphocytes at source and hence prevent release of cytokines on storage. They can also be used at the bedside while transfusing the blood. The advantage of WBC filter is its high efficacy and simplicity to use. The disadvantages include its high cost and inability to prevent TAGVHD. Each filter costs Rs. 600 - 700/- and is not re-usable. Ideally all transfusions should be given using filters especially if patient needs recurrent transfusions or develops NHFTR.

2. Washed cells: Washing with saline or blood processor not only removes WBC but also plasma. The efficacy of WBC removal is 90% and that for plasma 99%. Hence it not only will reduce NHFTR, allosensitization and other toxicities related to WBC but will also reduce allergic reactions to plasma proteins. Preparation is simple. Disadvantages are that it is not very effective in leucodepletion and cannot prevent TAGVHD. Besides it needs cold centrifuge to prepare washed cells. All red cell transfusions should be given using at least washed cells and preferably with WBC filters in patients needing recurrent transfusions and those with NHFTR or allergic reactions. Washed platelets from mother are given to a baby suffering from alloimmune thrombocytopenia.

3) Gamma irradiation: TAGVHD can be only prevented by gamma irradiating the blood. It was found that doses up to 10000 cGy do not alter

RBC function and doses up to 5000 cGy do not alter platelet functions. Hence dosage of 2500 - 3500 cGy are used to irradiate the components. One can use 137-cs insulator or 60 CO machine. The only disadvantage is need for the sophisticated irradiator and chances of membrane leak of the cells irradiated and increased potassium levels. Hence blood should be irradiated just before infusion or else supernatant plasma should be removed before transfusion.

Ideally all blood should be irradiated where there is risk of TAGVHD. This includes transfusion given to newborn especially preterms < 1200 gms, intra-uterine transfusion, patient with primary or secondary immunodeficiency, cancer patients, organ transplant recipients and transfusion given to normal person from a first degree relative donor.

4) Frozen cells: RBC can be frozen at - 70°C and be kept for 5-7 years. While freezing cryopreservation with glycerol is done to prevent intracellular ice formation. It should be thawed gradually and deglycerolized. Once thawed should be used within 24 hours. The efficacy for leucodepletion is 90% and plasma depletion is 99%. Hence it reduces toxicities related to both lymphocytes and plasma. Advantage of frozen cells is its availability in emergency where one can use O-ve frozen cells in AB negative plasma. One can collect blood from CMV negative donors, HLA matched donor or rare blood group donors and freeze it for future use. Lastly autologous blood collected for surgery can be frozen and used in future, if surgery gets postponed for some reasons. Disadvantage of frozen cells is that it needs sophisticated instruments to prepare and store and is extremely costly. It cannot prevent TAGVHD.

Fresh Frozen Plasma (FFP)

Platelet poor plasma obtained at the end of centrifugation while making components is frozen

at - 30°C to make FFP. The shelf life of FFP is one year and it is stored at - 30°C. It should be transfused within 4 hours of thawing to room temperature. FFP contains all the plasma proteins including albumin, gamma globulins and the most important clotting factors. As labile factor V and VIII tend to decrease on storage, freezing of the plasma should be done within 4-6 hours of collection to prevent loss of these factors. One unit of FFP has 150 cc - 200 cc of plasma and 1 ml. of plasma contains approximately 1 unit of each clotting factor. One can use 10-15 cc/kg. body weight of FFP given every 12 hourly. Hence one cannot raise the factor levels beyond a certain limit without leading to volume overload.

FFP is often misused as a volume expander. As FFP contains plasma, it can lead to allergic reactions, anaphylaxis in IgA deficient patient and can transmit all the plasma borne infections. Hence, albumin should be used as a volume expander as it is much safer. Similarly albumin and not FFP should be used to replace proteins or albumin. If patient needs both volume expansion as well as clotting factors like in DIC, sepsis, NEC etc. one can use FFP.

FFP is mainly used to replace clotting factors. It can be given when the patient presents with bleeding for the first time where the diagnosis is uncertain as to which factor is deficient. In known cases of hemophilia, it is better to use factor concentrates, as they are more efficient and safe. FFP is used for deficiencies of other factors like factor V, VII etc. where factor concentrates are not available. It is also used where multiple factors need to be replaced as in case of hemorrhagic disease of newborn, liver disease, preterm with liver dysfunction, DIC, etc. FFP also contains AT III < protein C and protein S and hence is useful in the deficiency of these factors too. It is used for plasma exchange in patients with TTP. It can be used to reconstitute whole blood along with PRBC or to adjust

hematocrit of PRBC for exchange transfusion in newborn. Lastely, FFP is useful to prevent and treat coagulopathy due to L-asperagenase in cancer patients.

FFP leads to all the side effects related to plasma like allergic reactions like urticaria, anaphylaxis in IgA deficient patient and transmission of plasma borne infections to the recipient. In small babies, it can lead to hemolysis if it contains high levels of antibodies against recipient's blood group antigens.

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NEWS AND NOTES

XIII CONGRESS OF THE INTERNATIONAL PEDIATRIC NEPHROLOGY ASSOCIATION

Date: 29th August - 2nd September, 2004

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HEMATO-ONCOLOGY

AN APPROACH TO A CHILD WITH RECURRENT BLEEDING

* **Revathi Raj**

As early as the eighteenth century, Hebrew law in Bologna stated that if two sons of the same mother died of uncontrollable bleeding following circumcision, subsequent offspring were not circumcised.

To evaluate a child with excessive or recurrent bleeding, an understanding of basic clotting mechanisms is necessary. The blood circulates in a fluid phase that is controlled through a series of coagulation proteins that are balanced by natural inhibitors. Once a blood vessel is injured, the vessel contracts, and platelets adhere to the site. The platelets then undergo the aggregation and release reaction that is triggered by exposure to sub-endothelial collagen. A series of changes in the platelets produces a platelet plug. The plasma coagulation system is then activated to form fibrin, the final result of the haemostatic mechanism.

The history is extremely important in evaluating children with disorders of haemostasis. Children with severe haemostatic defects often have repeated episodes of bleeding that occur without apparent cause, or severe bleeding in response to relatively minor stimuli. Spontaneous bruising or petechiae, excessive bleeding after a dental extraction, a surgical wound or an accidental laceration point towards a bleeding tendency. Excessive bleeding during

menstruation may be the first presentation of a bleeding diathesis.

Since many of these disorders are inherited, the family history is crucial. The family history of children with factor VIII or factor IX deficiency shows the characteristic pattern of sexlinked inheritance. However, about a third of haemophilic patients are spontaneous mutations with no family history and sometimes X linked disorders may skip generations. Von Willebrand disease and dysfibrinogenaemia are usually autosomal dominant. All other coagulation factor defects are autosomal recessive. Platelet function disorders are usually autosomal recessive apart from Wiskott Aldrich syndrome which is inherited as X linked recessive.

Physical examination of children with haemorrhagic disorders involves evaluation of the type of bleeding (petechiae, ecchymoses, haematoma, haemarthrosis or mucous membrane bleeding). The characteristic bleeding manifestation in a patient with a vascular or platelet defect are skin and mucous membrane bleeding. The typical bleeding signs in a patient with a defective coagulation system are deep bleeding into joints and muscles, large spreading ecchymotic lesions and haematomas. Examination must include looking for dysmorphic features to suggest Fanconi anaemia or partial albinism associated with platelet type bleeding.

The usual lab screening tests for a patient with a suspected haemostatic defect include platelet count, bleeding time, prothrombin time, activated partial thromboplastin time and thrombin time. The whole blood clotting time is

* Consultant in Pediatric Hematology and Bone marrow Transplantation
Apollo Hospitals, Chennai

prolonged only when factor VIII is less than 1% and hence is an insensitive screening test. An APTT on the other hand is abnormal when factor VIII is done to 30%. (Fig 1). Bleeding time gives an accurate estimate of vascular integrity and platelet function provided it is standardised.

A child with extensive scarring from small superficial wounds and a prolonged bleeding time is most likely to have Ehlers Danlos syndrome. A child with a prolonged bleeding time with large platelets on smear could have Glanzmann's thrombasthenia and a child with eczema, recurrent rectal bleeding, prolonged bleeding time with small platelets on smear could have Wiskott Aldrich syndrome (Fig.2).

Automated cell counters estimate mean platelet volumes accurately and will give a clue regarding platelet size. Formal platelet aggregation studies will help to arrive at a diagnosis in children with a history of platelet type bleeding and a prolonged bleeding time. However, these tests require a significant volume

of blood to separate platelet rich plasma and we may have to wait until the child is a little older. The recent introduction of an automated platelet function analyzer (PFA 100) has revolutionized screening for platelet disorders. The analyzer requires only small volumes of whole blood to assess platelet function.

Isolated prolongation of PT is suggestive of factor VII deficiency, Whilst a prolonged APTT is suggestive of factor VIII, IX, XI or XII deficiency. When both PT and APTT are prolonged, Von Willebrand disease, factor X, V, II or fibrinogen deficiency should be suspected. When all haemostatic screen results are normal with a significant bleeding history, then a Factor XIII screen is indicated (Fig. 3).

Once the diagnosis is established, all children with recurrent bleeding problems should be managed along these broad principles. They should be vaccinated against hepatitis A and B viruses and be issued a card with their diagnosis and blood group on the same. The physician

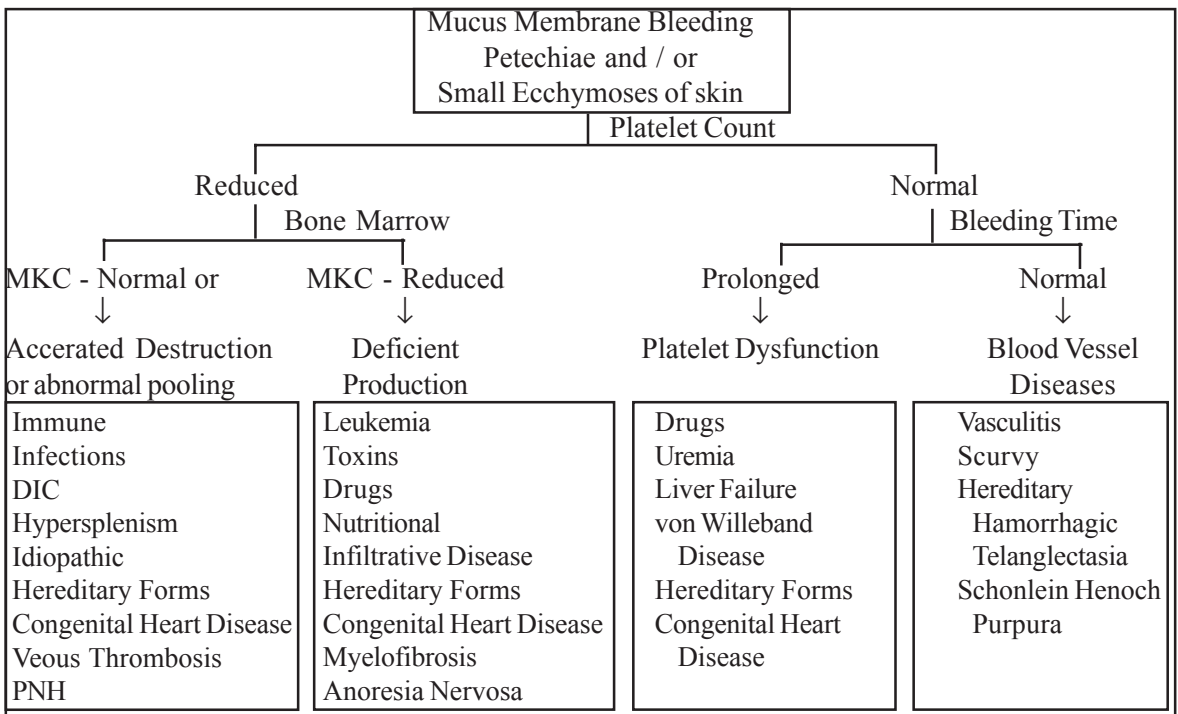


Fig 2. Workup of a patient with a defect in the primary hemostatic mechanism

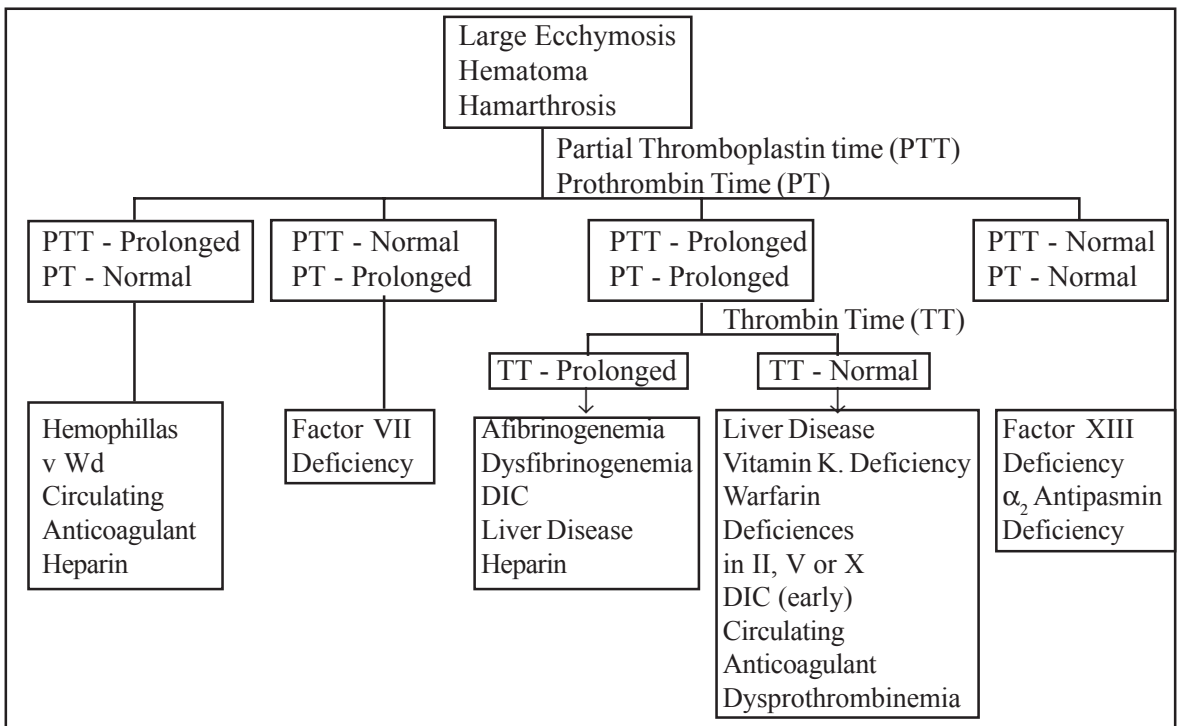


Fig 3. Workup of a patient with a defect in the secondary hemostatic mechanism

caring for the child should educate the family regarding avoiding aspirin, NSAIDs, IM injections, contact sports and head injury. Genetic counseling should also be provided, as the burden of caring for more than one child with a bleeding problem is high, both in terms of financial and emotional aspects. A lead clinician who is available at all times to provide advice and supportive care makes a big difference in not only arresting bleeds but also prevention of deformities.

Finally, both the physician and the family must be aware of the infectious complications associated with frequent use of blood products.

Platelets, fresh frozen plasma and cryoprecipitate should be used judiciously as and when required. If there are no financial constraints, the use of virally inactivated factor concentrates or recombinant factor concentrates can be used as and when appropriate. Gene replacement therapy has been tried in factor IX deficiency and has been successful. Liver transplantation offers a chance of cure for defects of secondary haemostatic mechanisms. Recombinant factor VIIa seems to be a promising agent that helps control bleeding in all defects of the coagulation pathway, but the tremendous cost precludes its widespread use at present.

NEWS AND NOTES

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HEMATO-ONCOLOGY

MANAGEMENT OF IMMUNOCOMPROMIZED CHILDREN WITH CANCERS - ROLE OF THE PRIMARY CARE PHYSICIAN

* *Saradha A. Sarnaik*

Introduction

Patients who are being treated for cancer have a predisposition to a variety of infectious complications because of abnormal host defense mechanisms. Normal host defense mechanisms include firstly, an intact surface skin and mucous membranes in the mouth and GI tract that act as a mechanical barrier to invasion with microorganisms. A second defense are neutrophils and monocytes that can migrate, phagocytose and kill invading microorganisms. Thirdly cell-mediated immunity that is conferred by lymphocytes (T & B cells) results in a secretion of specific antibody that participates in lysis of invading organisms.

Pathophysiology

Patients who are being treated with chemotherapy and/or radiation often develop painful mucositis, with mucosal ulceration in the mouth, esophagus and the entire GI tract. Thus, the first physical barrier to microorganisms is disrupted, nutrition is interfered with because of poor feeding from mouth pain and problems with

swallowing. The resultant abnormal nutrition is a contributing factor to increased difficulty with fighting infections.

Almost all cancer chemotherapeutic agents cause neutropenia (vincristine, steroids, and asparaginase do not usually produce neutropenia). Thus, a second important barrier to infection is lost in patients being treated for malignancy. The severity, duration and timing of neutropenia depend on the particular drugs used and their dosage. The usual nadir is between 10 and 14 days after administration, with recovery to baseline by day 21. Anemia and thrombocytopenia usually accompany low neutrophil counts and contribute to an increased susceptibility to infectious complications. While neutropenia is defined as absolute neutrophil count (ANC) $< 1500/\text{mm}^3$ the risk of infection increases when PMNs drops to $< 1000/\text{mm}^3$. Modern, more aggressive treatment protocols, withhold therapy when patients have ANC between 500 - $750/\text{mm}^3$. Profound neutropenia (ANC <100) has a high risk of serious infections. Also, neutropenia lasting longer than 7 days is associated with multiple and severe infections.

Defective cell mediated immunity is associated with steroid use. Steroids are a major agent in the treatment of ALL. Other chemotherapeutic agents such as methotrexate, 6-mercaptopurine and cyclophosphamide also impair CMI, probably by causing lysis of lymphocytes as well as interfering with lymphocyte function. Splenectomized patients or those rendered functionally asplenic by irradiation of the spleen have problems with humoral immune responses.

* Attending Hematologist/Oncologist,
Children's Hospital of Michigan, and
Professor of Pediatrics,
Wayne State University School of Medicine,
Detroit, Michigan, USA

Management of patients with immunocompromized states: practical considerations.

Monitoring of CBC

Weekly CBCs are usually performed to monitor the need of transfusion of RBC or platelet concentrates as needed to support the patient. RBC transfusions are given to maintain hemoglobin levels $>7\text{gm}\%$, platelets are generally infused for gross bleeding, particularly from mucous membranes (epistaxis, gum bleeding), spontaneous severe bleeding is not usual with counts $> 20,000/\text{cubic mm}^3$. Thus, in a non-bleeding child, platelet transfusion may be used for counts of $15,000/\text{cmm}$ or less.

Dietary considerations

As previously discussed, children with cancer are at risk for malnutrition, particularly those who have sub-optimal nutritional status before treatment is begun. Factors that contribute to poor nutrition include mechanical obstruction from the tumor itself, increased metabolic and caloric needs from tumor growth, ileus and delayed gastric emptying from surgery, chemotherapy and/or radiation treatment also worsen weight loss.

The task force of the American Academy of Pediatrics has published criteria for nutritional intervention. Criteria include weight loss of $>5\%$ of the pre-illness weight, low weight for height, or serum albumin level $<3.2\text{gm}/\text{dl}$. Nutritional intervention should focus on caloric dense foods. If financially feasible, commercially available supplements should be used. If acceptance or cost are barriers, favorite high caloric foods should be offered. Frequent small feeds (6 to 8 times a day) and bland and cold foods if there are mouth sores are often more acceptable to children. Tube feedings should only be used if the neutrophil and platelet counts are not low, because trauma from passing the tube and

infectious complications from aspiration can be a risk in such patients. Finally, if feasible and necessary, parenteral nutrition by central line catheters can be used. Patients who have severe neutropenia should best avoid raw foods (raw fruits and vegetables) because despite washing these foods carry the risk of ingestion and colonization of molds or other infectious organisms. Cooked foods are more likely to be sterile.

If chemotherapy-related nausea and vomiting is a problem, giving a dose of an antiemetic just prior to meals is a good practice. Parents should be encouraged to remain positive and should be given supportive guidance, because children may request a food item, only to refuse it after a bite or two, and can be perceived to be "difficult". Actually, this behavior is because of therapy-related hypoguesia or abnormal taste and smell sensation. Experimentation with texture and different added condiments may be helpful.

Isolation procedures

It is not feasible (nor indicated) to completely isolate children for fear of contagious exposure during immunosuppressive therapy. The most over-looked and very simple precaution of good hand washing when taking care of the child is both important and inexpensive. While contact with peers or others who have infections is often anxiety-provoking to parents, only an exposure to varicella is of particular importance to the management of immunosuppressed children. The period of infectivity for varicella is 48 hours before appearance of the eruption and for 6 days after the last new lesion appears. Patients who are exposure to an infectious person should receive passive immunization with zoster immune globulin within 72 hours of the exposure. Acyclovir should be given if varicella occurs in an immunosuppressed child. The intravenous route is preferred. Data from studies in India point

out to the efficacy of oral acyclovir in this situation. (20 mg/kg/dose four times a day for 5 days)

Pneumocystis prophylaxis

Children undergoing chemotherapy are prone to pneumocystis carinii infections that are potentially life-threatening. They should thus receive oral trimethoprim and sulphamethoxazole combination as prophylaxis (75mg/M² of trimethoprim) twice daily on 3 consecutive days a week while they are on chemotherapy.

Management of fungal colonization

Colonization with candida (thrush) can be controlled by oral topical mycostatin, 1 cc four times a day for the duration of expected neutropenia.

Management of febrile episodes

History: History should be obtained, particularly regarding the chemotherapeutic drugs used, home medications, (including steroid use) prophylactic antibiotics, recent antibiotic administration. the status of the malignancy (remission of relapse), most recent blood counts. Presenting complaints are important, particularly cough, abdominal pain, ongoing fluid losses from diarrhoea or vomiting, exposure to infectious agents.

Physical examination: The vital signs, particularly the respiratory rate and presence of respiratory distress or hypotension, rashes, petechiae or bruising, paronychia, infections at sites of skin puncture (finger sticks, venepuncture sites, catheter sites). Potential sites for infections include the teeth and gums, sinuses, abdomen for typhlitis (right lower quadrant pain and/or tenderness, a sign of caecal inflammation and potential for bowel rupture in neutropenic patients). The perirectal area should be inspected and palpated for tenderness or erythema. A rectal

examination (or rectal temperature) should be avoided in a neutropenic patient, particularly with thrombocytopenia, as the trauma itself can set up a parirectal infection.

Laboratory investigation: As a minimum, a CBC, blood culture from a peripheral vein as well as a central line if present should be obtained. Urine culture should also be obtained. Other investigations should be done if clinically indicated. These include liver and kidney function tests and chest X-Ray if pneumonia is suspected. Thick and thin smears for malarial parasites, testing for dengue fever should be done if these infections are suspected.

Antibiotic choices - a) If patients are not neutropenic and do not have an indwelling central line, empiric treatment with a single antibiotic such as a third generation cephalosporin to cover gram positive and gram negative organisms after cultures are obtained is a good treatment plan.

b) Patients with an indwelling catheter, should be treated with oxacillin and an aminoglycoside regardless of whether they are neutropenic or not.

c) For patients with neutropenia and an indwelling catheter, oxacillin and an aminoglycoside can be used.

d) For patients with neutropenia and an indwelling catheter, vancomycin and gentamicin should be used.

Recent studies favor the use of monotherapy with agents such as ceftazidime in patients who do not have an indwelling catheter.

Systemic antifungals - It is recognized that patients with prolonged profound neutropenia are at risk for deep seated fungal infections with organisms such as aspergillus. There is a growing practice to treat such patients with systemic parenteral antifungal agents such as amphotericin

B. Patients with more than 7 days of persistent febrile neutropenia are candidates for such therapy. Newer agents such as the liposomal formulations of amphotericin are less toxic but more expensive. Voriconazole and casperfungin are newly released agents in the US for difficult to treat severe fungal infections.

Viral Infections- Disseminated varicella-zoster infections are amenable to treatment with acyclovir. CMV and herpes simplex infections can likewise be treated with gancyclovir. Thus, it is of some importance to establish the presence of these infections by appropriate laboratory investigations, if these are available.

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NEWS AND NOTES

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Oncology - Hematology 2003

Contact:

Dr. Purvish M. Parikh, Program Director,
Room No. 33,
Tata Memorial Hospital, Parel,
Mumbai 400 012.

Tel. 022 4177213; Fax 022 4154005
E-mail : oncology india@rediffmail.com

February 23, 2003

CME on Common Renal Disorders, Chandigarh

Contact:

Dr. J.S. Goraya, Organising Secretary,
Department of Pediatrics,
Govt. Medical College,
Chandigarh 160047.

Tel. 0172 665253-59 ext. 2503 (O)
0172 616128 (R)
E-mail : goraya@glide.net.in

HEMATO-ONCOLOGY

COMPLETE BLOOD COUNTS IN PEDIATRIC PRACTICE

* **Ganthimathy Sekhar**

The modern era of hematology began in the early 1900s. Ever since, this field has flourished and the knowledge and understanding is ever expanding and ever accelerating. Several laboratory tests form the backbone of diagnostic hematology, the most important being the complete blood count or hemogram.

The complete blood count (CBC) is a simple and inexpensive test, which is relatively easy to order the interpret. However it should be carefully analyzed, based on the knowledge of the methodologies used and the pitfalls in these. However it can still give valuable clues to diagnosis of disease states.

Over the years the components of the CBC have expanded with the introduction of increasingly sophisticated instruments. The basic parameters are:

- Hemoglobin
- Hematocrit
- Total red cell count (RBC count)
- Red cell indices - MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration) and RDW (red cell distribution width).

- Total white cell count (WBC count)
- Differential WBC count (Diff. count)
- Platelet count

By convention the Peripheral blood smear examination is done as part of the CBC. In some centres the reticulocyte count is also done as part of the CBC.

‘Correct collection of blood specimens is the cornerstone of accurate diagnosis in Pediatric Hematology’ and nowhere is this more felt than is estimating CBCs. Free flowing blood, correct volume of blood to anticoagulant, collection from a correct site (avoid IV lines) and avoidance of squeezing of the site are all crucial factors affecting the outcome of test results. The ideal anticoagulant is EDTA in the concentration of 1 to 2 mg per ml of blood. (EDTA should be preferably in a powdered form, for which usage of vacutainers give more accurate results).

Methods of determination of CBC

CBC estimations may be done manually or by automated hematology analyzers.

Manual counts: Manual methods are more ideal for measuring single parameter and calibrating parameters like hemoglobin and hematocrit.

Automated analyzers : These increase the accuracy and speed of analysis. However the automated instruments have to be regularly calibrated using reference methods and the reproducibility frequently measured. Ideally the calibration settings are checked at the time of installation of a new machine, at the time of any equipment malfunction or monthly intervals.

* Consultant Clinical Pathologist
Kanchi Kamakoti CHILDS Hospital,
Chennai - 600 034.

Commercial controls with known values should be run everyday to check the performance of the machine. However these machines are estimated to have a false 'flagging' rate of about 10 to 25 % of patient samples. requiring a blood smear examination.

Hemoglobin (Hb)

Hemoglobin estimation is done on any child with symptoms or signs of anemia where the hemoglobin levels are below the reference range. Polycythemia is present with the Hb levels are increased. The unit of measurement (UOM) is g/L (g/dl).

In most automated systems, Hb is measured as cyanmethemoglobin by absorbance spectrophotometry. This relies on complete lysis of the RBCs and reliably measures all the hemoglobin variants except sulfhemoglobin. Some instruments now include sulfhemoglobin in the total hemoglobin measurement.

Hematocrit (Packed cell volume, PCV, Hct)

Hematocrit is the volume of the red cells as compared to the volume of the whole blood sample. Estimation of this parameter is used in the diagnosis of anemia and polycythemia. It should be kept in mind that hemoconcentration due to various causes can affect the true levels. Both manual and automated methods can be used. On the automated systems these are calculated as MCV multiplied by the red cell count. In manual methods a timed application of

centrifugal force on a column of blood is done. However manual methods are preferred in polycythemia and when there is abnormal plasma oncotic pressure. Hematocrit estimation is also affected by alteration of RBC shape. Hematocrits are conventionally reported as a percentage. (%). In SI units it is expressed as l/l. eg. hematocrit of 35% will be 0.35 l/l.

Red cell count

This is the measure of the number of RBCs in a unit volume of blood, the present UOM being RBCs $\times 10^{12}/L$. As manual methods of estimating RBC count are quite inaccurate, they were not used much. With the advent of accurate counting by automated analyzers they are now being utilized more in the diagnosis of anemia and calculation of the RBC indices. It is also useful in roughly correlating hemoglobin levels and hematocrit levels.

Correlations of hemoglobin with hematocrit and RBC count

$$\text{RBC count} \times 3 = \text{Hemoglobin}$$

$$\text{Hemoglobin} \times 3 = \text{Hematocrit.}$$

However this is affected by many artifactual changes which are detailed later.

Red cell indices

These include the MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration) and RDW (red cell distribution

Table 1. Definition of anemia based on hemoglobin and hematocrit

Age	Hemoglobin	Hematocrit
6 mos - 4 yrs	< 11.0 g/dl	< 33.0%
4 years - puberty	< 11.5 g/dl	< 34.5%
Postpubertal males	< 14.0 g/dl	< 42.5%
Postpubertal females	< 12.0 g/dl	< 36.0%

Table 2. Classification of anemia based on MCV and RDW

MCV	RDW	
	NORMAL	HIGH
Low	Thalassemia, chronic infections, sideroblastic anemia	Iron deficiency anemia,
Normal	Anemia of chronic disease, post hemorrhagic anemia, hereditary hemolytic anemias, red cell aplasia bone marrow replacement	Early iron deficiency anemia
High	Reticulocytosis	Megaloblastic anemia (Fig.3) Immune hemolytic anemias

width). Used in the classification of anemias (Tables, 1 and 2) and hence gives clues to the possible etiology. The reference ranges for the various age groups are mentioned later.

MCV : This is the average volume of the red blood cell and is measured directly in automated counters. Manual calculation is as follows:

$$\frac{\text{Hematocrit (l/l)}}{\text{Red cell count (x 1012/L)}} \times 1000$$

The UOM is femtolitres (fl).

MCH: This is a measure of the hemoglobin content per red cell. In automated counters this



Fig. 1 Microcytic hypochromic anemia (peripheral blood smear (PS))

is computed using the measurements of each red cell. Manual calculation formula is:

$$\frac{\text{Hemoglobin (g/dl)}}{\text{Red cell count (x 1012/L)}} \times 10$$

The UOM is picograms (pg)

MCHC: This is the average concentration of hemoglobin per red cell and may be calculated by the formula:

$$\frac{\text{Hemoglobin (g/dl)}}{\text{Hematocrit (L/L)}} \times 100$$

The UOM is g/dl or %



Fig. 2 Normocytic, normochromic anemia (peripheral blood smear)



Fig. 3 Megaloblastic anemia (Bone marrow smear)

RDW : This measurement is the coefficient of variation of the mean corpuscular volume distribution expressed as a percentage. In other words it reflects the range of red cell sizes or anisocytosis measured within a sample.

$$RDW = \frac{\text{Standard deviation}}{\text{mean MCV}} \times 100$$

In normal individuals the RDW from most automated instruments in about 11.5 to 14%⁴.

Classification of anemia based on MCV

If the MCV is less than 80 fl = microcytic (Fig.1)

If MCV ranges from 80 to 100 fl = normocytic (Fig. 2)

If MCV is more than 100 fl = macrocytic

If MCHC is less than 31g/dl and or MCH is 27pg = hypochromia

Reticulocyte count

This parameter is the traditional measure of RBC production and is usually expressed as a percentage of circulating RBCs. However this measurement is affected by the lifespan of the reticulocytes in circulation and by anemia (hematocrit). Hence the reticulocyte production index (RPI) which corrects for both is a more

reliable measure of RBC production. Reticulocyte production index is a measurement which converts reticulocyte count (%) to an index reflecting production with corrections being made for 1. Degree of anaemia 2. Early release of reticulocytes from the marrow. The calculation is as follows :

$$\frac{\text{Reticulocyte \%}}{\text{Retic. maturation time in days (RMT)}} \times \frac{\text{Patients hematocrit (l/l)}}{\text{Normal hematocrit (l/l)}}$$

RMT is 1.0 day when hematocrit is 0.45 l/l, 2.0 days at 0.25 l/l, and 2.5 days at 0.15 l/l. eg. if hematocrit is 0.25 l/l and retic count is 20% then

$$RPI = \frac{20}{2.0} \times \frac{0.25}{0.45} = 5.5$$

Normal RPI is 1 wherein the reticulocyte % is 1, the RMT is 1 day, hematocrit value of the individual is the same as the normal hematocrit.

If the RPI exceeds 3, production of red cells is increased and anemia is due to hemolytic anemia. If RPI is less than 2 a defect in production of red cells (bone marrow failure) is presumed to be the cause of anemia. This anemia could also be due to ineffective erythropoiesis (megaloblastic anemia, thalassemia). To further differentiate between anemia due to bone marrow failure and ineffective erythropoiesis, some centres do measurement of serum transferrin receptors to TfR, TfR is elevated in ineffective erythropoiesis and is reduced in bone marrow failure.

Points to remember while interpreting CBCs with RBC indices

1. In children less than 3 years, MCV is usually lower than 80 fl and at times may even be around 75 fl.

2. The first hematologic manifestation of iron deficiency in children is an increase in the RDW.
3. RDW is increased in iron deficiency anemia and normal in thalassemia. (both microcytic, hypochromic anemias)
4. MCHC is increased in hereditary spherocytosis.
5. Errors due to inherent problems while using automated instruments, in certain clinical conditions, should be kept in mind.



Fig. 4 Acute lymphoblastic leukemia (PS)

A good, well stained, peripheral blood smear is however more useful as along with the differential count morphological changes in the WBCs can be studied simultaneously.

The UOM for the WBC count is $\times 10^9/L$ and % for the differential count. Both these parameters are used most often to support the diagnosis of infections either bacterial or viral.

For example: In children aged 3 to 36 months (febrile, sick child) the total WBC count correlates with the presence of bacteremia.

While blood cell count (TC) and differential count (DC)

White cells are counted after dilution in a diluent that lyses the RBCs both in the manual method and in automated machines. Automated methods of differential counting include a flow through system that identifies cells on the basis of cell size and staining characteristics.

Table 3. Hematologic scoring system for the early diagnosis of neonatal sepsis

Parameter	Finding	Score
Total WBC count	less than 5000	1
	more than 25000 at birth	1
	more than 30000 at 12 to 24 hours	1
	more than 21000 at day 2 onwards	1
Total neutrophil count	No mature neutrophils seen	2
	Increased or decreased	1
Immature neutrophil count	Increased	1
Immature : Total neutrophil count	Increased	1
Immature Mature neutrophil count	more than or equal to 0.3	1
Platelet count	less than or equal to 1.5 lakhs per cubicmm	1
Degenerative changes in the neutrophils	more than 3 + for vacuolation, toxic changes or Dohle bodies	1

Table 4. Some sources of error* in estimating complete blood counts

1. Cold agglutinins	seen in infectious mononucleosis and mycoplasma pneumonia	↓ RBC count ↑ MCV ↑ MCH
2. Fragmented RBCs and very small RBCs	seen in disseminated intravascular coagulation, hemolytic conditions, severe microcytosis	↓ RBC count ↑ Platelet count
3. Platelet clumps Platelet satellitosis	seen when there are small fibrin clots in the blood sample and some EDTA samples	↓ Platelet count
4. Giant platelets	seen in reactive conditions and in platelet function disorders	↑ RBC count
5. Nucleated red cells	seen increased in many conditions, are counted as WBCs	↑ WBC count
6. High blood glucose levels (400-600) uremia	Hyperosmolar plasma causes cell swelling	↑ MCV ↑ Hct
7. Very high WBC counts	when WBC count is more than 50,000 / cumm	↑ Hb ↑ Hct ↑ MCV ↑ RBC count

* The above can be checked by a careful scrutiny of the peripheral blood smear and other appropriate investigations

When the total WBC count is

- more than 15,000 there is 16% incidence of bacteremia
- more than 20,000 there is 25% incidence of bacteremia
- more than 30,000 there is 40% incidence of bacteremia

In bacterial infections there is usually neutrophilia, with increased band or stab forms, and morphological changes like toxic granules, vacuolization and Dohle bodies in the cytoplasm of the neutrophils. In viral infections and enteric fever there is usually a reduced total count or

leucopenia. Lymphocytes are seen increased in viral infections, tuberculosis and pertussis, Eosinophils are increased in parasitic infestations and allergic disorders. In severe sepsis they are reduced in number. Monocytes are increased in conditions like malaria, kala azar, and viral infections. Basophils are increased in myeloproliferative disorders. Haematological malignancies like leukemias are diagnosed by doing the TC and DC.

Platelet count

The normal range is usually about 1.5 to 3.5 or 4 lakhs / mm³. Reduced platelet count or thrombocytopenia is when the platelet count is

Table 5. Pediatric reference ranges for commonly used red cell parameters

Age	Hb g/dl	Hct%	RBC count	MCV fl	MCH pg	MCHCg/dl	Retics %	NRBCs /100 WBCs
Full term newborn	18.4 ± 2.2	61 ± 7.4	5.1 ± 1.0	108 ± 9	35 ± 4	36 ± 2	3.2 ± 1.4	7.0
7 days	17.9 ± 2.5	56 ± 9	5.1 ± 1.0	99 ± 11	32.5 ± 4	35 ± 2	0.5	3-10
2 weeks	15.6 ± 2.6	46 ± 7.3	-	-	-	-	1.0	3-10
3 months	11.3 ± 0.5	33 ± 3.0	4.5 ± 0.7	88 ± 8	29 ± 5	33 ± 3	0.7	0
1 year	11.8 ± 0.5	39 ± 2.0	4.5 ± 0.7	78 ± 8	27 ± 4	32 ± 3	0.9	0
3-6 years	12.7 ± 1.0	37 ± 3.0	4.5 ± 0.7	78 ± 8	27 ± 3	33 ± 2	1.0	0
10-13 years	13.2 ± 1.0	39 ± 3.0	4.7 ± 0.6	86 ± 8	27 ± 3	33 ± 2	1.0	0
Male adult	16.0 ± 2.0	47 ± 5.0	5.2 ± 0.8	85 ± 8	29.5 ± 2.5	33 ± 2	1.0	0
Female adult	14.0 ± 2.0	42 ± 5.0	4.8 ± 0.6	85 ± 8	29.5 ± 2.5	33 ± 2	1.0	0

Table 6. Pediatric reference ranges for commonly used white cell parameters

Age	Total WBC Count 10 ⁹ /L	Neutrophils %	Lymphocytes %	Monocytes %	Eosinphils %
Birth	9 - 30	61	31	6	2
12 Hours	13 - 38	68	24	5	2
24 Hours	9.4 - 34	61	31	6	2
1 week	5.0 - 21	45	41	9	4
2 weeks	5.0 - 20	40	48	9	3
1 Month	5.0 - 19	35	56	7	3
6 Months	6.0 - 17	32	61	5	3
1 Years	6.0 - 17	31	61	5	3
2 Years	6.0 - 17	33	59	5	3
4 Years	5.5 - 15	42	50	5	3
6 Years	5.0 - 14	51	42	5	3
8 Years	4.5 - 13	53	39	4	2
10 Years	4.5 - 13	54	38	4	2
16 Years	4.5 - 13	57	35	5	3

less than 1.5 lakhs/mm³. This is seen in infections, immune destruction and acute leukemias. Thrombocytosis in children is usually reactive as in infections but may also occur in conditions such as hemorrhage, collagen vascular diseases, tumors and drugs. A few clues as to the presence or absence of functional or qualitative platelet disorders can be got by a careful perusal of a well stained, finger prick, peripheral blood smear. Small platelets are seen in Wiskott Aldrich syndrome and giant platelets are seen in reactive conditions and functional platelet disorders.

Complete blood counts in newborns

The CBC is an invaluable tool for evaluating conditions like infections, anemia and jaundice in newborns. It must be kept in mind that premature infants have a lower Hb than term infants and RBCs are usually macrocytic in newborns. The common causes of anemia in newborns are blood loss (due to placental transfusion, fetomaternal hemorrhage, umbilical cord hemorrhage, twin-twin hemorrhage and internal hemorrhage, iatrogenic), hemolysis and

aplasia. Acute blood loss produces a normochromic, macrocytic anemia while chronic blood loss produces a hypochromic, microcytic anemia⁷. The CBC is also useful in the haematological scoring for sepsis in newborns Table 3 and for this the parameters used are: WBC count, Differential count, Platelet count Nucleated red blood cells (NRBC) count, (got from the peripheral blood smear study) and Neutrophil morphology (vacuolation of the cytoplasm, toxic granules etc.),

Peripheral blood smear

Careful evaluation of a well prepared blood smear is a very important part of evaluation of hematologic disease especially in the pediatric age group. Many diseases are diagnosed by looking at the peripheral blood smear (Fig.5 - 8). It also serves as a check to discern the otherwise unexplainable changes and artifactual changes in the CBC. Table 4 (eg. detection of sources of errors in estimating CBCs). Hence it is vital for the clinician to interpret the CBC in the light of the findings in the peripheral blood smear.

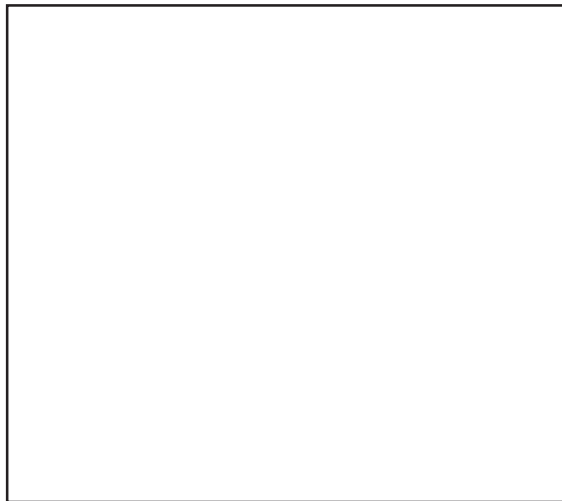


Fig. 5 Hereditary elliptocytosis (PS)

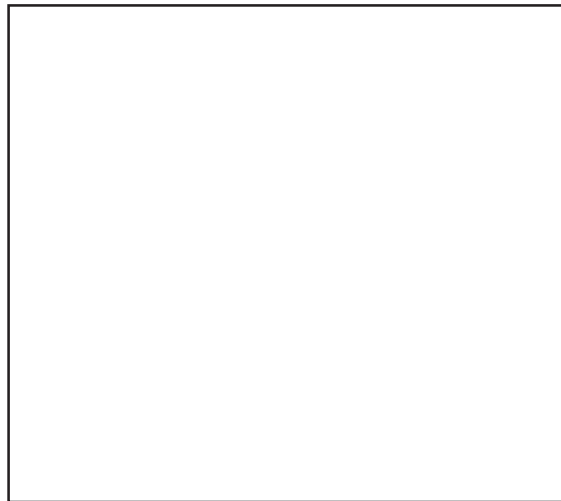


Fig. 6 Sickle cell anemia (PS)



Fig. 7 Malarial parasite (PS)

Fig. 8 Malarial parasite (PS)

Summary - Clinicians and the CBC

1. The CBC is an invaluable diagnostic tool.
2. The clinical should optimize the use of this diagnostic modality.
3. The CBC should be interpreted cautiously in light of the methodology used to do the test and the clinical condition.
4. Interaction between the clinician and the laboratory is very important.
5. No laboratory test can fully replace the role played by a carefully taken history and meticulous physical examination, in diagnosing pediatric ailments.

NEWS AND NOTES

2nd Multidisciplinary CME in Pediatrics 2003

The Department of Pediatrics of All India Institute of Medical Science, New Delhi is organizing the 2nd Multidisciplinary CME in Pediatrics 2003 on March 29-30, 2003 at AIIMS.

The theme of this year's CME is "Pediatric Emergency and Intensive Care". The CME will consist of symposia, case discussions and lectures by distinguished faculty of the Institute. Registration is limited and will be done on 'first come first served basis'.

The registration fee is Rs 750/- for general delegates and Rs 500/- for postgraduate students. The fee should be sent as demand draft drawn in favor of 'CME Program in Pediatrics' payable at New Delhi before 15 February 2003.

For further details or correspondence contact:

Dr. Pankaj Hari or Dr. Rakesh Lodha, Department of Pediatrics, AIIMS, New Delhi 110 029, Phone No. 6561123 (Ext 4858, 3621)

E-mail: pankajhari@hotmail.com, rakesh_lodha@hotmail.com. Fax: 011-6862663.

HEMATO-ONCOLOGY**RECENT ADVANCES IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA**

* ***Kusumakumary P***

Over the past few decades there has been dramatic improvement in the prognosis of children with leukemia. Incremental advances in treatment success span a 30 year period, during which ALL has gone from a uniformly fatal disease to one with an overall cure rate greater than 75%.^{1,2,3} (Fig - 1&2.) The strategic success results from a series of advances like the recognition of diversity of ALL, identification of clinical and biological prognostic factors that resulted in tailoring therapy according to prognostic factors and avoidance of potential late effects of therapy. Improved techniques of supportive care and intensive therapy for recurrent disease have also contributed to treatment success.

ALL is characterised by an excessive accumulation of lymphoblasts within the marrow space and to a variable extent elsewhere. The genesis of childhood ALL is still not known. According to current view the leukemic process is assumed to begin in a single hematopoietic cell of any lineage varying in maturity from the multipotential primitive stem cell to the more differentiated cells. The critical defect is intrinsic to the cell and inheritable by its progeny. Establishment of an accurate diagnosis based on

available morphologic, biologic and cytogenetic data is essential for risk categorization.

Morphologic, immunologic and molecular characterization of lymphoblasts has confirmed that ALL is a biologically heterogeneous disorder. This heterogeneity reflects the fact that leukemia may develop at any point during the multiple stages of normal lymphoid differentiation. Morphologic classification uses the criteria such as cell size, nuclear cytoplasmic ratio, nuclear shape, number and prominence of nucleoli etc. and groups ALL into L1, L2 & L3 (FAB system). Cytochemical stains have been studied but the practical use of this type of information is limited and has been supplanted by more sophisticated immunologic techniques such as immunopheno-typing and cytogenetics.

Immunophenotype

Lymphoblasts express on the cell surface a variety of antigens which correspond to developmental stages of 'T' & 'B' cells. In the early 70's, 3 immunologic subtypes were delineated 'T' cells, 'B' cells and non T/ non B cells or null cells. Using receptors for sheep erythrocytes, approximately 20% of paediatric patients with ALL were found to have 'T' lymphoblasts, cell surface immunoglobulin in 1-2% and the remaining patients were considered to have null cell leukaemia. The development of heterogeneous antisera and monoclonal antibodies against human leukemia associated antigens indicated that approximately 80% of patients formerly presumed to have had null cell ALL had common ALL antigen CALLA (CD-10) on their cell surface. This leukemic subset is now referred to as CALLA +ve ALL. Using a

* Addl. Professor & Head,
Division of Pediatric Oncology
SAT Hospital, Trivandram
Kerala.



Fig.1. Improvement in survival of children with acute lymphoblastic leukaemia (A. Bleyer, H. Sather)

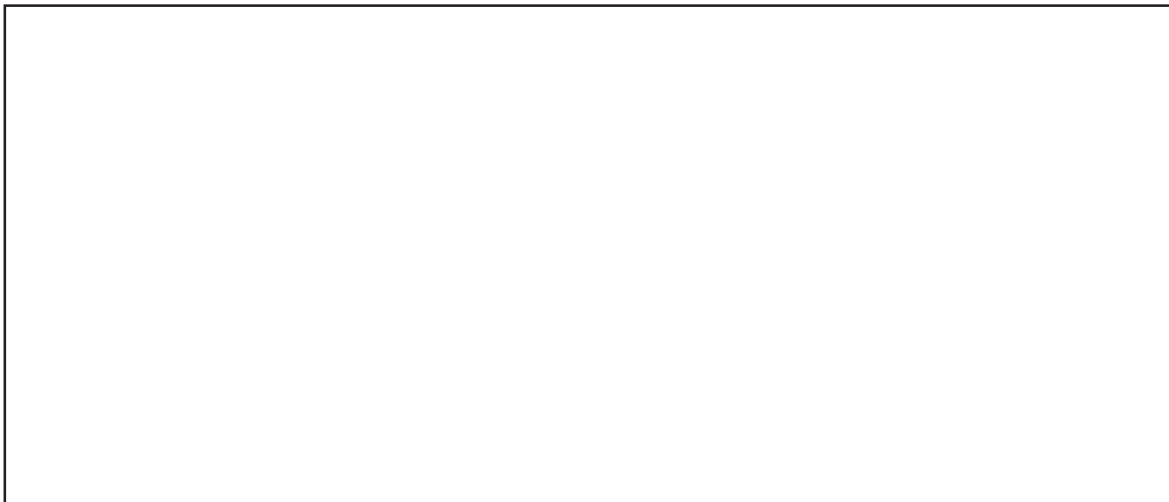


Fig.2. Outcome of 2600 children with acute lymphoblastic leukaemia stratified according to prognostic groups and treated by the Childrens Cancer Study Group (W.A. Bleyer, H. Sather)

panel of monoclonal antibodies associated with various stages of B cell differentiation along with information on the presence or absence of cytoplasmic and surface immunoglobulin investigators have classified B-lineage ALL into discrete stages according to the degree of differentiation or maturation. Although more than 200 different monoclonal antibodies are commercially available that can detect antigens

associated with different haematopoietic lineages, only a few of those antigens are truly lineage specific⁴.

The specific markers are CD-79a for B-lineage, cytoplasmic CD-3 for 'T' lineage and cytoplasmic a -MPO for myeloid cells. The sensitive markers include CD-19 for B - lineage. CD-7 for T - lineage, and CD-13 and CD-33 for

myeloid cells. With this panel a firm diagnosis of ALL is possible in all cases.

Immunophenotyping has the potential to improve risk assessment. Mature B cell ALL has a poorer prognosis than earlier 'B' lineage subgroup. Patients with B cell precursor ALL whose lymphoblast manifest CALLA (CD 10) have a more favourable prognosis. Identification of immunoglobulin gene rearrangement is helpful in confirming the B cell precursor lineage of ALL cells otherwise devoid of other B cell markers. T cell has distinctive immunologic as well as clinical features. 3 stages of normal intrathymic differentiation have been proposed, early, intermediate and late, but prognostically these types are not important as in the case of B cell lineage.

Not all cases adhere to a specific lineage. Expression of myeloid associated antigens on otherwise typical lymphoblasts has been recognised since the early 1980's and is known as mixed lineage leukaemia. The biologic basis for the appearance of mixed lineage leukaemia is not understood.

Cytogenetics and molecular genetics

Lymphoblasts from various patients with ALL differ with respect to DNA content, cytogenetic abnormalities, kinetic properties and cell derivation. All these differences bear on the ultimate clinical manifestation of the disease. Clonal chromosomal abnormalities are found in more than 90% of childhood ALL cases⁵. These abnormalities can be either numerical or structural. In children ploidy is the most important prognostic factor, with hyperdiploidy having a better prognosis. Those is pseudo diploid category with normal chromosome number but other chromosomal abnormalities like translocations have a relatively poor prognosis. The worst prognosis occurs in the rare group of

patients with near haploidy which has an event free survival less than 25%. Translocations are most frequent in the pseudodiploid group and there appears to be an association between certain translocations and immunophenotypes. The t.(8;14), t.(4;11) and t.(1;19) are associated with high rates of early treatment failure but the most common ALL translocation t.(12;21) appears to have a good prognosis. The t.(9;22) (philadelphia chromosome) was one of the first leukaemic translocation described and remains the translocation with the worst prognosis in paediatric ALL. One exception is a subset of children with philadelphia chromosome positive ALL and low presenting leukocyte count or good initial response to prednisolone therapy who appear curable with intensive chemotherapy alone.

Molecular analysis has proved indispensable for identifying certain prognostic and therapeutically important genetic subtypes of ALL. E.g. Childhood ALL associated with cryptic translocation, t.(12;21) (p13.q22) results in a fusion gene TEL - AML1 which confers a favourable response to treatment. The t (1;19) (q23; p13) translocation results in fusion of the transcriptional activation domain of E₂A on chromosome arm 19 p with the DNA binding homeodomain of PBX located on chromosome 1 and the ALL cases that express E₂A-PBX protein appear to have a poor prognosis. Approximately three quarters of childhood ALL cases have identifiable specific genetic abnormalities with prognostic relevance⁶.

Pharmacogenetics

The field of pharmacogenetics studies the genetic basis for the difference between individual responses to specific drugs. It is reasonable to assume that individual patients will demonstrate differences in drug metabolism and response which may have important effects on therapeutic efficacy and toxicity. One of the best

examples of pharmacogenomic effects in ALL relates to the isoforms of thiopurine methyl transferase (TPMT). This is a crucial enzyme that metabolizes parent 6 - mercaptopurine into an inactive metabolite. Patients homozygous for TPMT null mutation have been shown to have severe 6MP related toxicity, whereas heterozygous patients appear to have moderate toxicity with 6MP⁷. Again, patients with TT genotype were reported to have an increased risk of methotrexate induced oral mucositis.

Risk classification

It is common practice to assign patients on the basis of prognostic factors into different risk groups and to tailor therapy accordingly. Unfortunately there is no consensus on specific risk criteria and the terminology that best defines the relapse hazard in discrete group of patients. Initial leucocyte count and age at diagnosis have traditionally provided the most reliable basis for patient stratification. Age between 1 & 9 years and a leukocyte count $<50 \times 10^9/L$ are commonly used as minimal criteria for low risk B-Cell precursor ALL. In the vast majority of clinical trials, T-cell ALL is considered to carry a standard risk of relapse and is treated accordingly. Among other clinical and biologic variables that might be used to guide the selection of treatment, early treatment response as indicated by the rate and degree of clearance of leukaemic cells from blood or bonemarrow during the early phase of remission induction therapy is perhaps the most important⁸. This factor shows independent prognostic significance in both B-cell precursor and T-cell ALL, with slow early response conferring a poor prognosis.

Minimal residual disease (MRD)

The availability of immunologic and molecular techniques has increased our ability to detect residual disease at levels below the sensitivity of morphologic evaluation. These

techniques include cytogenetics, flow cytometric sorting and immunophenotyping, clonogenic assays and detection of leukaemia specific DNA or RNA sequences by southern blot or polymerase chain reaction. The most widely applicable system available for the measurement of MRD involves polymerase chain reaction of gene rearrangements. The risk of relapse as defined by MRD analysis was more accurate than that achieved by clinical methods, but single time point analysis fails to account for the efficacy of subsequent treatment. It is becoming clearer that the rapid lowering of MRD levels below 10^{-4} correlates well with relapse free survival⁹. Conversely patients with whom MRD doesn't clear below this point or more slowly goes below the same level have a higher risk of relapse. Multiple issues remain to be clarified and eventual applicability in clinic are still under investigation.

Advances in treatment

The treatment should be specific and intensive enough to induce a complete remission and attempt a cure by keeping the child in remission long term. Since ALL is a heterogeneous disease, it is inappropriate to give single treatment regimen for all children with ALL.

Infants with ALL are often considered to be a unique subgroup and treated with intensive chemotherapy. ALL-L3 is again a separate entity and should be treated with short term intensive chemotherapy as for B Cell lymphomas. Most investigators would divide the remaining cases of ALL into low risk, standard risk and high risk groups. Unfortunately there is no uniform criteria for defining ALL risk groups.

Irrespective of the risk group for which it is intended, all treatment regimens embody 4 major phases; remission induction, CNS preventive therapy, consolidation and maintenance therapy. In patients with high risk ALL, intensive

remission induction seems to have improved treatment outcome. Less intensive remission induction may be sufficient for low risk cases provided they are given post induction intensification therapy.^{2,3} In the clinical trial by the Childrens Study Group it was observed that intensive induction - consolidation therapy did not add benefit to 'intermediate risk' patients who received delayed intensification therapy. Most remission induction regimens include minimum of 3 drugs and maximum of 5 drugs. Recently dexamethasone has replaced prednisolone as a glucocorticoid of choice to improve outcome, but dexamethasone may be associated with higher acute and long term complication rates. Failure of induction therapy occurs in less than 5% of children with ALL.

With the recognition that cranial radiation predisposes to neuropsychiatric and neuroendocrinologic disturbances in young children, alternative CNS prophylaxis approaches were evaluated. Several randomised studies demonstrated that cranial radiation could be eliminated in children with low and intermediate risk ALL if intrathecal methotrexate is continued at intervals throughout maintenance. Investigators of the Berlin-Frankfurt-Minster consortium has demonstrated that a radiation dose as low as 12Gy, together with intrathecal methotrexate and effective systemic chemotherapy can provide adequate CNS control even in patients at high risk of CNS relapse¹⁰.

Early studies demonstrated that without additional therapy, most patients relapse within a median period of 1-2 months. To effectively prevent relapse, post induction therapy must suppress leukaemic growth and provide continuing leukaemic cytoreduction without permitting the emergence of a drug resistant clone. The first strong proponents of the benefits of this phase of therapy were the West German BFM group. Now most investigators agree that

intensification therapy is necessary to maximise early cell kill. Delayed intensification, double delayed intensification and so called protocol III were demonstrated to improve outcome further¹¹. Treatment strategies differ, optimum timing, dose intensity are yet to be clarified.

Methotrexate administered weekly and 6 - Mercaptopurine given daily constitutes the standard back bone of continuation treatment. Tailoring doses to the limits of tolerance has been associated with improved outcome. The addition of intermittent pulses of vincristine and prednisolone to the antimetabolite regimen improves survival. The optimal length of maintenance chemotherapy has not been established. It is likely that intensification of therapy has a bearing on the optimal duration of therapy¹². Most centers treat patients for a total of approximately 2.5 to 3 years. Attempts to shorten the treatment duration to 12 months or 18 months have resulted in inferior overall event free survival in two randomized trials. Philadelphia chromosome positive leukaemia is the only subtype of childhood ALL that clearly benefits from allogeneic bonemarrow transplantation from an HLA matched donor.

Treatment of relapse

Bone marrow relapse is the principal form of treatment failure in patients with ALL. Marrow ablative chemotherapy followed by allogeneic transplantation of stem cells is the ultimate form of treatment intensification and is therefore preferred treatment for patients with early bone marrow relapse who have attained a second remission. Patients with late bone marrow relapse should be treated with intensive chemotherapy alone because they have a reasonable chance of cure with intensive chemotherapy.

Complications of therapy

Delayed sequelae observed in survivors of ALL include second neoplasm, neuropsychological changes, endocrine

dysfunction and cardiomyopathy. Long term neurologic and neuropsychological functioning may be impaired following CNS therapy even when irradiation is avoided.

Future challenges

The major issue in the therapy of ALL is how to improve the outcome of high risk children. Current investigations have focused in the use of newer therapeutic agents and interventions based on the persistence of MRD. The role of multidrug resistance in ALL remains to be determined. Newer chemotherapeutic agents undergoing trials in ALL include carboplatin and the combination of ifosfamide and etiposide. The use of monoclonal antibodies to deliver toxins directly to the leukaemic cell is undergoing active exploration.

A recent report demonstrated that childhood ALL has an angiogenic phase suggesting a therapeutic role for anti angiogenic drugs such as endostatin. Perhaps the most exciting approach to prevention of relapse lies in the use of novel tumour vaccines that are designed to prevent relapse by stimulating the host immune response to leukaemic cells.

The current research in developing gene therapies like suicide gene insertion, antisense modulation, antigen upregulation or biologic modifiers of disease progression, including immunotoxins or differentiating agents will add to out potential for making leukaemia another childhood illness that can be conquered.

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CRITICAL CARE**HYPOVOLEMIC
HYPERNATREMIC
DEHYDRATION IN INFANTS**

* *Nair PMC*

Dehydration is classified as isotonic, hypotonic or hypertonic, based on the serum osmolality. Hypernatremic dehydration is usually caused by gastroenteritis, but can result from other causes also (Table 1). This type of dehydration is very dangerous. The hyperosmolar state can lead to brain shrinkage, venous thrombosis and subdural capillary hemorrhage. In addition, rehydration can cause cerebral oedema and subsequent seizures. At the same time early recognition is extremely difficult and dehydration is often missed. Hence awareness is very important for the general pediatrician so that early treatment is possible to avoid the fatal complications.

Hypovolemic hypernatremia is the commonest in pediatric practice, the most common cause being acute gastroenteritis, where the water loss is far greater than salt loss. 90% of cases occur in children below 2 years and the worst outcome is in babies less than 6 months^{1,2,3}. We had a few cases of rotavirus gastroenteritis with associated hypernatremia. Similar reports are there in literature^{4,5}.

Iatrogenic cases due to formula feeds and treatment of diarrhoea with wrong dilution of oral rehydration solution has also occurred in our

experience with infants. The formula-fed infant is at higher risk of hypernatremic dehydration during common situations which reduce body water (reduced intake, increased evaporative water loss due to fever or elevated environmental temperature and diarrhoea)³. Infants with hypernatremic dehydration secondary to so called lactation failure are typically encountered during the first and third weeks of life⁶. These infants are strikingly lethargic, dehydrated and malnourished with a weight loss equal to or more than 10% of the body weight. The first signs of neonatal dehydration include failure to have bowel movements or the presence of urate crystal, combined with weight loss⁷. Daily weight evaluation, careful breastfeeding assessment and early routine postpartum follow-up are effective methods to prevent hypernatremic dehydration and promote breastfeeding.

Why hypovolemic hypernatremic dehydration most common in infants?

Infants are worst affected with hypovolemic dehydration, because of (a) immaturity of the kidney to excrete an excess sodium load, (b) limited ability to express thirst and (c) reliance on others to provide appropriate fluids⁷.

Early recognition is extremely difficult and dehydration is often underestimated, as water shifts from the intracellular to the extra-cellular compartment. There may be fever, tachycardia with poor perfusion and hypotension with hypovolemia. The skin appears thick, doughy and may even be warm. The mucous membrane is dry, with depressed fontanel and sunken eyes. An important finding is intense thirst. Once

* Consultant, Neonatal & PICU,
Child Health Department,
Sultan Qaboos University Hospital,
Muscat, Sultanate of Oman

Table 1. Hypernatremic dehydration

I. Hypovolemic hypernatremia (loss of water in excess of salt)	
1. Extra - renal loss	: GI loss: vomiting, diarrhoea
2. Cutaneous loss	: Excessive sweating: extensive burns, increased insensible water loss in ELBW babies.
3. Third space loss	: Ileus, Peritonitis
4. Renal loss	: Osmotic diuresis secondary to glucose, Mannitol, urea
II. Euvolemic hypernatremia (Pure water loss)	
1. Insensible loss	: Fever, high ambient temperature, hyperventilation
2. Renal loss	: Central and nephrogenic diabetes insipidus
3. Insufficient fluid intake	: Decreased level of consciousness Lack of access to water
III. Hypervolemic hypernatremia (Pure sodium excess - Usually iatrogenic)	
1. Salt poisoning	: Hypertonic IV solutions; incorrect preparation of infant formula / ORS
2. Mineralocorticoid excess	: Cushing syndrome
3. Salt water drowning	

Table 2. Diagnostic approach

1. Careful History
2. Assessment of clinical volume status
3. Neurologic examination
4. Determination of serum electrolyte and blood urea nitrogen
5. Determination of plasma glucose
6. Determination of serum osmolality
7. Simultaneous determination of urinary electrolyte
8. Blood gas estimation for base deficit.

serum Na is > 145 mmol/L or osmolality is > 300 mOsm/kg, the thirst center in hypothalamus is stimulated and water will then be ingested. Another mechanism tightly controlling serum osmolality is the release of Anti-Diuretic Hormone from the neurohypophysis making the kidney to concentrate urine, thus conserving free water^{3,8}.

Complications

The most hazardous effect of hypernatremia is on the brain. During the development of

hypernatremia, brain cells shrink leading to rupture of bridging vessels with hemorrhages (subarachnoid and parenchymal), thrombosis and occlusion of dural sinuses^{8,10,11}. During rapid rehydration with relatively hypotonic IV fluids, excess water enters the cerebral cells, leading to rebound cerebral oedema and seizures.

Permanent cognitive impairment, cerebral dysfunction, spastic hemi and monoplegias and seizure disorders have been reported. Children with early neurologic symptoms have a 50% chance for neurologic sequelae¹⁰. Extensive lateral, central pontine and extra-pontine myelinolysis have been reported^{12,13}. Renal vein thrombosis and renal tubular injury may also occur¹⁴. hyperglycemia and hypocalcemia can occur¹⁵. Mortality in acute case with serum Na > 160 mmol/L is around 45% (10-70%), while it is around 10% in chronic hypernatremia¹⁶.

Calculation for volume and water deficit is done in the following steps

I. Consider percentage of dehydration (10%)

II. Then calculate free water deficit in 3 steps

a) Usual (normal) total body water (TBW) = weight g x 0.6 (L)

b) Current TBW

$$= \text{normal TBW} \frac{\text{measured Na cone}}{\text{Normal Na cone}}$$

(Even osmolality can be considered in the place of Na)

c) Free water deficit = Normal TBW - Current body water.

III. A simple calculation for free water deficit is

4 ml x weight x (sodium difference (deficit) if Na below 170 mEq/L)

If serum Na > 170 mEq/L it is 3 ml x weight x Na difference ^{21,22}.

IV. Free water has to be calculated, without electrolytes.

V. The rest of volume is calculated with electrolytes

VI. Combined deficit and maintenance fluid works out roughly, 1/4 to 1/3 isotonic, when run in over 24-48 hours.

Considering the above points, therapy guidelines are as follows:

Therapy Guidelines

1. Immediate rehydration

The first priority in a dehydrated patient is restoration of intravascular volume. Give 20 ml/kg normal saline (0.9% sodium chloride) or Ringer lactate sodium over 30-45 minutes. If the response is poor, repeat a bolus of 10 ml/kg over 30-45 minutes.

2. Correction of sodium and water deficit

Once the patient is stable, correct serum

sodium slowly over 48-72 hours with 5% Dextrose and 0.45% sodium chloride solution. The rate of reduction of serum Na should be less than 0.5 mmol/hour and should not exceed 10 mEq/L/24 hours. If extracellular osmolality is decreased rapidly, an osmotic gradient may develop between the brain and plasma resulting in a net movement of water into the brain producing cerebral edema, seizures and even permanent neurologic sequelae and death. Avoid hypotonic solution. Initial fluids should have sodium concentration of 75 mEq/L.

3. Maintenance fluids and electrolyte must be given in addition to calculated water deficit in quantities sufficient to replace urinary output and insensible losses.

Maintenance fluids

< 10 kg = 100 ml/kg/24 hrs.

for each kg above 10 kg

11-20 kg = 50 ml/kg/24 hrs + 1000 ml

21 kg and above = 20 ml/kg/24 hrs for each kg above 20 kg + 1500 ml

4. Oral rehydration solution

When Na level has decreased to 150 mmol/L, oral fluids can be substituted. (Oral rehydration solution 10 ml/kg with each diarrhoeal stool). Appropriate and slow reduction in serum Na level has been attained with classic WHO ORS as well as with rich starch based, low sodium (60 mmol/L) ORS with less incidence of complications ^{17,18,19}.

5. Treatment of complications

If seizures occur, treat carefully with anticonvulsants, IV 3-5 ml/kg of 3% sodium chloride, mannitol or hyperventilation and close monitoring of serum Na.

6. Dialysis

In acute severe hypernatremia with serum Na > 300 mmol/L peritoneal dialysis with 4.5 initially and later 1.5% dialysis fluid is recommended.

Hemodialysis and hemofiltration have been successfully tried²⁰, but venoarterial access may be difficult.

Hyperglycemia more often is an accompaniment more so when the serum Na is very high. Primary correction is not attempted. But occasionally it is done but with great caution. Hypocalemia may also occur which is to be treated cautiously.

Conclusion

Hypovolemic hypernatremic dehydration in an infant is an acute medical emergency and should be diagnosed and treated promptly, as mortality is around 45% and can be as high as 70%. Diagnosis is extremely difficult and dehydration is most often underestimated. Complications result not only from hypernatremia but from aggressive and inappropriate rehydration. The serum sodium should be lowered slowly and cautiously using the fluid that will not drop the serum sodium level by more than 10 mmol/24 hrs.

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PRACTITIONER'S COLUMN

APPROACH TO THE CHILD WITH FEVER AND RASH

* ***Benjamin B***

Introduction

The child with febrile illness and rash is a common problem presenting to the pediatrician. The medical literature is replete with elegant descriptions of the classical infectious exanthems.

The field of childhood febrile rash syndromes is an evolving one with several new developments over the years. Improved living standards and widespread immunization have contributed to eradication or reduced prevalence of some febrile exanthems¹. On the other hand, fresh challenges are posed by the spectrum of new and emerging infections². There is also concern about the reemergence of old diseases in new locations or in more virulent forms³. New syndromes have been recognized and known clinical entities have had their etiological association with viral agents defined⁴. The role of toxins and immune mechanisms in the pathogenesis of disease has been the subject of study^{5,6}. In this evolving context, this article seeks to provide an overview of this topic that focuses on a clinical and differential diagnostic approach to the problem.

It would be pertinent to mention certain aspects of febrile rash syndromes that might have a bearing on their evaluation. A specific clinical syndrome may have several predisposing causes.

Conversely, a specific agent may be associated with more than one syndrome. Gianotti-Crosti syndrome (GCS) has, for example been associated with several agents including hepatitis B, Epstein-Barr (EBV) and Coxsackie virus. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema nodosum are examples of hypersensitivity disorders that may be triggered by factors as diverse as infections, drugs, connective tissue disease and malignancy. Human herpesvirus 6 (HHV-6) may cause classical roseola or, rarely, an infectious mononucleosis (IM)-like syndrome (4). Variations in host-parasite interactions may lead to varied spectrum of presentation of a specific illness, ranging from subclinical to disseminated and fatal disease.

Classification

Fever and rash are featured in a large and diverse number of conditions. Table 1 provides a classification of categories of such diseases, with representative examples in each category. Infectious diseases remain a predominant cause of febrile illness with rash in children throughout the world, particularly in developing countries. There are geographic variations in the prevalence of specific illnesses and the physician should familiarize himself with exanthems that are common in his area of practice.

Pathogenesis of rash

There is now a better understanding of the mechanisms involved in the production of rash and other manifestations of many childhood exanthematous illnesses, though many questions remain unanswered. The superantigen theory

* Consultant Pediatrician,
Malar Hospitals, Chennai - 20.

Table 1. Classification of illness associated with fever and rash

Infections	
Viral	Bacterial
Varicella	Scarlet fever
Measles	Scalded skin syndrome
Rubella	Toxic shock syndrome
Roseola (HHV-6, HHV-7)	Meningococemia*
Erythema infectiosum (Parvovirus B19)	Gram negative sepsis*
HFM disease (Coxsackie A16 virus)	Infective endocarditis*
Enteroviral exanthems	Spirochetal infections*
HSV infections	Leptospirosis
Infectious mononucleosis (EBV)	Syphilis
Viral hemorrhagic fevers (e.g. Dengue)*	Lyme disease
Hepatitis B	
Rickettsial, Fungal, Heminthic and Protozoal infections	
Inflammatory disease	
Systemic-onset juvenile rheumatoid arthritis (Still's disease)	
Systemic lupus erythematosus	
Vasculitis syndromes: e.g. Kawasaki disease, Henoch-Schonlein purpura *	
Inflammatory bowel disease	
Malignancy: e.g. Leukemia, lymphoma	
Miscellaneous	
Histiocytosis syndromes	
Erythema multiforme major (Stevens-Johnson syndrome)	
Toxic epidermal necrolysis	

* Conditions Commonly associated with purpuric rash.

postulates that a bacterial exotoxin stimulates immune activation and release of cytokine mediators, which results in rash or vasculitis that characterizes the disease⁵⁻⁷. Examples include erythrotoxic toxins A - C in scarlet fever, toxic shock syndrome (TSS) toxin-1 in staphylococcal TSS, exfoliative toxins A and B in staphylococcal scalded skin syndrome (SSS) and an unidentified toxin in Kawasaki disease (KD). In dengue fever, the hemorrhagic/shock variant occurs in individuals who have developed non-neutralizing antibodies from a primary infection when a secondary infection with another serotype leads to immune enhancement of viral replication⁸. Hemorrhagic rashes are mediated by thrombocytopenia, vasculitis or coagulopathy.

Clinical presentation

Knowledge of the natural history and the course of specific childhood illnesses with fever and rash should form the basis of a proper evaluation of the problem. Detailed history and diligent physical examination will enable recognition and differentiation of most childhood febrile rash syndromes. Table 2 lists relevant aspects of history and examination that merit special attention.

History

Certain exanthems have typical age distribution patterns. Roseola occurs in infancy. KD predominantly in children under five years.

Table 2. Relevant history and physical examination in a child with fever and rash

History
Age and sex
Contact history
Immunization history
Past history of specific exanthems
Recent medications (e.g. Antibiotics, anticonvulsants, sulphonamides etc)
Recent travel
Underlying illness (e.g. Immunodeficiency, heart disease, bowel disease etc.)
Prodrome
Fever, associated symptoms, sequence of events
Rash
Onset, nature, distribution, evolution and resolution
General examination
Vital signs, cardiorespiratory status, sensorium
Systemic examination
Evidence of organ involvement

and infectious mononucleosis in older children and adolescents. The age distribution of scarlet fever reflects that of streptococcal throat infections. Transplacental immunity protects the young infant against a variety of viral exanthems. A susceptible neonate may however experience disseminated forms of varicella and herpes simplex virus (HSV) infections. As several of these infections are highly contagious, history of contact with a case in the household, school or day-care setting would be relevant. An immunization history may be sought for the vaccine-preventable diseases such as measles, rubella and varicella. A recent drug history would be relevant as antibiotics, often prescribed for children with fever, might be responsible for an allergic rash.

Prodrome

A detailed elucidation of the duration, severity, symptoms and sequence of events in the prodromal (pre-rash) stage of the illness may provide early clues to the diagnosis. Certain

illnesses such as rubella and varicella are associated with short and mild prodromal phase. In some bacterial infections such as meningococemia and scarlet fever, the brief prodrome is associated with severe constitutional symptoms. The prodromal stages of measles and roseola have a similar duration of 3-4 days, but strikingly different symptomatology. The former is associated with florid symptoms of respiratory and conjunctival catarrh in contrast to the paucity of findings to explain the fever in the latter. The chronic inflammatory diseases tend to follow a course of prolonged pyrexia with rash appearing at a variable stage in the illness.

Rash

The stage of rash is often the defining part of the illness. A detailed evaluation of the nature of the rash including its onset, distribution, evolution and resolution is often of diagnostic help. The presence of associated mucosal lesions (enanthem) and involvement of other organs and systems will also need to be assessed.

Erythematous maculopapular rashes are seen in many childhood exanthems such as measles, roseola and rubella. 'Scarlatiniform' denotes a punctate papular eruption in an erythematous background that is typically seen in scarlet fever, but also occurs at the onset of staphylococcal and streptococcal toxin-related SSS and TSS. Lesions with clear centers and active erythematous margins are featured in rheumatic fever and Lyme disease. Acute meningococemia is heralded by purpuric rash, which may progress rapidly to confluent skin necrosis (purpura fulminans). Allergic vasculitides such as Henoch-Schonlein purpura (HSP) are associated with palpable purpura. Examples of vesicular eruption include varicella-zoster and HSV infections, hand-foot-mouth (HFM) disease and Steven Johnson Syndrome whereas large bullae are seen in SSS and Toxic Epidermal Necrolysis. An infiltrative type of rash is seen in histiocytosis and the malignancies.

Distribution of rash

A generalized rash distribution is seen in measles, scarlet fever and disseminated HSV infections, whereas a central, predominantly truncal, rash is noted in varicella, roseola and Still's disease. A peripheral distribution with acrodermatitis and relative sparing of the trunk is a feature of GCS and HFM disease and late KD. Prominence of rash in the flexures is a feature of scarlet fever (Pastia's lines) and SSS and an extensor distribution over the limbs is seen in HSP, erythema nodosum and the later stages or erythema infectiosum. A localized skin lesion is a feature of Lyme disease (erythema migrans), herpes zoster (dermatomal distribution), anthrax, streptococcal erysipelas and pseudomonal ecthyma gangrenosum.

Evolution and resolution of rash

Several childhood exanthems follow a characteristic pattern of evolution that aid in their

recognition. The rash of measles, for example, commences over the hairline of the forehead and neck and progresses caudally over the face, trunk, upper and lower limbs over a 3-day period. Fine desquamation and residual brown staining characterize the convalescent stage. In varicella, there is rapid evolution of each lesion through stages of macule, papule, vesicle, pustule, umbilication and scab over a 24 - 48 hour period. The lesions appear in crops over a 3 - 4 day period resulting in a characteristic pleomorphic appearance. The 3-stage rash of erythema infectiosum evolves from erythema of the cheeks to a generalized maculopapular rash, which then gradually fades centrally to leave a reticulated lacy pattern over the limbs. In dengue, the eruption mirrors the biphasic course of the illness; a transient generalized macular erythema at the onset is followed by a maculopapular rash in the secondary phase. It becomes purpuric in the few patients who develop a hemorrhagic diathesis. In KD, a truncal maculopapular or polymorphous rash is followed in the second week by painful edema and erythema of the distal extremities, which progresses to the characteristic periungual desquamation. The eruption of SSS evolves from painful scarlatiniform erythema to flaccid blister formation. Resolution is by generalized desquamation with crusting and fissuring around the mouth and eyes. A desquamative resolution is also seen in scarlet fever, TSS and TEN.

A polymorphic eruption and the characteristic 'target lesions' are seen in SJS, whereas in GCS, there are monomorphic firm, flat-topped dusky papules that later turn purpuric.

A **typical facies** is seen in some febrile rash syndromes. A malar rash is noted in systemic lupus erythematosus (SLE) (butterfly distribution) and early erythema infectiosum (slapped-check appearance). A flushed appearance of cheeks with circumoral pallor is a feature of scarlet fever. Periorbital and perioral

crusting gives the face a characteristic appearance in children with SSS.

In many childhood exanthems such as measles, erythema infectiosum, varicella, roseola, scarlet fever, SSS, TEN and HSP, the presence of rash is invariable and essential for the diagnosis. In certain conditions, cutaneous manifestations are present in a variable proportion of cases and their diagnosis is based also on other criteria. For example rash is reported to occur in a majority (80-96%) of children with SLE⁹ and Still's disease (95%) but is only an occasional feature of other illnesses such as leptospirosis (10%). The overall incidence of rash in Infections Mononucleosis is 3-13%; this rises to 90% in patients administered ampicillin or amoxycillin and the reason for this phenomenon remains unexplained.

Enanthem

Involvement of mucocutaneous junctions is a salient feature of some childhood febrile exanthems and their appearance may be sufficiently distinctive to be of diagnostic help. In measles, conjunctivitis is accompanied by stomatitis and the pathognomonic Koplik spots. Congested pharynx and 'strawberry' tongue are common to scarlet fever and KD. In the latter condition, these are accompanied by non-exudative conjunctivitis and cheilitis. Primary HSV infections involve the eyes or mouth (HSV-1) or genitalia (HSV-2). These sites may also be involved in SJS, TEN and TSS. Oral ulcers accompany the acral lesions in HFM disease. It is, therefore, evident that the clinical evaluation of a child with fever and rash in incomplete without a thorough examination of mucosal sites for 'hidden' lesions.

There may be associated involvement of other specific organs and systems whose recognition may provide additional diagnostic clues. Exudative tonsillitis is a feature of scarlet

fever and IM. Cervical or generalized lymphadenopathy may accompany a variety of infections such as rubella, IM and syphilis as well as in inflammatory disorders such as KD and Still's disease. Hepatomegaly with or without splenomegaly may be present in IM, leptospirosis, still's disease and GCS. Chronic symmetrical polyarthrititis is a cardinal feature of Still's disease. Arthropathy is also featured in many inflammatory and connective tissue disorders and some infections such as rubella and parvovirus B19 infections in older girls. Severe myalgia is present in leptospirosis, TSS and dengue. Myopericarditis is noted in rheumatic fever and some enteroviral syndromes. Polyserositis may complicate Still's disease, SLE and dengue shock syndrome. Nephropathy is a feature of SLE, HSP and leptospirosis, Encephalopathy with convulsions may complicate several viral and rickettsial infections. Multisystem involvement is a feature of disseminated varicella and HSV infections, leptospirosis, TSS and the chronic inflammatory disorders. A progressive course leading to shock and multiorgan failure is noted in meningococcal and gram-negative sepsis, TSS and the viral hemorrhagic and shock syndromes.

Drug reactions

Adverse reaction to drugs is often overlooked as a cause of fever and rash in children. The mechanism is often related to allergy by any of the known mechanisms of hypersensitivity. In some instances, as in ampicillin-induced rash, the pathogenesis is unknown. The rash is usually urticarial or maculopapular, but may be vesicular, hemorrhagic, desquamative, nodular or polymorphous. It may present as a recognizable clinical syndrome as in SJS, TEN, serum sickness, photodermatitis, exfoliative dermatitis or fixed drug eruption. Predisposing factors include past or family history of drug allergy and

underlying immunodeficiency. Drug-related factors predisposing to rash include dose, frequency, duration and route of administration. Topical application is most likely to sensitize, oral administration least so. Commonly implicated drugs include antibiotics, sulphonamides and anticonvulsants. The incidence of antibiotic-associated fever and rash is estimated to be 0.2-1.6%¹⁰. Diagnosis rests on careful history, clinical suspicion and exclusion of other causes. Discontinuation of the offending medication would usually result in quick resolution.

Diagnosis

Many childhood exanthems such as measles, varicella, roseola, erythema infectiosum and HFM disease follow a fairly typical pattern and this permits a purely clinical diagnosis of these entities. Diagnostic criteria combining clinical and laboratory features have been accepted for diseases such as rheumatic fever, SLE and KD, which have varied features and no specific diagnostic test^{11,12}.

Hematological variations are common and may serve as useful adjuncts to diagnosis, though they are neither constant nor specific. Significant elevation of erythrocyte sedimentation rate is seen in the inflammatory disorders and malignancies and is used to monitor disease activity and progress. Various cytopenias are noted in viral infections and SLE. Neutrophilia occurs in Still's disease, KD, rheumatic fever and most bacterial infections (unless overwhelming). Marked thrombocytosis is characteristic of KD. A peripheral smear would provide diagnostic clues in infectious mononucleosis and leukemia. The coagulation profile would be deranged in children with fever and a hemorrhagic rash.

Serologic tests for high or rising antibody titres are used for detection of viral, spirochetal or rickettsial infections and autoantibody tests may aid the diagnosis of connective tissue

diseases. Smear from the cutaneous lesion may prove useful in meningococemia (gram stain), rickettsial infection (immunofluorescence), varicella (Tzanck smear) and HSV infections. Bacterial cultures can be taken from appropriate sites such as the blood, skin lesions, CSF and pharynx in bacterial infection syndromes. Newer techniques such as polymerase chain reaction are being used for a widening variety of infections though their availability and cost may be limiting factors. More extensive investigation including imaging, bone marrow aspiration and diagnostic biopsies would be considered for a few children with unexplained fever and rash to exclude infection, inflammatory disease or malignancy.

Diagnostic dilemmas

These arise on account of atypical presentations of the classic exanthems or overlapping features between various exanthematous illnesses. Measles, for instance, may be attenuated in children with partial immunity acquired passively transplacentally or actively through past infection or immunization. At the other end of the clinical spectrum, a severe hemorrhagic form of measles with high mortality is recognized in malnourished, immunocompromised children. SJS may present without rash and with stomatitis as its sole manifestation in up to 25% cases, making it difficult to differentiate from other conditions such as herpetic gingivostomatitis. Parvovirus B19 may be confused with SLE as both have, in common, manifestations such as fever, malar rash, arthropathy, anemia and induction of autoantibodies¹³. Confluent skin erythema and tenderness progressing to bullae are common to SSS and TEN. KD may mimic other exanthems such as scarlet fever and leptospirosis because of overlapping features. In immunodeficient patients, diagnostic difficulties occur because of atypical presentation and protracted courses of infection.

Management

The management is largely symptomatic and supportive in the self-limited viral exanthems. Antipyretic measures may be used, particularly in those prone to febrile convulsions. Maintenance of skin hygiene, and antipruritic measures would help prevent secondary infection from breakdown of cutaneous barrier in children with vesiculobullous eruptions such as varicella, SSS, SJS and TEN. Attention to hydration and nutrition is important in children with poor intake on account of stomatitis in measles, SJS and HSV infection and with excessive skin fluid losses in those with extensive bullous eruptions.

A more aggressive management approach including ventilatory and circulatory support is warranted in patients with a progressive course and potentially life threatening complications such as bleeding, shock, respiratory failure, encephalopathy or multiorgan dysfunction syndrome. The various hemorrhagic and toxic shock syndromes come under this category.

Specific management

Antimicrobial drugs are used in the management of specific infections. Examples include penicillin for meningococemia, scarlet fever and spirochetal infections, cloxacillin for eradicating the primary infective focus in TSS and SSS and appropriate antibiotics in infective endocarditis, sepsis in immunocompromised hosts and secondary bacterial sepsis in conditions such as varicella, SJS, TEN and SSS. Acyclovir reduces mortality and morbidity in disseminated HSV and varicella in immunocompromised hosts. When varicella is anticipated to be more severe as in adolescents, adults and secondary cases in the family, early use of acyclovir within 24 hours of onset of rash has been shown to abort its progress¹⁴. Antimicrobial drugs against fungal, protozoal and viral infections are available for a

variety of infective complications in immunodeficient children with fever and rash.

Other examples of specific management modalities include the use of intravenous immunoglobulin in KD¹², blood components in coagulopathic states and the use of steroids, immunosuppressive and non-steroidal anti-inflammatory drugs in the chronic inflammatory and connective tissue diseases¹¹.

From a management perspective, it would be useful to differentiate the following groups of children presenting with fever and rash:

1. Known viral or virus - associated syndrome which can be identified because of its distinctive clinical morphological pattern and which is expected to follow self-limited natural course. Clinical diagnosis and supportive treatment would suffice in this group. Examples in this category include classical measles, rubella, varicella, GCS and HFM disease.
2. Non-specific fever and rash where a specific diagnosis is awaited and depends on clinical evolution of illness and rash or on laboratory features. Two subgroups may be differentiated.
 - a. A presumed viral exanthem where the child looks well and a benign course is anticipated. Examples include roseola and enteroviral illness.
 - b. An ill looking child with presumed bacterial infection or potential for serious consequences, (e.g. Scarlet fever, early SSS, KD) where immediate investigation and/or specific treatment could be initiated⁶.
3. A critically ill child with progressive course and compromised vital signs (with features of sepsis, shock, respiratory failure or altered sensorium) where urgent referral, admission, monitoring, investigation and prompt institution

of optimum specific and supportive treatment could minimize risk of death or sequelae. Examples in this group include meningococemia, late TSS and SSS, and the viral hemorrhagic fevers^{6,15}.

4. Prolonged fever and rash group where a planned protocol of investigation can be undertaken to establish the nature of the illness before commencing appropriate treatment.

Conclusion

Unraveling the problem of the child presenting with fever and rash represents a challenge of diagnostic skills even to the astute clinician. The numerous infectious, inflammatory and drug-related problems and their varied presentations that need identification and differentiation highlight the complexity of the problem. However, with a sound knowledge of the locally prevalent common childhood exanthems and a methodical clinical evaluation of the nature and course of the illness through its prodromal and exanthematous stages, supported in a few patients with further investigation, this diagnostic exercise can be an interesting and rewarding experience. There remain several mysteries with regard to this important field of childhood disease that will maintain the interest of clinicians and researchers in the years ahead.

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MANAGEMENT OF ACUTE ASTHMA

* *Vijayasekaran D*

The prevalence of asthma is increasing throughout the world both in developing and developed countries¹. For the past one decade, the concepts regarding the pathophysiology and consequently the management principles of asthma has changed. Asthma is no longer a bronchospastic disease. In addition to the bronchospasm the underlying mucosal inflammation play a major role in outcome of asthma. In susceptible individuals, this inflammation increases bronchial hyper responsiveness resulting in recurrent episodes of wheezing, breathlessness, chest tightness and cough particularly at night and in the early morning. Several triggers unique to each patient initiate the inflammatory process. During an acute exacerbation, treatment of acute bronchoconstriction remains an important aspect of management. However controlling the underlying inflammation is an important aspect to prevent recurrence of such attacks. Once asthma is diagnosed, the following management principles to be followed strictly lest recurrent acute exacerbation of asthma is inevitable when such children are exposed to inciting events. The important management principles are (a) the child should be on long term maintenance therapy with inhaled corticosteroids to control the inflammation (b) to be away from inciting / precipitating triggers (c) understanding the nature

of disease and change in the life style. (d) practicing the correct inhaler technique with appropriate inhalation devices(e) to monitor the course of the disease with peak expiratory flow meter for objective assessment.

Natural course of asthma

Asthma is a chronic disease like rheumatoid arthritis characterized by repeated courses of remission and exacerbation. The disease is usually mild and episodic in nature during the initial course and when it gets established becomes persistent. The persistent asthma can be classified as mild/moderate and severe persistent types. All the four divisions of chronic asthma (mild intermittent, mild persistent, moderate persistent and severe persistent) on exposure to inciting events (triggers) may present as acute attack with varying severity. (Fig.1)

Acute asthma

Most acute attacks of asthma are usually mild responding to conventional line of management and at times it is so severe that the child needs intensive therapy and rarely even ventilatory support. The frequency of acute attack is disproportionately higher for children living in urban and low-income environments and urban children often use the emergency department as the primary source of asthma care².

Assessment of acute asthma

Since acute asthma always endangers life, attention should be focussed on maintenance of airway, breathing and circulation. Before commencing treatment, careful brief history and clinical examination should be done emphasizing

* Asst. Professor of Pediatrics
Institute of Child Health & Hospital for
Children, Egmore, Chennai 600 008.

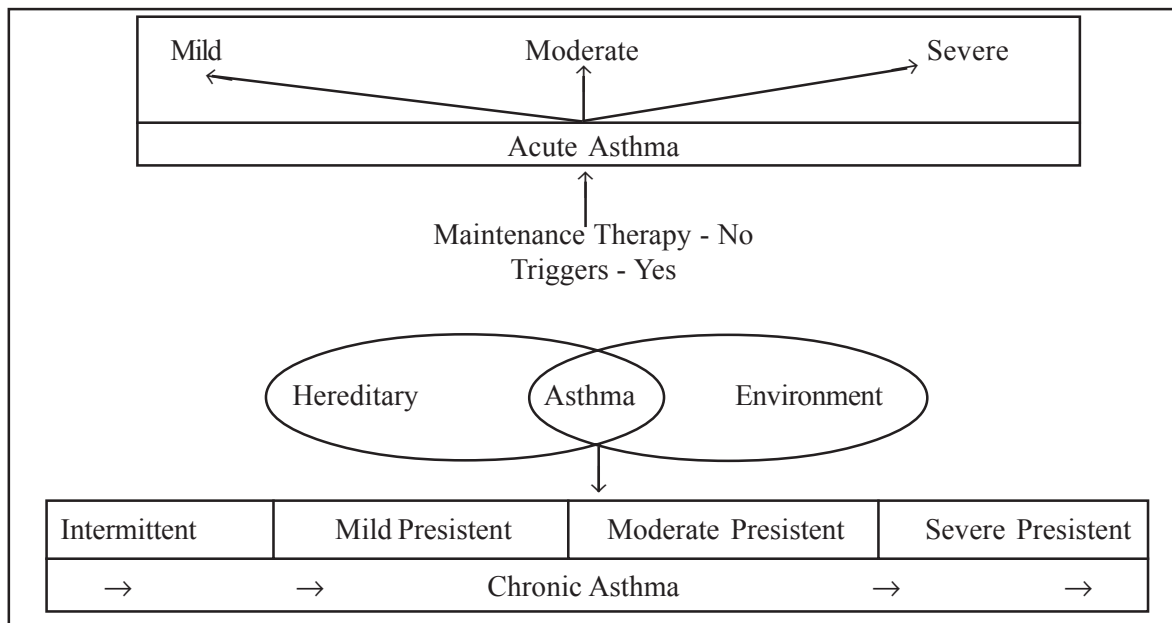


Fig 1. Natural course of asthma

the following aspects for successful outcome. The brief history should include factors regarding the duration of symptoms, exposure to triggers, medicine taken, food intake, prior emergency visits and hospitalization. Quick physiological examination should be done to assess the level of consciousness, check the vital signs, activity, work of accessory muscles and extent of wheeze (Table 1).

Though several methods are available to assess the severity of acute attack of asthma,

the pulmonary score based on the age, respiratory rate, wheezing and activity of accessory muscle is found to be the simple and practically feasible one on emergency visits (Table 2).

Based on the above, the severity of an acute asthma can be classified as mild, (PS<3), moderate (PS 4-6) and severe (Ps>6). Children above 6 years can be encouraged to do peak expiratory flow rate along with PS score for objective assessment as PS correlates with PEFr (PEFR > 70 = PS<3; PEFr 40-70 = PS 4-6; PEFr < 40 = PS > 6)³.

Table 1. Acute asthma - Assessment

History	:	onset / duration / hospitalisation
Walking	:	normal; prefer sitting; bend forward
Speech	:	sentences; phrases; words
Accessory muscles	:	+; ++; paradoxical. thoraco abdominal movement
Wheeze	:	expiratory; exp & insp.; silent chest
Pulse	:	Infant>160; preschool;>120; school;> 110
R.R	:	<2mo>60; 1-12mo>50;1-5yr. >40
SaO2	:	95-100; 91-95%; <90%
Pulsus paradoxus	:	<10; 10-15;>15;

Table 2. Pulmonary score (PS)

Score	Respiratory Rate		Wheezing	Accessory Muscle use (Sternocleidomastoid)
	< 6 Yr	> 6 Yrs		
0	< 30	< 20	None	No apparent activity
1	31 - 45	21 - 35	Terminal expiration	Questionable increase
2	46 - 60	36 - 50	Entire expiration	Increase apparent
3	> 60	> 50	Inspiration and expiration	Maximal activity

Treatment of acute attack of asthma

When a child present with acute asthma, assessment and treatment should go simultaneously. Decisions should be based upon clinical evaluation coupled with experience and methodical approach is essential to avoid missing of the associated problems.

Mild acute asthma

Inhaled bronchodilators are the main stay of therapy to relieve acute spasm, can be administered through nebuliser along with supplement oxygen. The ideal does of salbutamol (2.5 mg) 0.5 ml (below 20 kg) as nebuliser solution diluted with 2ml of normal saline to be nebulised for 5 minutes. If there is no adequate response, the above dose can be repeated once in 15 minutes with a maximum of three doses. If nebuliser is not available salbutamol can be delivered by metered-dose inhaler with spacer. A number of studies indicate that MDI is combination with a spacer is as effective and most cost efficient than nebuliser.⁴ Four puffs (100 mcg / puff) are given every 15 minutes for a maximum of three times. After each puff the child should take atleast five breaths to ensure adequate intrapulmonary delivery. Significant proportion of children with mild attack can be safely discharged from the outpatient service with the above therapy. Salmeterol, longer acting beta

agonist, is not indicated in the treatment of acute asthma due to the relatively slower onset of action⁵

While discharge, detailed information about the use of medicines should be given as written protocol and advised to go for follow-up with primary care provider or to attend speciality clinic (Asthma Clinic) for comprehensive follow-up. (Fig. 2)

Moderate acute asthma

Children who have not responded to above said protocol can be classified as having moderate acute attack which needs immediate administration of systemic steroids in addition to the liberal use of humidified oxygen (3-6 litres) either through canula or mask. Though intravenous methyl prednisolone (2mg/kg/stat followed by 1mg/ kg sixth hourly) is the preferred one, other steroids like hydrocortisone (10mg/kg to start with followed by 5 mg/kg 6 hourly) or oral prednisolone (2mg/kg/day) can be used depending upon the availability. Delayed institution of steroids will reflect delayed resolution of symptoms though onset of action of steroid take 6 to 8 hours. Since ipratropium has synergistic bronchodilator effect with salbutamol, ipratropium (125mcg = 0.5ml below 1 year and 250mcg = 1ml above 1 yr) can be added along with salbutamol especially in the management of acute attack of asthma in

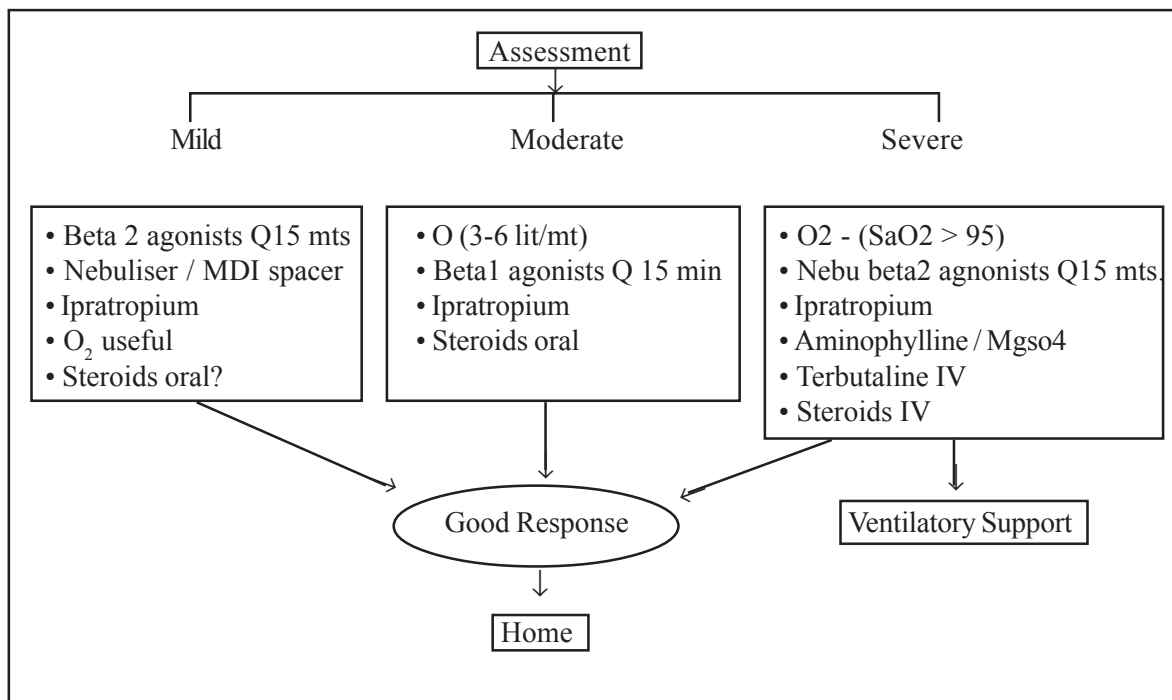


Fig 2. Management of acute asthma

extremes of ages. Ipratropium blocks acetylcholine receptors at the neuromuscular junction of bronchial smooth muscle resulting in bronchodilation. Though ipratropium produce less bronchodilation than beta agonists, the duration of action may be prolonged.⁶ Ipratropium should always be used along with beta agonists because of its mild bronchodilator action⁷.

The bronchodilator nebulisation should be continued for every one to 2 hours depending upon the response. If the response is good the child can be discharged with continuation of inhaled bronchodilators (Salbutamol) 100 mcg 2-3 puffs 5-6 times per day along with oral steroids with proper discharge advice as mentioned.

Severe Acute Asthma

If the above protocol fails, the attack should be classified as acute severe attack and the

following drugs can be tried in addition to the drugs which have already been instituted.. Though the added bronchodilator effect of theophylline is controversial when maximum dose of inhaled beta agonists has been used, few pulmonogists prefer to use aminophylline at this juncture (5mg/kg in 20 ml of normal saline to be run for 20 minutes 8th hourly iv) as aminophylline achieves the desired effect by acting on several sites (stimulation of respiratory centre, stimulation of mucociliary mechanism, direct spasmolytic action on bronchial smooth muscle, stimulation of muscles of respiration, immuno modulation of T cell, in addition to the well recognised actions like phosphodiesterase inhibition and adenosine inhibitor mechanism). Since the therapeutic window of aminophylline is narrow the dose should be cautiously planned. Children below 10 years tolerate better. The dose should be modified on concurrent administration with other drugs like macrolides cimetidine which interfere with aminophylline metabolism.

Few studies supported that a dose of magnesium sulphate (25 to 50mg/kg in 20ml of normal saline to be run as infusion of 30minutes) may be worth the trial in severe asthma. Magnesium works by modulating calcium channels causing a decrease in acetylcholine with subsequent bronchodilation and inhibition of histamine release from mast cells.⁸ If the response to magnesium sulphate is good, one more dose can be administered after 6 hours otherwise the drug should be abandoned, Adverse effects include flushing, nausea and hypotension.

When the obstruction of the airway is severe, the tidal volume is too low to allow any aerosol medication into intrapulmonary tree. Children who show poor response to aerosol drugs should be benefitted with systemic intravenous beta₂ agonists before other invasive measures.. Intravenous terbutaline is preferred, to be started with 10mcg/kg/stat as an infusion for 10 minutes followed by 2 mcg/kg/ every hour. Salbutamol can also be used at a dose of 0.5 to 5 mcg / kg / min. Majority of children with acute asthma do respond to above protocols if associated complications are looked in to and mechanical ventilation may rarely be resorted.

Monitoring

Monitoring of vital signs like respiratory rate, pulse rate, sensorium and intake - output is important at every level of asthma care. Pulse oximetry and peak expiratory flow rate play a significant role in the objective assessment and SaO₂ should be maintained above 95% with liberal use of oxygen. Arterial blood gas analysis should be considered for children with continued O₂ saturation of less than 90% on maximal oxygen therapy. Measures should be taken to maintain adequate nutrition and fluids. The adverse effects of beta² agonists like tremor, V / Q mismatch, agitation and hypokalemia should be anticipated.

Differential diagnosis of acute wheeze

All that wheezes is not asthma and so when a child presents with first attack of acute wheeze not responding to the above line of therapy the most common differential diagnosis should be considered is the nonopaque foreign body aspiration especially in toddlers. Other diseases to be considered in the differential diagnosis are heart failure, metabolic acidosis and structural anomalies of airway.

Discharge advice

80% to 90% of mild attacks of acute asthma may respond to the above protocol and the child can be discharged. However if a child fails to improve with therapy, he or she is moved up to the next category (mild to moderate & moderate to severe). Before discharge the child's pulmonary score should be less than 2 or PEFR 80% or above the depending upon the response the child should be advised to continue both inhaled bronchodilator and steroids.

Ventilatory Support

The use of accessory muscles of respiration, a pulsus paradox greater than 12 mm Hg, diaphoresis, inability to recline, hypercapnea, or a peak expiratory flow rate less than 40% of predicted all suggest that the patient has no respiratory reserve. If the patient does not improve within 4 hours of initiating therapy in the emergency department, or the patient requires ventilatory support.

Complications associated with acute asthma

1. Nebulised medications should be delivered with oxygen rather than air, as bronchodilators can occasionally cause transient oxygen desaturation because of ventilation perfusion imbalance (V/Q

imbalance). Administering humidified oxygen 3-5 litres in the nebuliser circuit will avoid the above complication and O₂ administration is preferable even in children with mild acute attack.⁹

2. Associated pulmonary complications like underlying pneumonia, airleak syndrome should be thought of if the respiratory distress continues, where skiagram chest play a major role.
3. Since the asthmatic children miss regular food intake, underlying metabolic derangement is inevitable and respiratory acidosis gets added up with the bronchospasm is severe. Though respiratory acidemia may be useful to stimulate the respiratory centre initially, when the carbondioxide accumulation is fast (5mm of Hg Co₂ per hour) the child needs ventilatory support.
4. Asthmatic children should be allowed one to one and half times and requirement of maintenance fluid to avoid water retention (reduced ADH secretion).

Health education

Children who develop acute severe attack may be prone to get repeated attacks if they are not placed on maintainance steroid. Avoidance to trigger play a significant role in children with asthma. Illiteracy, poor medical compliance, poor family infrastructure are the risk factors for acute attack. Again, the cycle of poor regular care leading to emergency department visits and subsequent inadequate or undertreatment of chronic asthma contribute to the increasing morbidity and mortality of children with asthma.¹⁰ So health education plays a major role to break this vicious cycle and it has been strongly recommended that child with asthma should have regular visits with primary care providers

especially after discharge from emergency room, The whole family members especially the parents should be imparted asthma education during each visit to achieve positive asthma care and long term remission.

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SOME COMMON DERMATOLOGICAL PROBLEMS IN CHILDREN

** Jayakar Thomas*

Introduction

It is estimated that about 25% to 30% of all outpatient visits to a pediatrician consist of dermatological problems and around the same percentage of all outpatients to dermatologist comprises the pediatric age group. This presentation discusses the diagnosis and treatment of some of the commonly seen childhood dermatoses.

Scabies

An infection caused by the itch mite, *Sarcoptes scabiei var hominis*, scabies is by the commonest of all skin disorders in our country. The cutaneous manifestations are the much-overrated burrows in the interdigital spaces or on the flexure of the wrists, and numerous itchy small excoriated urticarial papules at these sites and over the elbow, axillae, inner thighs, buttocks, and periumbilical area. Diagnosis can be made by the history of intense itching and the associated clinical findings. The management of scabies is not as easy as it is so often mentioned. The good old sulphur ointment (3%), still rules roost in spite of its offensive odour and messy state after application. A good scrub bath followed by rubbing the ointment from neck to toes for three days and three nights, followed by a hot bath is

the advice given. Benzyl benzoate (25%) emulsion is also used in the same manner. Then comes gamma benzene hexachloride (1%), which is claimed to be useful in a single 12-hour application. Decades have passed and now we have the newer molecule, permethrin. Used as a 5% cream, it is found to be scabidical in a short period of two to four hours.

Impetigo

Impetigo is a common disease of children. Its highly contagious nature is responsible for the former name impetigo contagiosa. A break in the skin such as occurring with a cut, an insect bite or skin trauma is enough to allow the causative agents, streptococcus or staphylococcus to grow under the stratum corneum of the skin. The disease tends to involve the face more often. Clinically the lesion starts as vesicles or pustules and rapidly forms honey-coloured crusts. Spread frequently occurs from autoinoculation. Treatment is directed primarily towards sparkling personal hygiene. Saline compresses are acceptable to debride the crusts. Systemic antibiotics such as penicillin and a wide range of topical antibiotics serves good purpose as remedies. The choice of topical antibiotics for long had been framycetin sulphate. The last decade has found sisomycin sulphate very useful. The recent trend has been towards using topical mupirocin (1%) ointment that is claimed to be most effective and not warranting the use of systemic antibiotics.

Tinea capitis

Children seem to be infected by dermatophytes more often on the scalp than on

* Consultant Dermatologist,
Kanchi Kamakoti CHILD Trust Hospital,
& Apollo Hospital, Chennai

other sites. Clinically, tinea capitis starts as a circumscribed patch of scales, gray to black in colour. Quite often the lesions tend to get secondarily infected with bacteria, to form a boggy swelling that shows signs of acute inflammation. This is the usual kerion type of tinea capitis. History of recurrent tonsuring may contribute in diagnosing most cases. From the treatment point of view, it may be said that oral griseofulvin 250mg to 500mg daily for about three to six months is quite satisfactory, in terms of resolution of skin lesions and prevention of relapses. But, of late, the physician is being confronted by cases of griseofulvin resistance. The imidazoles like ketoconazole and intraconazole have now come to offset this situation of griseofulvin resistance. Intraconazole /ketoconazole (100mg) daily for two weeks has shown to give excellent results in most cases of dermatophyte scalp infection.

Pityriasis Versicolor

Pityriasis versicolor (more often called tinea versicolor) is a non-inflammatory yeast infection caused by *Pityrosporon orbiculare*. It affects health children, with nearly half of them in the tropics. Principle sites of involvement are the upper back, upper chest, sides of the neck and the proximal arms. Asymptomatic hypopigmented well defined macules and patches that reveal slight scaling when scratched (*coup de ongle sign*) are the typical lesions. Occasionally the lesions are hyperpigmented and itchy. Management of pityriasis versicolor can be a very tiring and trying exercise. Prudence demands routine laundering of clothing. The benzoic-salicylic acid combination has been the treatment of choice even since Whitfield described it in 1907. Gone are those days and now we have more than a dozen topical antifungals useful in the treatment of pityriasis versicolor. These include 2% miconazole, 1%

clotrimazole, 1% ketoconazole, and 1% tolnaftate. But the newer ones are those belonging to the group of allylamines (e.g. terbinafine). One percent terbinafine today is the recent topical answer to the treatment of pityriasis versicolor.

Urticaria

Hives or urticaria is known to affect large number of children. It is said that all children suffer from at least one episode of urticaria. Urticaria is a reaction patterns of the skin characterized by transient, itchy, oedematous, and erythematous swelling (wheals) of the skin, caused by a wide range of agents acting from inside the body, outside the body, or both. When the condition goes on for more than six to eight weeks, it is classified as chronic urticaria, and as acute urticaria when seen for less than six weeks. Intermittent attacks of 'acute on chronic urticaria' have also been noticed. The purpose of this categoriation as acute and chronic is from the therapy point of view. Acute urticaria responds well to sufficient doses of antihistamines, while the chronic type requires a thorough workup for its aetiology. It is mandatory that bacterial infection and gastrointestinal parasitic infestations are ruled out or are treated. However, antihistamines from the gold standard in the treatment of urticarias. When have today a conglomeration of antihistamines ranging from sedate and potent to the non-sedate and less potent ones. It has become a useful changing trend to turn towards the non-sedate antihistamines for the treatment of chronic urticaria. The newer antihistamines like astemizole, terfanidine, cetirizine, loratidine and desloratidine have all been found useful. A once daily dose of 5mg to 10mg cetirizine hydrochloride for a period of 4 to 6 weeks has given good results.

Pityriasis alba

This a type of non-specific dermatitis that

characteristically produces hypopigmented patches most commonly on the face of atopic children. The patches show very fine scales and tend to disappear and reappear. Although regarded as a manifestation of atopic dermatitis, it is certainly not confined only to atopics. Less commonly, the face is spared and there are scattered lesions on the trunk and limbs that then give some diagnostic difficulty. Treatment is often disappointing. Avoidance of frequent washing with soap and water must be advised. Today's trend is towards treating pityriasis alba with topical mometasone furoate (0.1%) with excellent results.

Diaper dermatitis

Diaper dermatitis or napkin rash is a multifactorial disorder. No single agent is responsible for its cause even in a single patient. Participating factors include irritation from prolonged contact with moisture from urine and faeces, ammonia from diapers, loss of normal skin acidity and microbial colonization. Children, two to four months old are usually affected, with those having an atopic or seborrhoeic background being even more susceptible. Diaper dermatitis tends to spare the creases and demonstrates a smooth erythematous involvement or a scaly and exudative reaction over the convexities of the thighs, pubis and buttocks. The presence of satellite lesions indicates a yeast infection. Topical corticosteroids are helpful in the treatment, and are indicated in all but the mildest cases. There is, however, virtually never any need to use applications containing more than 1% hydrocortisone. Twice daily application is presently advocated. Fears that corticosteroid might interfere with the descent of testes in boys have not been confirmed, but the possibility remains that such a problem could arise in low birth weight babies.

Lichen planus

Lichen planus is not an uncommon condition. It typically presents with itchy flat-topped violaceous papules on the flexural aspects of the wrists, about the ankles, and over the male genitalia. Oral mucosal involvement may occur either alone, as a lacy network on the buccal mucosa, or in combination with skin lesions. Intolerable itching is the hallmark of lichen planus. Oral lesions may ulcerate and cause pain and dysphagia. Although nearly 70% of cases resolve spontaneously within 12 to 15 months, even in the best of circumstances lichen planus is not an easy disease to treat. Doubly so is lichen planus in children. Topical steroids remain the sheet anchor in the treatment. But the problems in lichen planus therapy is that proven medicines are not safe and safer medicines are not proven. For instance the choice of topical steroids is very significant. A potent steroid like clobetasol may prove to be dangerous and suppress the HPA axis by percutaneous absorption. More recently 0.1% mometasone furoate has proved to be as safe as and more effective than 1% hydrocortisone.

Conclusion

Any childhood dermatosis confounds and humbles even the most experienced dermatologist in practice. The problem is not so much as lack of effective therapeutic modalities but the efficiency, dependability, and safety profile of such treatment in children. The critical question every clinician finds addressing himself is: what shall I prescribe for this child and how? To end, it is worthwhile remembering that "behind the towering spires of medical knowledge, therapy sits as a small cottage.... yet, it is to this cottage of therapy that the patient most wants to come", and how hard and difficult indeed the road to this cottage is for the tender-footed little children.

RADIOLOGIST TALKS TO YOU

THE BLADDER AND A GENERAL APPROACH TO IMAGING

* **Vijayalakshmi G**
 * **Natarajan B**
 ** **Ramalingam A**

The ultrasound picture that a clinician receives cannot be read like the plain X-ray or CT films that accompany a report. The sonologist has studied the patient in many planes - sagittal, coronal, axial and oblique - and then has given representative sections. So the operator would have seen much more than the pictures he has sent.

One of the common films that accompanies the report is a cross-section of the bladder taken immediately above the symphysis pubis. Fig.1 shows the normal bladder. The contents of the bladder are normally black or anechoic. This is a feature of any fluid in the body - bile in the gall bladder, blood in the vessels or fluid collection in any space. Now try to read Fig.2. There are white specks within the bladder. This is an abnormal finding. It is due to minute particulate matter because of pus or blood. Fig.3a shows something very common that you all must be familiar with, which is a vesical calculus. This is seen as a white or echogenic focus. Calcification and bone also appear like this. Deep to this focus is seen a dark aftershadow. This is the hallmark of a calculus. It appears because bone or calcium

or metallic elements block ultrasound completely. Clots or debris, though white, do not cause an aftershadow.

Remember that every investigation has its own pitfalls. Look at Fig.4. Here also you can see a white focus behind the bladder. Is this a calculus? No. This is rectal air behind the bladder. How do you decide? When the patient is turned to a lateral decubitus position the calculus also moves to the dependent wall (Fig.3b) while the air in the rectum remains in the same position. This brings us to the appearance of gas in ultrasound. Air or gas appears white as it reflects all the sound waves completely so that nothing is seen deep to it. This is why ultrasound has not found much use in the evaluation of the chest unless it is filled with mass or fluid. Air is white and also casts an aftershadow, but this does not have the sharp edge of the acoustic shadow of the calculus.

After examining the contents of the bladder look at the wall. Does it show any asymmetry in shape or indentation due to a lesion in the neighbourhood? (Fig.5). Now look at the thickness of the wall. It should be regular or uniform. Mild thickening is seen in cystitis. Fig.6 shows a grossly thickened bladder wall in a case of severe proliferative cystitis. The bladder wall is also thickened in case of posterior urethral valves. So check for the presence of dilatation of ureters and the pelvicalyceal system which is almost always present in this condition. Cystitis is rarely associated with uretero hydronephrosis and even then it is only mild.

Fig. 7 shows irregular thickening of the bladder wall with a large polypoidal mass

* Addl. Professor in Pediatrics

** Addl. Professor in Radiology
 Department of Radiology
 Institute of Child Health and Hospital for
 Children, Egmore, Chennai



Fig 1 - Normal bladder

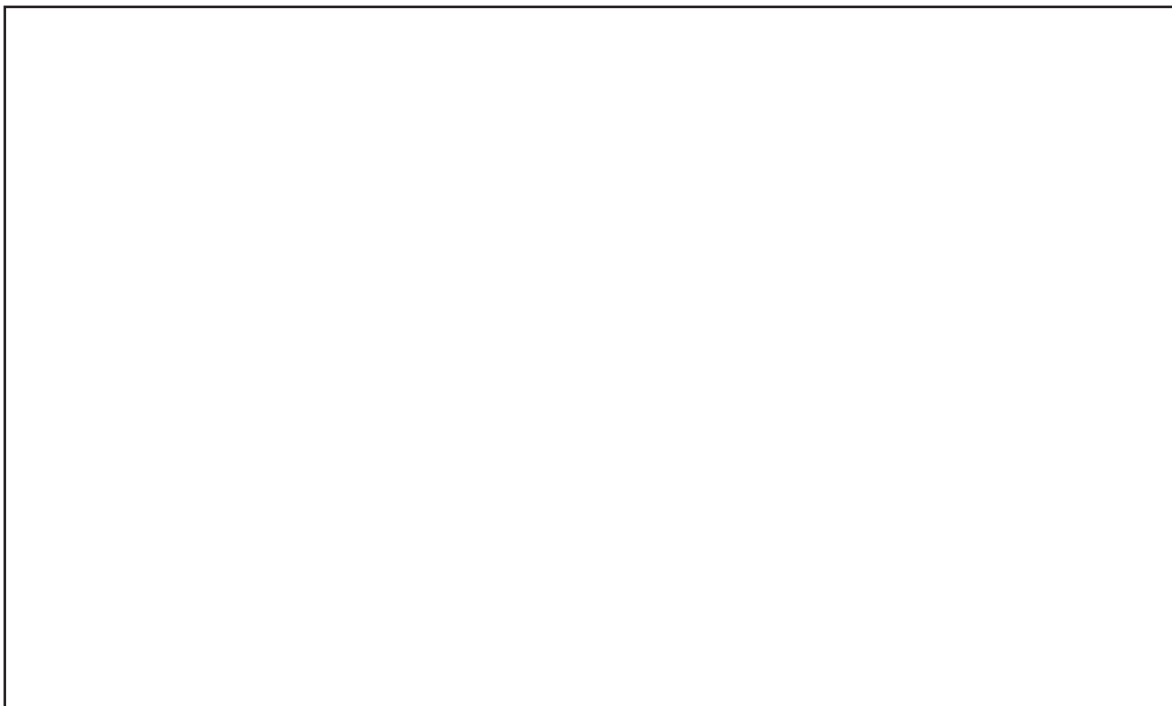


Fig 2 - Turbidity of bladder contents

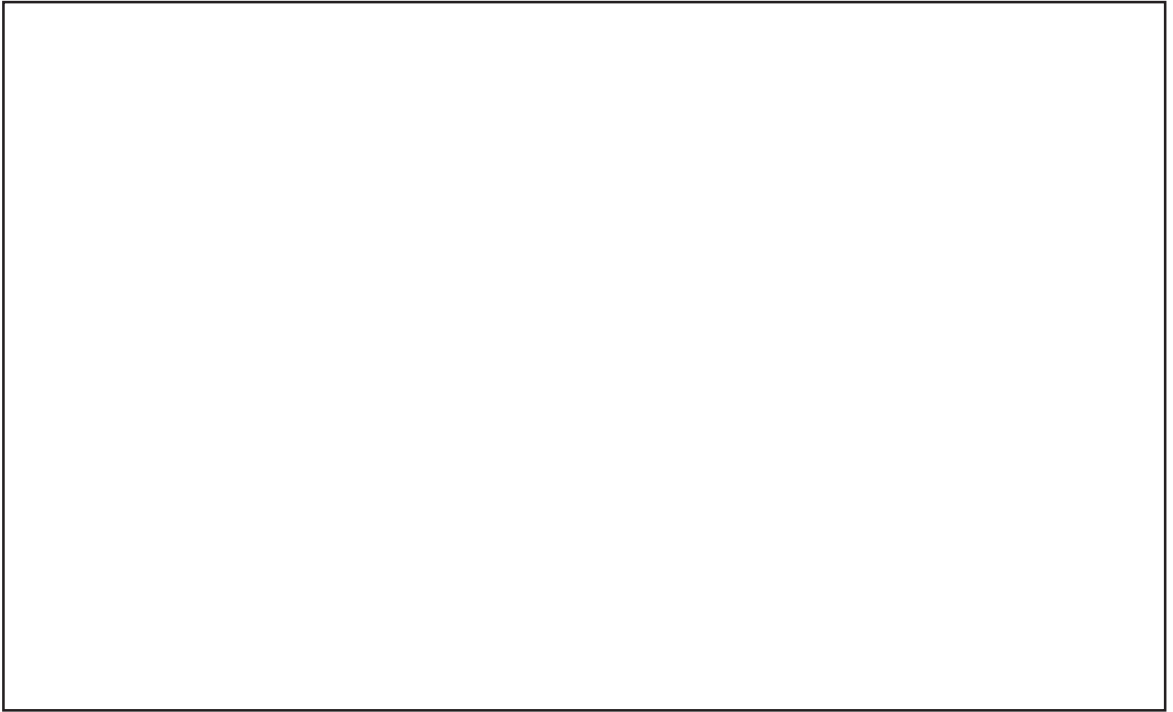


Fig 3a - Vesical calculus

Fig. 3b - Decubitus position. Where is the calculus now?

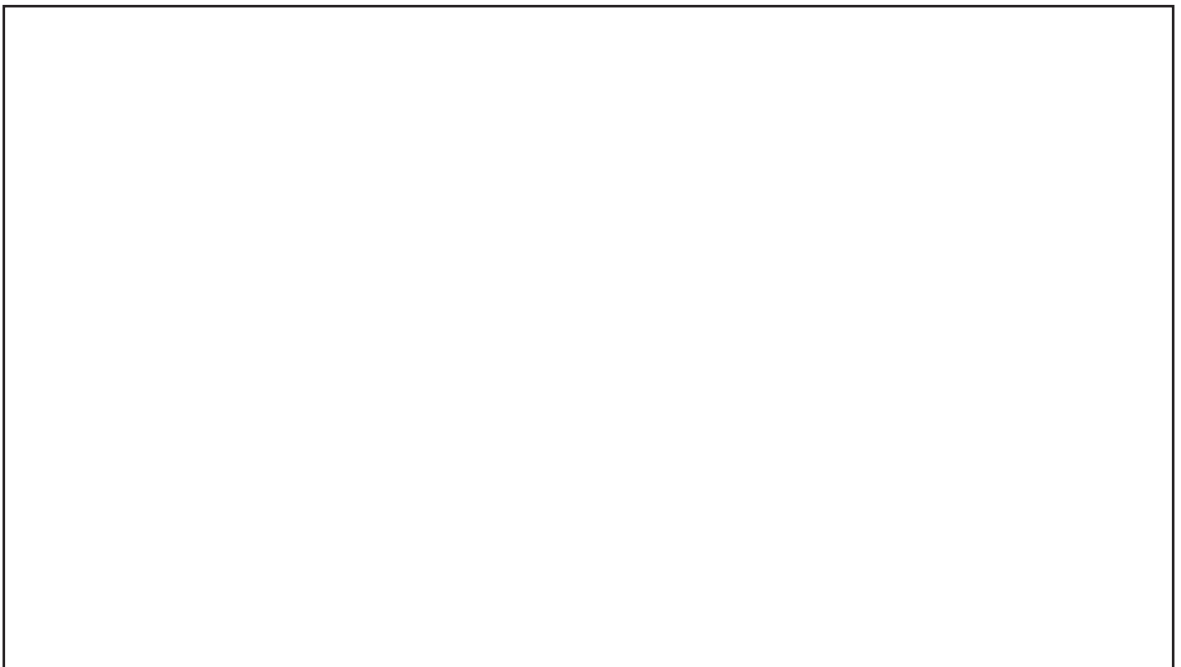


Fig 4 - Air in the rectum seen behind the bladder. See the aftershadow.

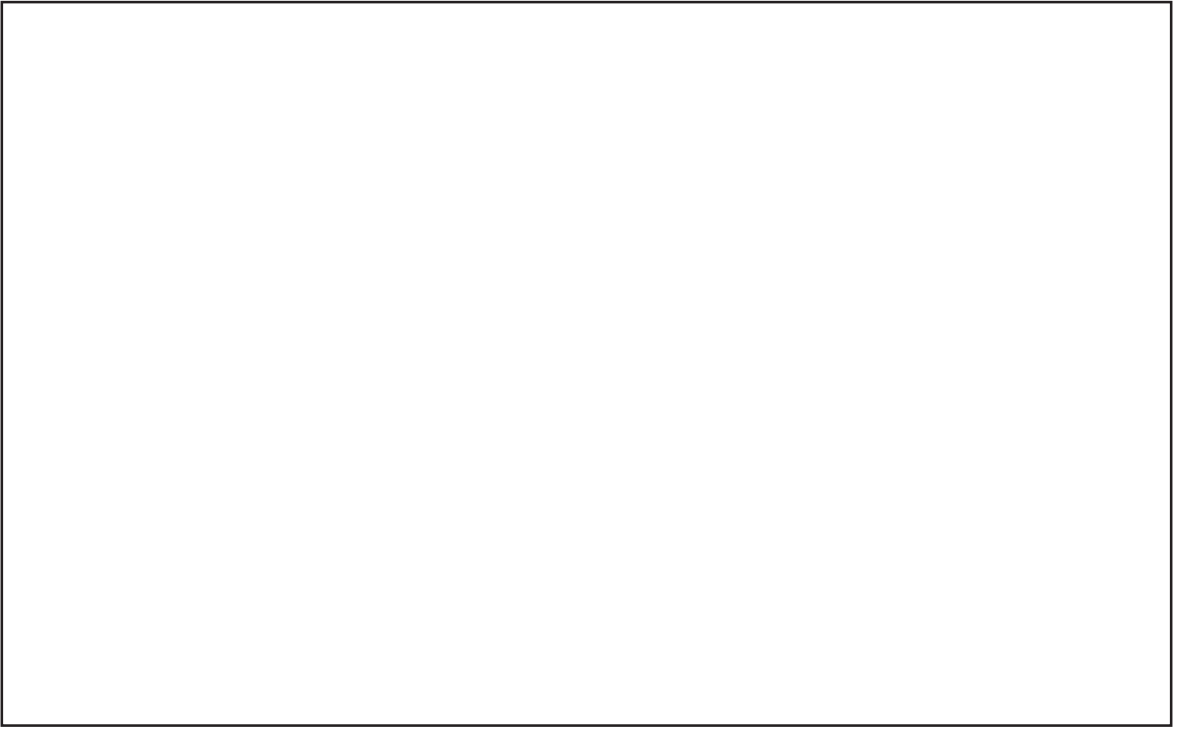


Fig 5 - A lymph node indenting the left wall of the bladder

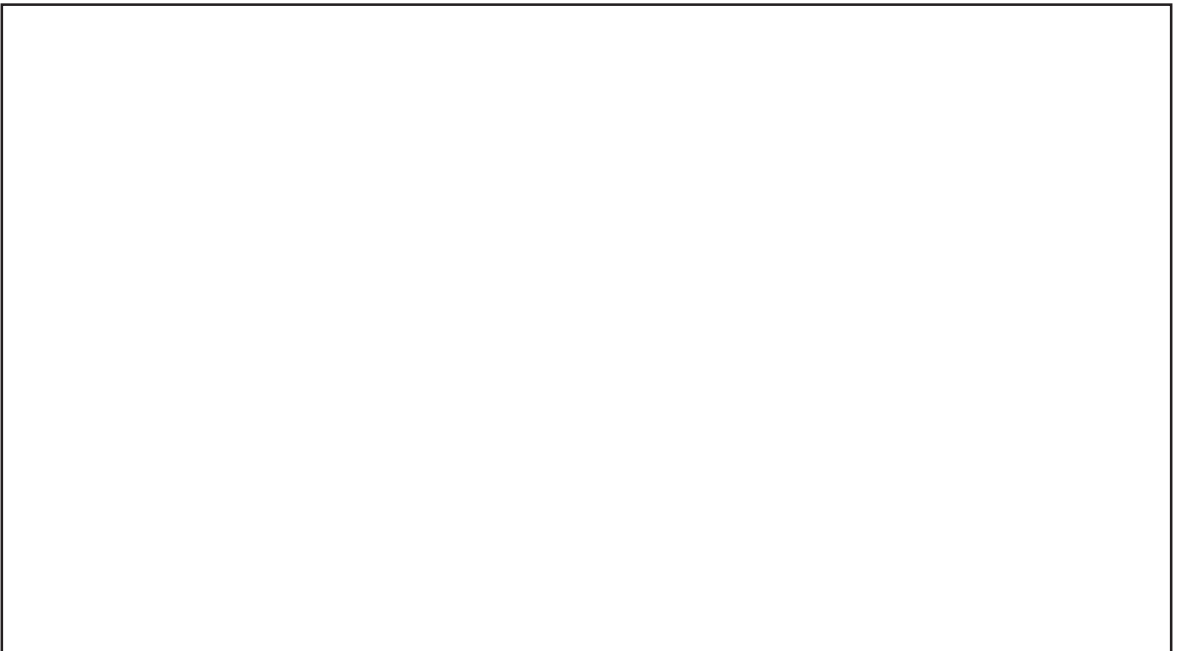


Fig 6 - Thickened bladder wall in case of severe proliferative cystitis.

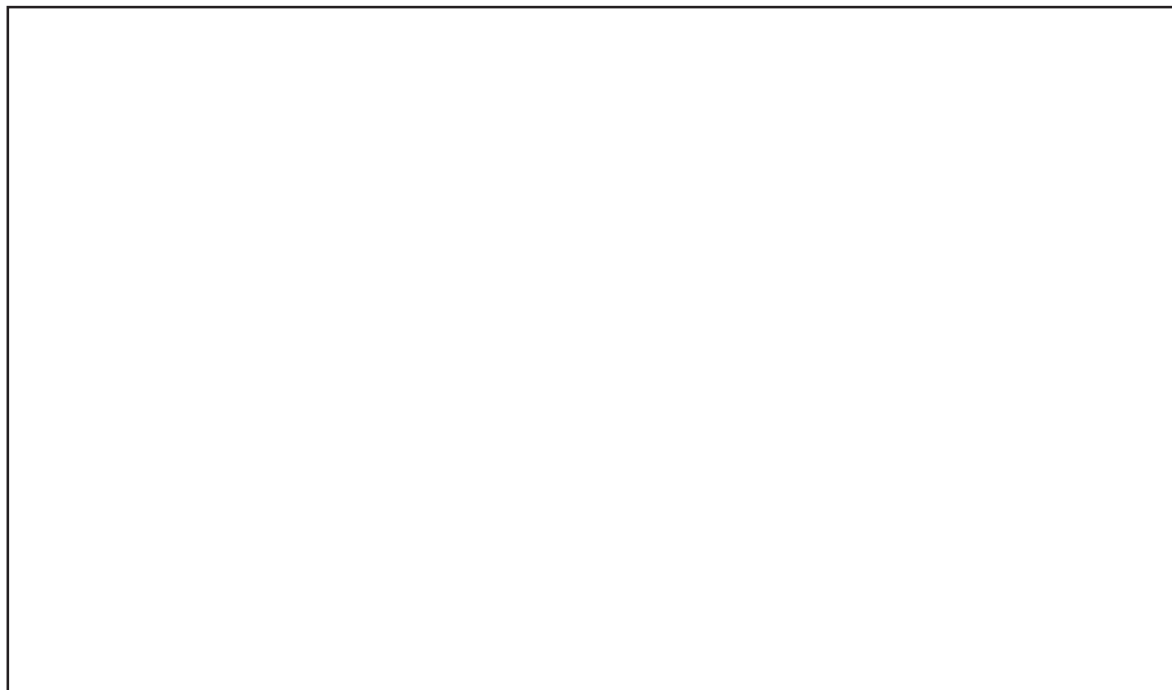


Fig 7 - Rhabdomyosarcoma-bladder.

projecting inside from the right anterolateral wall. This is a case of rhabdomyosarcoma of the bladder. So, following the same concept as clinical examination, identify the shape, size,

contour and contents of any lesion or fluid space, This will help you to assess the type and severity of the existing pathology.

CONGRATUATIONS

Dr. H. Paramesh MD, FAAP, FIAP, FIAMs., has been awarded fellowship (FIAA) by the Indian Academy of Allergy for his contribution to allergic diseases in India and Growth of Academy, during the National Conference in Pune between 28th - 30th November, 2002.

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Dr. K. Srinivas, Chennai, Tamilnadu

CASE STUDY

METATROPIC DYSPLASIA* **Raveendranath S**** **Ravisekar CV**** **Venkataraman P***** **Vasantha Mallika TK****** **Elizabeth John**

Metatropic Dysplasia is rare skeletal dysplasia characterised by a non-lethal type of congenital dwarfism with a typical skeletal dysplasia (micromelia), joint changes with or without a tail like skin appendage over the sacral region.

Case report

A 12 years old boy, 1st born of a nonconsanguinous parentage presented with a history of multiple symmetrical joint swelling involving both small and larger joints. There was no history of joint pain, fever, weight loss or skin rashes, or similar history in family members. On examination, he was undernourished with Grade II PEM, short statured (less than 5th percentile), normal intelligence and facial appearance. Patient was having brachydactyly with fusiform swelling involving all interphalangeal joints with restricted movements and exaggerated lumbar lordosis. Systemic examination including cardiovascular system was normal.

Investigations revealed a serum calcium of

* PG Student

** Asst. Prof. of Pediatrics

*** Readers of Pediatrics

**** Prof. of Radiology

Institute of Child Health & Hospital for
Children, Chennai.

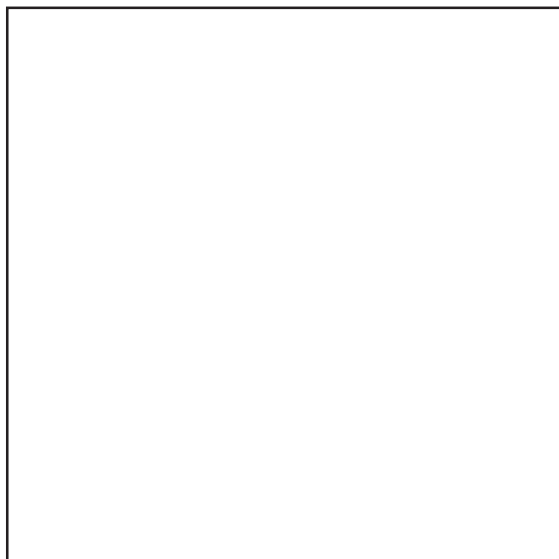


Fig 1. Showing multiple symmetrical joint swelling

9.8mg%, phosphorous 4 mg% serum alkaline phosphatase of 10 KA unit and ESR-10/20mm, Skeletal survey showed normal skull, platyspondyly of the cervical spine and elongation of AP diameter of the dorsolumbar vertebral body. Rest of the thorax was normal and the pelvis showed a small square ilia with an anterior superior iliac spine apparently more inferiorly placed than in normal. Long bones were showing diaphyseal constriction and widely flaring metaphysis. With this radiological finding diagnosis of metatropic dysplasia was made.

Discussion

Metatropic dysplasia is a genetically inherited skeletal dysplasia with genetic heterogenicity with a prevalence rate of one in one million population. This conditions was first described by Moroteaux, Spranger and Wiedemann. The term metatropic was selected to indicate the change in body proportion peculiar to this condition, that occur with passage of time.

At birth limbs appear short in relation to the trunk and hence a diagnosis of achondroplasia is made at birth, even though the total body length is usually normal. By early childhood the trunk becomes shortened because of kyphoscoliosis and the limbs appear disproportionately long. This general habitus look like Morquio's syndrome. At all time the head and face are normal. The thorax is normal and undergo progressive deformity including projection of the sternum, this at later stage leads to cardio-respiratory problem. Stature shows marked reduction with disproportionately short limb, reaches adult height between 110 and 120cm. Skin tag (tail-like) appendage may be seen over the sacral region.

Blood and biochemical investigations are normal. Radiological features and diagnostic in this condition. Normal skull with cervical spine showing platyspondyly and sometimes absence or hypoplasia of the odontoid peg. Thoracic and lumbar spine in neonate shows early platyspondyly, subsequently the appearance is variable with diamond shaped vertebra (or) with a hump superiorly, with irregular ossification of the end plate and finally mild platyspondyly with elongation of AP diameter of the vertebra. Thorax in neonate shows short ribs with widening of the costochondral junction. Pelvis

shows small square ilia with anterior superior iliac spine apparently more inferiorly placed than in normal with small sciatic notch and widened pubic symphysis. Diaphyseal constriction and widely flaring metaphyses in long bones, with deep intercondylar notches in knee joints. Most patients with this disorder die in early infancy from respiratory insufficiency and at a later age from cardio respiratory problem associated with the spinal and thoracic deformity. Secondary osteoarthritis develop following the disordered epiphyseal growth. Treatment is only symptomatic and supportive. The prognosis is guarded due to cardio-respiratory problems.

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- Editorial Board

CASE STUDY

CROUZON'S SYNDROME

* **Archana B Patal**
** **Ramesh L Renge**

Crouzon's syndrome is an autosomal dominant condition with craniosynostosis and facial anomalies^{1,2}. It has a wide range of expression and penetrance¹. A fourth of these cases do not have a family history and are new mutations³. Following is a case report of monozygotic twins with Crouzon's syndrome.

Case report

3½ year old monozygotic twins of non consanguineous marriage presented with convulsions and craniofacial dysostosis. They were born by caesarian section and their mother died of eclampsia a day later. Grandmother noticed flat occiput, small anterior fontanella and abnormal shape of skull of both the babies but did not seek medical attention. The parents or sibs did not have similar features.

They first reported to the hospital at the age of 9 months with generalized tonic clonic convulsions, which was their 2nd Episode, the first having occurred at the age of 2 months. The X-ray skull at this age showed sutural closure only (Fig.1). The fundus was normal. They were treated with carbamazepine and were subsequently free of seizures. There was no developmental delay. Parents did not report vision or hearing defect.

* Associate Professor

** Lecturer

Dept. of Pediatrics,

Indira Gandhi Medical College, Nagpur.

The twins reported again at the age of 3½ years. They had tower shaped skull, frontal bossing, shallow orbits, ocular proptosis and ridging of sutures (Fig.2). The palate was high arched and nose was beak like. Phenotypically the twins were identical with similar blood groups. Fundus examination of both the children revealed papilloedema with blurring of margins and pale disc. The x-ray skull at this age showed craniosynostosis and silver beaten appearance (Fig.3). The CT scan revealed diffuse effacement of ventricular system, subtotal obliteration of subarachnoid space, scalloping of inner table and fusion of all sutures except the lamboid (Fig.4).

Discussion

Total 58 syndromes with cranio synostosis have been described and limb findings are the principle distinguishing features^{1,4}. Of all the craniosynostosis, Crouzon's syndrome accounts for 3-7% of cases with a birth prevalence of 16.5/1,000,000^{5,6}. Crouzon's syndrome is a craniofacio synostosis characterized by brachycephaly, ocular proptosis, maxillary retusion, mid facial hypoplasia due to abnormal development and



Fig 1. X-ray skull showing sutural closure



Fig 2. Twins showing tower shaped skull, frontal bossing and propotosis

premature fusion of any or all cranial sutures, most frequently coronal⁷. In 1912, Crouzon for the first time described it in a 29 years old mother and her 3 years old son⁸.

Crouzon's syndrome manifests with facial dysmorphism in the form of hypertelorism, beaked nose, cleft, high arched palate (inverted v shaped), dental malocclusion^{1,9}. In addition to abnormal facies they can have complications like increased susceptibility to middle ear infection and conductive hearing loss due to atresia of external auditory meatus and progressive visual loss due to raised intracranial tension^{1,9}. Mental retardation may also be present in 10-30%¹⁰. Occasionally CNS, spinal and congenital malformations are associated^{11,12}. Because these children did not receive any intervention they



Fig 4. CT scan showing scalloping of inner table



Fig 3. X-ray skull showing craniostenosis, silver beaten appearance.

manifested with signs of raised intracranial tension (silver beaten appearance on X-ray skull) and optic atrophy on fundoscopy.

It has an autosomal dominant inheritance of which 65% are familial, the rest (35%) represent sporadic new mutations³. Mutations in the gene coding for fibroblast growth factor receptor 2 (FGFR2) are the cause of the syndrome³. Among monozygotic twins, 71% twins are reported to be concordant for oxycephaly (tower shaped)^{1,13}. There are few reports of Crouzon's syndrome in twins^{2,13,14,15,16,17,18}. We present monozygotic twins in which both are having identical features of Crouzon's. Unexpectedly there have been cases of monozygotic twins with differences in manifestation of the syndrome. Singh M (1983) reported Crouzon's in one of monozygotic twins where her counterpart was unaffected¹³. Lajeunie E, et al described monozygotic twins with Crouzon's syndrome in which one was having thumb duplication as an additional congenital anomaly¹⁴. The discordance between monozygotic pairs has been ascribed to differences in placental vascular supply and allocation of unequal number of cells due to abnormal separation of fertilized embryo¹⁴.

Patients with Crouzon's syndrome are to be managed with 3 primary goals of prevention of

increased intracranial pressure, prevention of constriction of brain growth and improvement of skull and facial appearance⁹. To be affective, craniotomy must be considered early in life, preferably during first 6 months of life¹⁹. Surgery halts the mental regression, lowers the intracranial pressure and most importantly prevents vision impairment¹⁹. It does not prevent development of mid face hypoplasia and does not improve IQ once it is already impaired¹⁹. Therefore early intervention needs emphasis. It consists of linear craniectomy along the obliterated sutures or parallel to it in case of sagittal suture²⁰. Polyethylene or tantalum strips are placed along the bone edge to prevent recalcification and bridging²⁰. The procedure may have to be repeated if bone bridges cross the suture lines early⁹. Hydrocephalus needs shunt surgery. Facial appearance can be modified by mid face advancement¹⁹.

Although Crouzon's syndrome is an autosomal dominant condition, sporadic mutations may occur as in this case where there was no family history. This mutation in the gene coding for FGFR2 occurred in the same embryo that cleaved to form monozygotic twins with identical phenotypic representation of Crouzon syndrome.

Crouzon's syndrome can be diagnosed antenatally by chorionic villous biopsy (11 weeks) and by searching for mutations in FGFR2 gene using PCR for amplification and single strand confirmation polymorphism analysis which detects abnormal coding sequence and splice junctions^{3,7}. In the second trimester binocular and inter orbital diameter measurements are useful to detect this syndrome.

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CASE STUDY

SCHIZENCEPHALY - A CASE REPORT

*** Geethanjali M**

**** Anuradha K**

Schizencephaly is one of the many disorders of cerebral contact development¹. It may present with a range of symptoms, one of which could be hemiplegia. Childhood hemiplegia, most often is caused by hypoxic vascular insults, infections such as bacterial meningoencephalitis, hypercoagulable states or thromboembolic phenomena. Less often, space occupying lesions like tuberculoma or malignancy could be the cause of stroke. A case of childhood hemiplegia caused by schizencephaly, is presented in view of its rarity and in order to highlight the fact that, it could be an uncommon cause of the commonly encountered hemiplegia. The diagnostic value of CT scan cranium in delineating the focal cerebral lesions is also emphasised.

Case report

A two and a half year old female child was brought to the out patient department with history of weakness of the left upper and left lower limbs noticed since the age of two years. This child was born to non-consanguineous parents as full term normal delivery at home. Antenatal, intranatal and perinatal periods were uneventful. The developmental milestones were marginally delayed. The weakness was heraddded by fever and first involved the left upper limb. Within a day, the child was found to drag her left foot while

walking. There were no seizures. There was no history of trauma to the head or antecedent oral surgery, no history suggestive of cyanotic heart disease, severe dehydration or contact with tuberculosis. Vision and hearing were unaffected. The child was able to comprehend speech and answer meaningfully with a few words.

On esamination, the child was conscious and oriented, there was no cyanosis or respiratory distress; there were no neurocutaneous markers. No limb length discrepancy was observed. The head appeared small (head circumference: 42cm against the expected of 47.5cm). The child had upper motor neuron type of facial palsy on the left. Spasticity and weakness were present in the upper and left lower limbs; ipsilaterally, the deep tendon reflexes were exaggerated and plantar response was extensor. The child walked with circumduction, the left arm held stiff. There were no involuntray movements cerebellar or meningeal signs. The other systems were clinically normal.



Fig 1. CT scan showing a cleft in the right parietal lobe extending upto the ipsilateral ventricle, communicating with it and causing dilatation by mass effect.

* Associate Prof of Pediatrics

** Reader in Pediatrics
Coimbatore Medical College & Hospital
Coimbatore

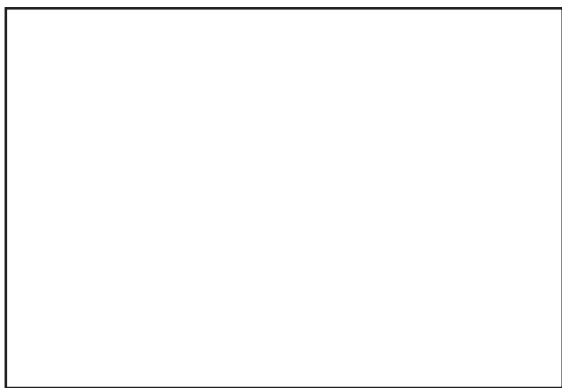


Fig 2. CT scan showing a cleft in the right parietal lobe lined by heterotopic grey matter. Mass effect on the ipsilateral ventricle is also seen.

Baseline investigations like complete blood count, x-ray chest, urine examination and screening for tuberculosis were noncontributory. X-ray skull revealed microcephaly. CT scan cranium revealed a cleft in the right parietal lobe extending from the cerebral convexity into the right lateral ventricle. There was ipsilateral dilatation of the posterior horn of the lateral ventricle, suggesting schizencephaly of open type. The child is undergoing regular physiotherapy and is on periodic follow up.

Discussion

Schizencephaly, an anomaly of neuronal migration is the result of an embryological insult occurring during the critical period of brain development². It is characterized by the formation of unilateral or bilateral clefts in the cerebral hemispheres³. It is usually sporadic, rarely familial⁴. It usually presents between one month and ten years of age. It may rarely manifest in the newborn period⁵. Few patients remain asymptomatic lifelong. Vascular insult, genetic factors⁶, cytomegalovirus⁷ infection, trauma⁸ in mid pregnancy, amniocentesis⁸, late fetal exposure to warfarin⁹ have all been implicated in the pathogenesis. Associated

anomalies¹⁰ may be, absent septum pulludicum, agenesis of corpus collosum, porencephalic cyst, septo optic dysplasia and holoprosencephaly.

The frequency of disorders of cerebral migration is 0.5% of all cranial MRI studies¹¹. In schizencephaly, there is an infolding of cortical grey matter along a hemispherical cleft near the primary cerebral fissures⁴. It may be of open type (type II) or closed type (type I). The cleft may be unilateral or bilateral¹. The clinical features reported in literature include tetraparesis, hemiparesis¹⁰, epilepsy, developmental delay, mental retardation, head nodding¹² and psychotic symptoms³. The unilateral closed type has the best neurological outcome¹. Intractable seizures and hydrocephalus usually complicate the open type¹. Language function is normal in unilateral schizencephaly¹. Clefts are usually located in the parasagittal, parietal or temporal regions of the brain¹³. Atypical features in this child are the absence of seizures and the presence of microcephaly instead of hydrocephalus.

Conclusion

Disorders of cerebral neuronal migration have a wide range of clinical manifestations. Although MRI is considered gold standard in the diagnosis¹⁴, CT cranium is very often a valuable tool in the precise delineation of the site and nature of pathology, in most disorders of cortical development. Also, CT cranium is indispensable in the diagnostic armamentarium of any child presenting with focal neurological deficit, because, it may spring a surprise many a time, regarding the ultimate diagnosis, as in this child.

Acknowledgement

We wish to record our sincere thanks to Dr.B.Ramesh Babu, MD(Ped.) for his immense help in this venture. Our thanks are also due to Dr.K.Palaniappan, MD, DCH., for his valuable suggestions in drafting this manuscript.

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NEWS AND NOTES

APLS: The Pediatrics Emergency Medicine Course 22nd and 23rd March 2003

The Department of Pediatrics, Sir Ganga Ram Hospital, Delhi and Indian Academy of Pediatrics, Delhi are organizing "APLS: The Pediatrics Emergency Medicine Course" as per guidelines of American College of Emergency Physician and American Academy of Pediatrics.

The course will be conducted at Sri Ganga Ram Hospital, New Delhi by eminent faculty in the field of pediatric emergency medicine.

The registration is restricted to 40 delegates on first come first serve basis. There is no sport registration.

The registration fee is Rs 1200/- (including course material) which may be sent by cheque/cash/bank draft in favour of "Ambulatory Pediatrics" to the Course Director, Dr. Suresh Gupta, Consultant, Pediatric Emergency Medicine, Department of Pediatrics, Sir Ganga Ram Hospital, New Delhi 110 060.

Phone: 5152656, 5917591, 9810124391, Email: drguptasuresh@yahoo.co.in

QUESTIONS AND ANSWERS

Q. 1: Medical representatives are coming out with Gatifloxacin. Can you please mention 1. its use in pediatrics 2. its dosage and routes of administration 3. any specific side effects?

Dr. J. Sheban,
Kanyakumari, Tamilnadu.

A. 1. After a systematic search for the query on Gatifloxacin, I have not come across any authentic literature or studies on Gatifloxacin in children. All the available studies pertain to those in adults. I have gone through pub med medline search. However my reply is as follows. The safety and efficacy of the Gatifloxacin is not yet established in children and hence presently there are no valid indications for its use in pediatric population. The drug has an expanded spectrum over ciprofloxacin and is recommended for use in adults for the treatment of acute exacerbations of chronic bronchitis and treatment of community acquired pneumonia.

Dr. Niranjan Shendurnikar,
Asso. Prof. of Pediatrics,
Medical College, Baroda,
Gujarat - 390 001..

Q. 2 How is a click produced?

(When a finger is pulled, a click may be heard at the metacarpo-carpal joint. But this click is not produced again if the finger is pulled soon, once more)

Dr. Yashpaul,
Jaipur

A. 2. Usually, the click is called “knuckle cracking”. This phenomenon, “kunckle cracking” is due to mechanical subluxation of

the joint, with gas formation in the joint due to the accompanying great decrease in intra articular pressure. The subsequent vaporization of joint fluid release enough free energy to produce an audible “crack.” Once cracked, a knuckle cannot be cracked again until the gas has been absorbed and increased space between the bone returns to normal. This takes about 30 minutes.

Dr.Panchapakesa Rajendran,
Professor and Head, Dept. of Rheumatology,,
Madras Medical College,
Govt. General Hospital,
Chennai - 600 003.

Reference

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Q. 3 What is the specific treatment of zoonotic diseases caused by 1)Wolf 2)Fox 3)Dog 4) Rat 5) Cat 6)Parrot 7) Lion 8) Cheetah 9) Monkey, Pet & Carnivorous, Herbivorous wild animals.

Q.4. Are Tetvac, anti rabies vaccine and suturing of wound, necessary? If so, in which type of animal bites? What are the specific indications for tetvac, anti rabies vaccines? Cat scratch disease is known to cause encephalitis. How do you differentiate encephalitis due to animal bite and anti rabies vaccine? What is the probable cause of the two?

Dr.B.C. Ramachandra,
Harihar, Karnataka

A.3. The Zoonoses, collectively refers to diseases transmitted by animals. These can be classified

under: Bacterial, Fungal, Parasitic, Chlamydial, Rickettsial and Viral diseases. Hence specific treatment depends on targeting the etiological agent and controlling of the transmitting vector

Note: For specific treatment refer to standard

treatment protocols of zoonoses management. For details for other carnivorous and herbivorous animal sources, kindly refer to zoonoses in standard books on zoonoses.

A.4. Tet Vac is necessary in all animal bites

- antirabies treatment is indicated in bites by the following: Dogs, Cats, Parrots, Bats, Snakes, Foxes, Woodchucks.

Table 1. Zoonoses and treatment

S.No	Name of the Animals	Diseases Caused	Specific treatment
1.	Wolf	Tetanus	Anti Tetanus
2.	Fox	Echinococcosis, Hydatid disease Rabies, Tetanus	Albendazole 15mg/kg/day (Max 80 mm.) x 1-6 Months Anti Rabies, Anti Tetanus
3.	Dog	Brucellosis (rarely), Campylo bacteriasis, (Campylobacter Jejuni), Leptospirosis, Pasteurella, Multocida (Infrequently), Solmenellosis, Visceral larva migrans, Ringworm, Yersiniosis (Rarely), Cutaneous larva migrans, Dog tape worm, Hydatid diseases, Rocky maintain spotted fever, rabies	<8 yrs TMP - SMX > 8 yrs Doxycyline & Rifampicin Antidiarrheal, antipyritic etc., Kindly refer to standard treatment protocols under specific headings
4.	Rat	Leptospirosis, Rat bite fever, Typhus, Flea-borne endemic typhus (Rickettsia typhil)	
5.	Cat	Bortenella henselae (Cat - scratch disease), campylobacteriosis, Capnocytophaga, Canimorus (rarely), Pasteurella multocida, Plague, Solmenellosis, Tularemia, Yersiniosis, Ringworm, Sporotrichosis, Cutaneous larva migrans, Dog tape worm (Dyphylidium caninum) Giardiasis, Toxoplasmosis, Visceral larva migrans, Rabies.	
6.	Parrot	West Nile encephalitis/ Histoplasmosis	
7.	Lion	Not an animal sources for zoonosis	
8.	Cheetah	Not an animal source for zoonosis	
9.	Monkey	Tetanus, B virus (formerly herpes virus simiae) by Macaque monkeys	
10.	Rolents/Wild Rodents	Plague, Relapsing fever, Tularemia Ringworm, Q fever, Rocky mountain, Spotted fever, Colaradotick fever, California encephalitis, Hanta virus infection, Lymphocytic choriomeningitis.	

- Suturing of wound is generally avoided except in lacerated wounds involving face, scalp. Thorough cleaning with soap and water is most important. No need for antiseptic application.
- Viral Encephalitis following mosquito / tick bite through animal sources viz califormia (Wild rodents), Eastern equine (wild birds, poultry, houses), western equine (Wild birds, poultry, houses) St. Louis (Wild birds, poultry), Venezuelan equine (horses), Powassan (Rodents, rabbits) West Nile (Birds) have been recorded with specific manifestations.
- Encephalitis following ARV treatment has not been reported.

Dr. A. Parathasarathy,
Retd. Senior Clinical Professor of Pediatrics
Madras Medical College, Chennai.

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Q.5. 1. What is the dose of inhaled salmeterol & formoterol and also oral deriphyllin retard tablets?

2. A 10 kg child is already on inhaled budesonide 600mcg/day+oral deriphyllin 150mg retard. She is havign nocturnal cough with wheeze. How to manage her symptoms?

3. How long ketotifen can be given to children with allergic rhinitis and atopy?

4. How long sodium cromoglycate and monteleukast can be given for children with mild persistent asthma?

Dr.R.Ramakrishnan,
Coimbatore, Tamilnadu,

A.5. 1. Formoterol and Salmeterol are long acting beta agonists used only by inhaled route. Their duration of action is about 12 hours. Salmeterol is a lipophilic molecule which has a slow onset but long duration of action (25mcg per puff, 2 puff bid or HS) whereas Formoterol being less lipophilic has fast onset of action and has an equally long duration of action (12mcg per puff, 2 puff bid or HS).

The oral dose of tab Deriphyllin ratard is 10 mg/kg/dose q 12h. (Formulation is Tab 150

Table. 2. Comparison between formoterol, Salmeterol and Salbutamol

Variable	Formoterol 24mcg	Salmeterol 50mcg	Sulbutamol 200mcg
Mean increase in specific airway conductance (SAW) at 1 min	44	< 16	44
Maximum increase in SAW (time to)	135 (2h)	111 (2-4h)	110 (30 min)
Mean increase in SAW at 12 h	56	58	---
Maximum increase in FEV ₁ (time to)	27 (2h)	25 (3h)	25 (30 min)
Mean increase in FEV ₁ at 12h	10	11	---

and 300mg). For Deriphyllin OD the dose is 16-20 mg/kg/dose q 24 hours.

2. There are several issues which one will need to look into. First, check the compliance, (how frequently is the canister purchased or consumed, does it relate with recommended rate of usage). Second, is the canister under use contains medicine and functional. Third, check the inhalation technique. At this dose my presumption is the patient is using MDI with spacer. Next, it may be pertinent to look for the other triggers and co-morbidities. Rule out GER, sinusitis etc. Look for any persistent triggers in the child's environment say environmental tobacco smoke or a pet or mold/dampness in the house. If all this is fine, only then there is a need to alter the drugs. Most formulations of the long acting theophyllines become short acting if the tablet is broken or crushed. Therefore, it may be better to look for formulations which can be broken or titrated e.g. Tab Theostan CR (scored tables which can be broken into two) or spansules of Duralyn. Should the child need further drug change the options available to us are either adding a long acting beta agonist like Salmeterol or Formoterol or adding Leukotriene antagonists like Montelukast or Zafirlukast before any further

increase in the inhaled corticosteroids is done.

3. The drugs like Ketotifen if used for perennial allergy may need to be given for a very long term. However in this situation the preferred alternative may be nasal topical sprays of steroids like budesonide, mometasone etc. Ketotifen has no role in abolishing atopy and hence the drug should be used selectively in the long term. The long term use may be associated with occurrence of obesity.

4. Treatment of persistent asthma requires attempt at decreasing or withdrawing drug(s), after symptoms are fully controlled for 12 weeks or so. This is the general rule followed for inhaled corticosteroids. We in our practice attempt to withdraw Cromoglycate if the patient is totally asymptomatic for a least 6 months. We have safely used the drug for as long as 2-3 years in some patients. There is as yet limited experience available for montelukast. However both these drugs do not require any tapering before withdrawal.

Dr. Varinder Singh,
200, Dhadral Apartments,
Pitampura, New Delhi - 110 034.

NEWS AND NOTES

Meeting of the International Pediatric Transplant Association

Rio de Janeiro (Brazil) 5-9 April 2003

www.iptaonline.org

BOOK REVIEW

Title : Fundamental of Pediatrics

Author : K.E. Elizabeth

Publisher : Paras Publishing, Hyderabad / Bangalore.

Constant updating of knowledge of pediatrics is essential for all practicing pediatricians. Undergraduate medical students also require a working knowledge of pediatrics, as Pediatrics is a separate paper for them as per the guidelines of Indian Medical Council. Postgraduate students are constantly on the lookout for textbooks which will improve their clinical skills and enhance their performance in examinations. 'Fundamentals of pediatrics' authored by Dr. K.E. Elizabeth meets the felt needs of the above three groups to a great extent.

The book is written in 23 chapters covering various aspects of pediatrics. The first chapter comprehensively deals with history taking and physical examination including anthropometry. The subsequent chapters on growth and development, nutrition and immunization contain all the important informations on these subjects. In the chapters on fluid and electrolytes, neonatology, immunology and infectious diseases, the author has included many practical aspects such as fluid and electrolyte therapy algorithms, neonatal resuscitation guidelines, graphic charts on phototherapy and exchange transfusion indications, acute flaccid paralysis (AFP) surveillance programme and revised National TB control programme, to name a few.

The pragmatic approach of the author is evident in her emphasis on topics of greater relevance to our country such as persistent diarrhoea and fulminant hepatitis in the chapter on Gastro Intestinal system, asthma management and postural therapy in the chapter on respiratory system and tetralogy of Fallot and rheumatic heart disease in the chapter on cardiovascular system. In all the chapters a working knowledge on anatomy and physiology of that system along with relevant investigations is provided first, followed by precise and recent information on various diseases. The chapter on neurology includes detailed clinical examination followed by description of common neurological problems highlighting head injury, cerebral palsy and bladder dysfunction. State-of-art information on gene therapy and human genome project are provided in the chapter on genetics. Various National health programmes such as Baby Friendly Hospital Initiative (BFHI). Reproductive and child Health (RCH) programme and Integrated Management of Childhood Illness are discussed under community pediatrics. This chapter has attempted to bridge the information gap in the minds of pediatricians regarding many child health programmes and health indices. There is an unique chapter on curriculum of Pediatrics to guide the teachers and students to focus on particular topics.

The printing and layout of the book is excellent and the language is user friendly. Tables, algorithms and highlighting of important points in boxes are used appropriately and correction of a few spelling and formatting errors in the subsequent editions will add to the reputation of this book.

Fundamentals of Pediatrics is a textbook, many learning and learned pediatricians will enjoy reading and get useful information.

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