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"IAP-IJPP CME 2014"

GENERAL ARTICLE

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IAP - IJPP CME 2014

NEWBORN METABOLIC SCREENING

***Durai Arasan G**
****Suba Karthikeyan**
*****Ratnakumari TL**

Abstract: *Screening for genetic and metabolic disorders is highly essential and productive, more so when devised early in the new born period itself. Development of technology in the field of molecular biology and biochemistry has gone a long way in detecting disorders even before the first of the earliest symptoms and signs of a metabolic disorder makes its appearance and helps to reduce morbidity and mortality. Universal newborn screening should be initiated for disorders which are relatively more prevalent and for which definitive and effective treatment are available. Screening tests are only tools to detect the disorder but confirmatory tests should follow, if screening tests are positive.*

Keywords: *Metabolic screening, Molecular test, Universal screening.*

Screening for any disorder in individuals is a strategy used for identifying a disease before the onset of signs or symptoms, thus enabling earlier detection and management with the aim to reduce morbidity and mortality. Although screening may lead to an earlier diagnosis, not all screening tests have been shown to benefit. With regards to new born (NB) screening, they are available in different domains such as developmental, clinical, hearing, metabolic and critical congenital heart defects. In the developed countries it has come to stay as public health programme, whereas in India it has not been universally mandated as a state programme.

Newborn metabolic screening

Newborn metabolic screening (NBS) is designed to screen infants shortly after birth for a list of conditions that are treatable, but not clinically evident at the time of screening. These conditions include inborn errors of metabolism, endocrine disorders, hemoglobinopathies, immunodeficiency, cystic fibrosis and so on. Early treatment of these rare disorders may significantly reduce mortality and morbidity in affected patients. Infants who screen positive undergo further testing to determine if they are truly affected with a disease or if the test result is false positive. Neonatal metabolic screening began in the early 1960s with the work of Robert Guthrie, who developed a screening test for phenylketonuria (PKU) and a system for the collection and transportation of small blood samples on filter paper (known as the Guthrie card).[1] This technique has been used to detect other inborn errors of metabolism including maple syrup urine disease, homocystinuria, tyrosinemia and histidinemia.

Technical advances have facilitated the expansion of newborn screening to include detection of additional disorders.

- Radioimmunoassay for TSH and thyroxine (T4) is made a screening test for congenital hypothyroidism.[2]
- Isoelectric focusing and liquid chromatography allow mass screening for hemoglobinopathies.
- The polymerase chain reaction (PCR) facilitate screening for mutations in the hemoglobin genes in DNA extracted from dried blood samples.[3,4]
- Tandem mass spectrometry (also referred to as MS/MS)[5-8] detects molecules by measuring their mass (weight) and uses a series of two mass spectrometers, which sort out the samples, and identify and weigh the molecules of interest. It is best used for screening inborn errors of organic acids, fatty acids and amino acid metabolism. Newer methods have been developed for using this technique, to screen for lysosomal storage disorders also.[9]
- New biochemical and genetic tests have been approved for newborn screening for cystic fibrosis[10] and severe combined immunodeficiency.[11]

Criteria for screening

The major hindrances for establishing an effective screening program in India are the costs involved,

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the non-availability of demographic data and true incidence data of the disease in question, massive annual birth cohort and the limitations of treatment modalities for some of the diseases.

The Wilson and Jungner criteria[12] mandate certain factors and data for the cost effective and efficient running of a screening program (Box 1).

Recently in India, some data have been made available for some of these disorders so much so that it has helped us to focus on a few core diseases such as congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), galactosemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, biotinidase deficiency and cystic fibrosis.[13-17] The incidence, diagnosis and treatment of some of these conditions are shown in Table I.

Timing of sample

The time of sampling for screening is critical to obtain accurate results. The American Academy of Pediatrics[18] has advocated the ideal time of sampling after 72 hours and within 7 days of life. In our country this has serious limitations, due to high home delivery rate, early discharge from hospitals and cultural taboos related to screening. But as the metabolites can be measured as early as 24-48 hrs when enteral feeding is started and renal and hepatic functions are mature, screening can be done after 24 hrs itself. Since a dried blood spot (DBS) remains stable for years, the accepted mode of collection is capillary blood from the heel puncture (Fig.1).[19] Advantages of DBS are ease of sample collection and transfer with relative cost effective testing method. The results of TMS are expressed as primary and secondary analytes with their cut off values

Box 1. Wilson and Jungner criteria for disease screening

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

Table I. Incidence, diagnosis and available treatment

Condition	Incidence	Diagnosis	Treatment
CAH	1:2575	ELISA	Steroids
G6PD Deficiency	1:15 to 1:200	Enzyme assay	Avoid hemolysis inducing drugs/food
CH	1:500-600 to 1:3400	ELISA	Thyroxine supplementation
Hemoglobinopathies	High in tribals. (Sickle cell disease / trait / Beta) SCD/SCT/S-beta	HPLC	Early appropriate treatment
Cystic fibrosis	1:40,000 & 1:100,000	ELISA	Drugs and physiotherapy
Galactosemia	1:10,000	ELISA	Special diet

as well as ratios of metabolites with their cut off values. These cut off values were derived by analysis of several million samples across all ethnicities. Pattern recognition and the ratios of key metabolites help us to ascertain true positive results and reduce the false positive rate to less than 0.3%.

Collection of cord blood may be a feasible alternative and has been used for newborn screening of congenital hypothyroidism (CH) in some countries e.g., Malaysia, but this is not a solution for other metabolic errors, which do not have elevated analytes before birth.

Factors that can affect the result

There are multiple factors that can affect the results and can give either false positive or false negative results. Hence, some mandatory information should be recorded on the newborn screening card to aid in the interpretation of results. These include gestational age of the neonate, birth weight (as prematurity and low birth weight can affect the results), neonatal jaundice, any treatment undergone, parenteral nutrition, any blood products received, and type of feeds the newborn is on. This information can help us in interpreting the results.

Available tests

Subsequent to the Guthrie bacterial inhibition assay for PKU, there have been many technological advances in NBS, including radioimmunoassay, colorimetric and fluorometric immunoassays, isoelectric focusing, high-performance liquid chromatography and MS/MS. In the 1990s, MS/MS allowed the simultaneous testing of an array of metabolic conditions using a single 3 millimeter-sized specimen punched from a dried blood spot[20] and is well-suited for the analysis of amino acids and acylcarnitines in dried filter paper blood specimens.[20,21] It has revolutionized the use of the limited blood specimen and enhanced the screening capabilities.[20]

Recent advances have made possible extraction of DNA from dried blood spots on filter paper. Subsequently, DNA testing was introduced into newborn screening (NBS), allowing the dual use of the dried bloodspot specimen matrices for both biochemical and molecular tests. DNA testing in the context of NBS has, until recently, been primarily used as a second-tier test.

Dried Blood Spots

Over the past several years dried blood spot (DBS) sampling technique has emerged as a pertinent method in both qualitative and quantitative bioanalysis context. In DBS method, blood sample is directly soaked on to a paper and after drying it can be analyzed by modern analytical, immunological or genomic detection systems. Several advantages of DBS technique such as low blood volume requirement, transportation and storage without special treatment, better stability of analytes and reduced unforeseeable exposure of bio-hazard to analysts, make it the most appropriate blood sampling technique.[22]

Recommended technique[19]

Ensure the baby is cuddled and in a secure position for taking the sample – swaddling the baby may reduce pain/discomfort. Clean the heel by washing thoroughly with tepid, plain water. If fecal matter cannot be removed from the foot with water, use a mild, unperfumed soap to clean away the fecal matter and then rinse the foot thoroughly. Do not use alcohol or alcohol wipes. The heel should be completely dry before taking the sample. Wash hands and apply gloves. Ensure the baby is warm and comfortable. Additional warming of the foot is not required. Obtain the sample using an automated incision device designed for use on newborns. Manual lancets must not be used. The external and internal limits of the calcaneus are the preferred puncture site. Avoid posterior curvature of the heel (Fig. 2). Allow the heel to hang down to assist blood flow.

The aim is to fill each circle on the newborn blood spot card, using a single drop of blood (Fig. 1). Wait for the blood to flow. Allow one spot of blood to drop onto each of the circles on the card. Do not allow the heel to make contact with the card. Do not squeeze the foot in an attempt to increase blood flow. Allow the blood to fill the circle by natural flow and seep through from front to back of the card. Fill each of the four circles completely and do not layer the blood. Do not compress the blood spot in order to ensure the blood has soaked through to the reverse of the card (Fig. 3). The quick transport of the sample is also essential, as some metabolites are relatively unstable and so exposure to heat and humidity can give false negative results.

Early antenatal metabolic screening

Most of the IEMs have autosomal recessive transmission at conception. Thus each sibling has a 25% chance of being affected and a 50% chance of being an asymptomatic carrier. Prenatal screening is done when there is previously affected sibling or if there are early markers in the prenatal ultrasound suggestive of a metabolic disorder. The options are chorionic villus sampling at 10-12 weeks or amniocentesis at 15-18weeks. The tests

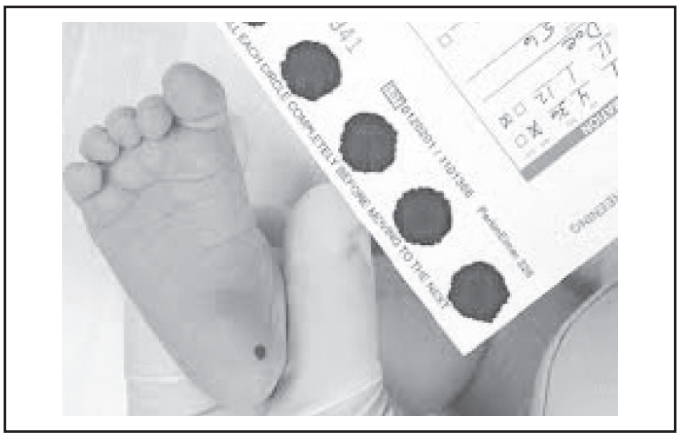

Fig. 1. Dried blood spot

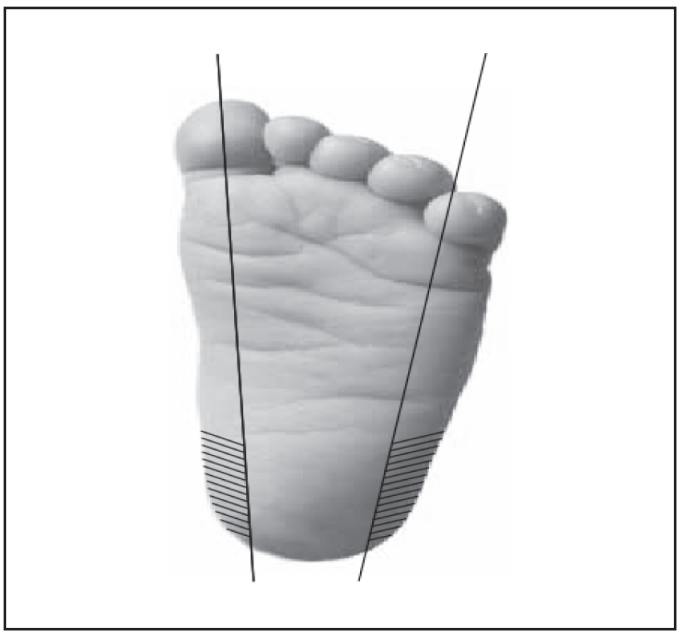

Fig. 2. Site of heel puncture

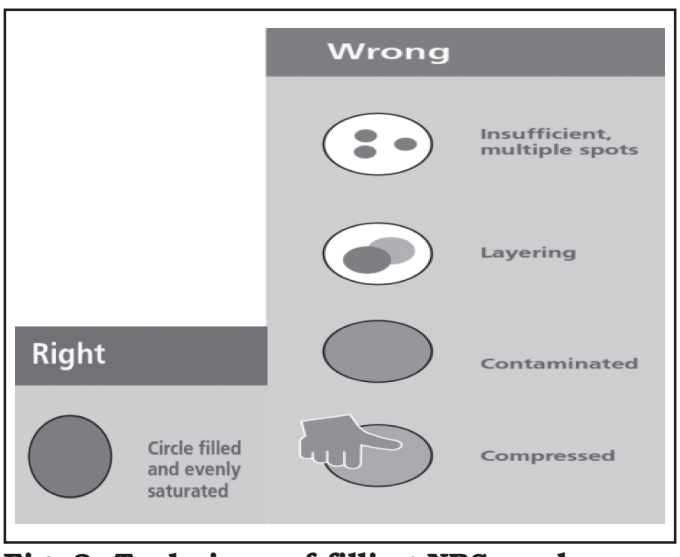

Fig. 3. Technique of filling NBS card

which form a part of prenatal screening are measurement of analytes (toxic metabolites), assessment of enzyme activity and molecular genetic testing using the DNA extract, the last one being the confirmatory test, but its availability in India for all the disorders is limited.

The approximate cost and some of the labs where the screening is done are shown in Annexure I & II.

Points to Remember

- ***Universal newborn screening should be initiated for disorders which are relatively more prevalent with definitive and effective treatment available for the same.***
- ***Screening test such as TMS is only a screening tool, confirmatory testing is mandatory for positive screens.***
- ***Early prenatal testing (screening) can be of immense help to families with affected siblings with no treatment options wherein the parents have a choice in the further course of pregnancy.***

References

1. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics 1963; 32: 338-343.
2. Dussault JH, Laberge C. [Thyroxine (T4) determination by radioimmunological method in dried blood eluate: new diagnostic method of neonatal hypothyroidism?]. Union Med Can 1973; 102: 2062-2064.
3. Githens JH, Lane PA, McCurdy RS, Houston ML, McKinna JD, Cole DM. Newborn screening for hemoglobinopathies in Colorado. The first 10 years. Am J Dis Child 1990; 144: 466-470.
4. Shafer FE, Lorey F, Cunningham GC, Klumpp C, Vichinsky E, Lubin B. Newborn screening for sickle cell disease: 4 years of experience from California's newborn screening program. J Pediatr Hematol Oncol 1996; 18: 36-41.
5. Chace DH, DiPerna JC, Naylor EW. Laboratory integration and utilization of tandem mass spectrometry in neonatal screening: a model for clinical mass spectrometry in the next millennium. Acta Paediatr Suppl 1999; 88: 45-47.
6. Naylor EW, Chace DH. Automated tandem mass spectrometry for mass newborn screening for disorders in fatty acid, organic acid, and amino acid metabolism. J Child Neurol 1999;14 Suppl 1: S4-8.
7. Bartlett K, Eaton SJ, Pourfarzam M. New developments in neonatal screening. Arch Dis Child Fetal Neonatal Ed 1997; 77: F151-4.
8. Meikle PJ, Ranieri E, Simonsen H, Rozaklis T, Ramsay SL, Whitfield PD, et al. Newborn screening for lysosomal storage disorders: clinical evaluation of a two-tier strategy. Pediatrics 2004; 114: 909-916.

9. Scott CR, Elliott S, Buroker N, Thomas LI, Keutzer J, Glass M, et al. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr 2013; 163: 498-503.
10. Gregg RG, Simantel A, Farrell PM, Koscik R, Kosorok MR, Laxova A, et al. Newborn screening for cystic fibrosis in Wisconsin: comparison of biochemical and molecular methods. Pediatrics 1997; 99: 819-824.
11. Chan K, Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol 2005;115: 391-398.
12. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from:http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf
13. http://news.chennaionline.com/chennai/ICMR-releasesresults-of-study-on-Congenital-Hypothyroidism/58cca920-765d-492b-8fd3-9b34a8ac2351.col
14. Kapoor S, Kabra M. Newborn screening in India; current perspectives. Indian Pediatr 2010; 47: 219-224.
15. Kaur G, Srivastav J, Jain S, Chawla D, Chavan BS, Atwal R, et al. Preliminary report on neonatal screening for congenital hypothyroidism, congenital adrenal hyperplasia and glucose-6-phosphate dehydrogenase deficiency: a Chandigarh experience. Indian J Pediatr 2010;77: 969-973.
16. Sahai I, Zytkowicz T, Rao Kotthuri S, Lakshmi Kotthuri A, Eaton RB, Akella RR. Neonatal screening for inborn errors of metabolism using tandem mass spectrometry: experience of the pilot study in Andhra Pradesh, India. Indian J Pediatr 2011; 78: 953-960.
17. Rao AN, Kavitha J, Koch M, Suresh Kumar V. Inborn errors of metabolism: Review and data from a tertiary care center. Indian J Clin Biochem 2009;24: 215-222.
18. American Academy of Pediatrics Newborn Screening Authoring Committee. Newborn screening expands: recommendations for pediatricians and medical homes — implications for the system. Pediatrics 2007;121(1): 192-217.
19. The UK Newborn Screening Programme Centre. The UK Newborn Screening Programme Centre's Guidelines for Newborn Blood Spot Sampling, February 2012. A UK National Screening Committee publication, ISBN: 978-0-9562374-2-2.
20. Chace DH, Kalas TA, Naylor EW. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003; 49: 1797-1817.
21. Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metab Dis 1990; 13: 321-324.
22. Sharma A, Jaiswal S, Shukla M, Lal J. Dried blood spots: concepts, present status, and future perspectives in bioanalysis. Drug Test Anal 2014; 6(5): 399-414.

Annexure - I

Cost of tests

Disorders	Amount
5 disorders	Rs. 1000-1500
45 IEMs	Rs. 2500-3000
5 + 45 IEM	Rs. 3500-4000
5+ 45 IEM+ Hb	Rs. 4000-4500
111 disorders - urine GC/MS	Rs. 4000

Annexure - II

Some labs where screening can be done
Sandor, Hyderabad http://sandorlifesciences.co.in
Babyshield www.babyshield.com
NIMHANS, Bangalore
Neogen labs www.neogenlabs.com
Sir Gangaram Hospital, Delhi

NEWS AND NOTES

Annual CME of Kalawati Saran Children's Hospital, New Delhi, India

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NON THRIVING YOUNG INFANT

***Manikumar S**
****Kumutha J**

Abstract: *Failure to thrive (FTT) is defined as an infant's inability to maintain a normal growth pattern. This can be identified early in a child if growth monitoring is carried out regularly. The preferred tool is WHO standard in our population. Although it is now accepted that FTT has a predominantly organic origin, the association of emotional and physical deprivation should also be borne in mind. Emphasis is given on recognition of certain patterns which will help in arriving at an etiological diagnosis. A targeted workup rather than a battery of investigations will yield a better result. Hospitalization is essential only for acutely sick neonates. Incorporating community nutritional interventions with specific therapy may be the way forward in comprehensive management of a non thriving neonate.*

Keywords: *Failure to thrive, Growth monitoring, Targeted work up, Integrated management.*

Growth monitoring by use of growth charts is an essential part of health assessment for all children. Divergence from the standard growth may occur at any time point during childhood. Failure to thrive (FTT) is a term used to describe inadequate growth or the inability to maintain growth, usually in early childhood. A neonate or an infant or a child whose current weight or rate of weight gain is significantly below that expected of similar children of the same sex, age and ethnicity is considered to be thriving poorly.[1]

Definition

Failure to thrive (FTT) is commonly defined as either a weight for age that falls below the 5th percentile on multiple occasions or a weight deceleration that crosses two major percentile lines on a growth chart.This might be simple in the office setting but has a low positive predictive value for true under-nutrition. The common anthropometric criteria for FTT are given in Box 1. There is no consensus on which criteria to use. But these criteria should be met on multiple occasions. FTT is often expressed by various terms like "Growth delay", "Growth failure", "Failure to grow", "Growth deficiency", and "Failure to gain weight".

Box.1 Common anthropometric criteria used for FTT[2]

- Weight deceleration crossing two major percentile lines
- Weight for age less than the 5th percentile
- Weight less than 75 percent of median weight for age
- Weight less than 75 percent of median weight for length
- Weight velocity less than the 5th percentile
- Body mass index for age less than the 5th percentile
- Length for age less than the 5th percentile

NOTE: Criteria should be met on multiple occasions

In a study by Olsen et al, 27% of all infants met at least one definition for FTT during the first year of life[1]. Wherever possible, the WHO growth standards are used and caution is exercised when using CDC reference charts, as they may overestimate poor growth.

A typical example is shown in Fig.1a and 1b. The CDC chart indicates that the weight is consistently below the 3rd centile (Fig.1a) whereas the same weight when plotted in the WHO growth chart shows that there is a significant catch up growth (crossing major centiles), which indicates a healthy trend (Fig.1b).

A decreased weight may not always imply a decreased growth. In fact some parents may rightly perceive this as - "My baby is just small for her age". Some babies are genetically small reflecting parent's size. Children born small for gestational age (SGA) may never catch up, whereas premature/intrauterine growth restricted(IUGR) babies show a good catch-up growth. For these babies, a single point measure of weight may be < 5th centile, but if it follows

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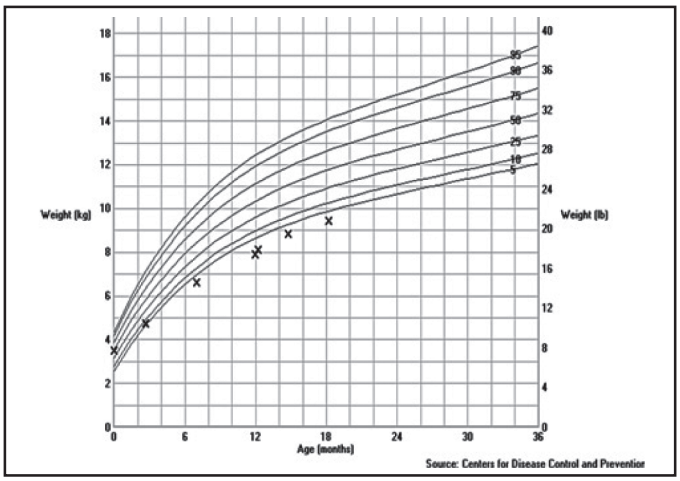

Fig.1a. Growth monitoring - CDC chart

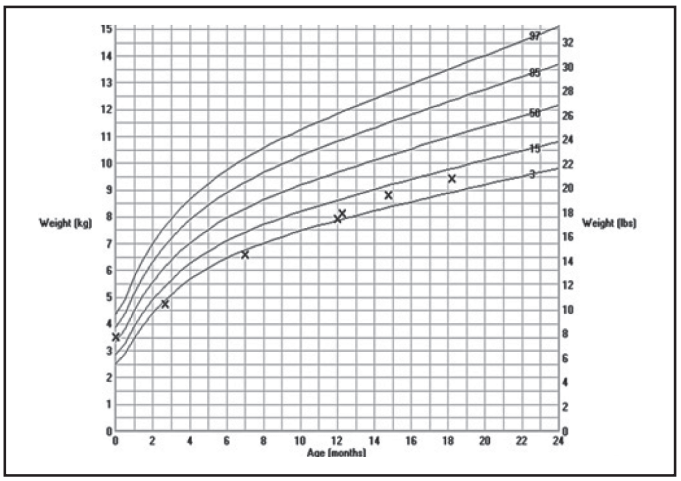

Fig.1b. Growth monitoring - WHO chart

a growth curve with good interval growth, it is of no concern. Similarly babies born larger than long-term genetic potential like infants of diabetic mothers (IDM) show decreased growth rate in the first 2 years. These young infants who show slow gain in weight, are usually alert, will have a good muscle tone, void straw coloured dilute urine at least six times per day, pass stools frequently, (or if infrequent, large and soft), take eight or more feeds and consistent weight gain is recorded, though slow. FTT is a common problem in pediatric population. It accounts for 1%-5% of referrals to children's hospitals/tertiary care centres.[3,4] FTT is often under diagnosed. As high as 20-50% may not be picked up by physicians.

Etiology

FTT is usually a sign of under nutrition and may be due to biologic, psychosocial and environmental processes. It is just a physical sign and never a diagnosis by itself. It is imperative that the exact cause and diagnosis is established by proper work up of the child. The biggest challenge to a physician in managing an infant with failure to thrive is establishing the etiology. It is very difficult to devise a single unified algorithm. Often it is a combination of many factors that leads to failure to thrive. The various factors include timing of the presentation, feeding pattern, type of feeding, environmental aspects and clinical abnormality.

Prenatal factors often predispose to non-thriving neonate. These factors include maternal malnutrition, alcohol consumption, smoking, medications, infections, IUGR, chromosomal anomalies and prematurity. Babies born with intrauterine infections (TORCH) and severe abnormalities may show signs of poor nutrition since birth and will continue to grow poorly. The common causes for a non - thriving neonate and infant include feeding dysfunction, hypernatremic dehydration, inborn errors of metabolism

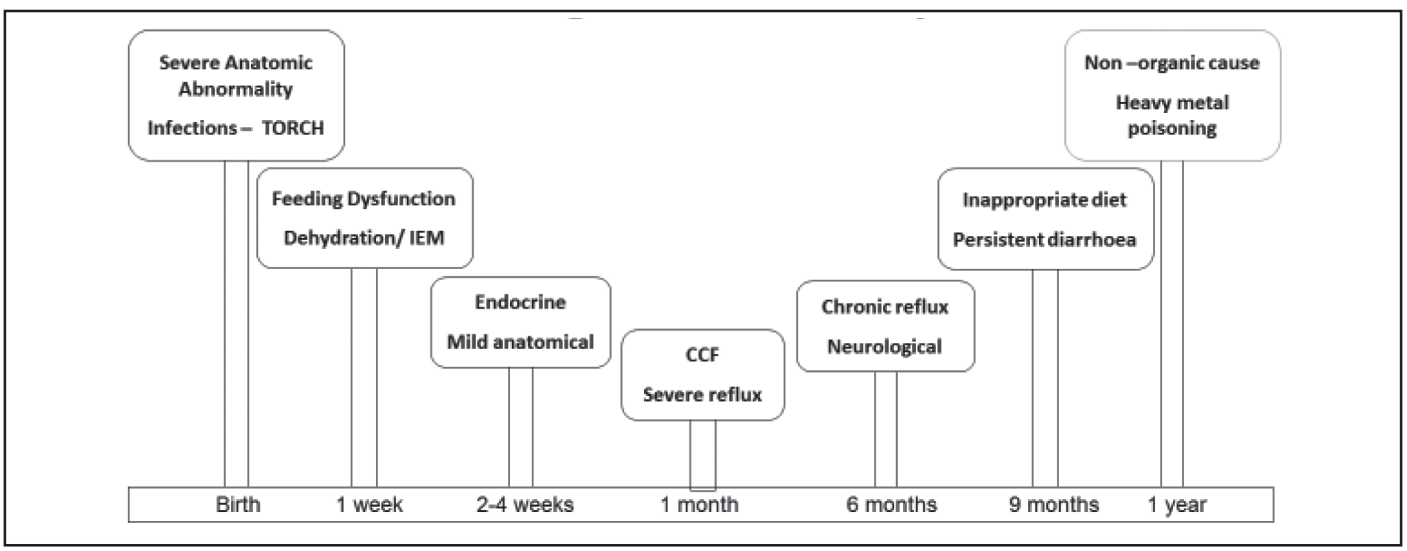

Fig.2. Timing of abnormality

(IEM), endocrine disorders, anatomical defects like cleft palate, congenital heart disease (CHD) with congestive heart failure (CHF), severe gastro esophageal reflux disease(GERD), malabsorption, short bowel syndrome, neurological abnormality, inappropriate diet, persistent diarrhea and environmental factors.

Usually in the immediate newborn period, the most common cause will be problems with breastfeeding. These will be compounded by certain other factors which include early term (37 to 38 weeks), milder degrees of IUGR, delay in initiation of breastfeeding, pre-lacteals, inexperienced mothers and lack of proper breastfeeding guidance. If these issues are not addressed properly and continue into the second week, especially in summer months, they can lead to hypernatremic dehydration. Endocrine causes usually present at 2-4 weeks (Fig.2). The most common cause will be salt losing variant of congenital adrenal hyperplasia(CAH). This goes unnoticed especially in a male neonate, as female neonates will get noticed or be diagnosed early because of ambiguous genitalia. By the end of first month, cardiac causes have to be thought of when the pulmonary pressures settle down and the shunt from left to right increases thereafter. Acyanotic heart diseases can typically manifest as CHF during this time (Fig.2).

Organic vs non-organic cause

Broadly, the causes can be classified as organic or non-organic based upon whether the problem is with the child or the environment. The physical indicators of non-organic causes include lack of age appropriate eye contact, vocalization, lack of interest in environment, chronic diaper rash and flat occiput. Though this organic/non-organic dichotomy approach appears simple, it poses some problems. It is often difficult to place a child in either category (Fig.3). It also fails to account for the compounding effect of problems in both the child and the environment.

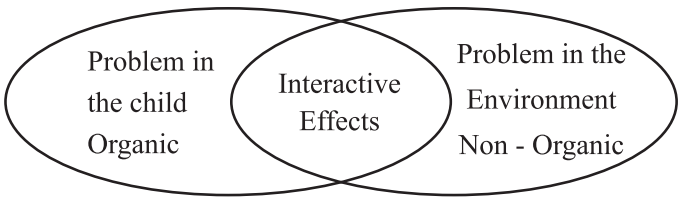

Fig.3.Spectrum of causes

System-wise approach

Most of the organic causes of failure to thrive have symptoms which localize to a particular system. Some of the commonest causes pertaining to each system are given in the Table I.

Table I. Common causes of FTT

Cardiac	CHF, cyanotic heart disease, vascular rings
Renal	Urinary tract infection, chronic pyelonephritis, renal tubular acidosis, renal failure
Endocrine	Adrenal insufficiency, CAH, hypo/hyperthyroidism, rickets
Respiratory	Cystic fibrosis, BPD, chronic respiratory failure
Infectious Disease	TORCH, chronic infections, TB/HIV
Genetic / Metabolic / Chromosomal disorders	IEM, congenital syndromes, fetal alcohol syndrome
CNS	Cerebral palsy, hypothalamic / CNS tumours, neuromuscular disorders.
Gastrointestinal	Pyloric stenosis, GERD, malabsorption,short bowel syndrome, Hirschsprung disease, chronic cholestasis, chronic diarrhea

Normal nutrition is maintained in an infant when there is perfect balance between food intake, utilization, output and growth. A problem in any of these steps can be a reason for poor growth. Some of the typical examples are outlined in Box.2.

Box 2. Factors affecting nutritional status

- **Inadequate caloric intake**
  Breastfeeding problem, improper formula preparation, gastro-esophageal reflux, caregiver depression, lack of food availability, cleft lip or palate
- **Inadequate caloric absorption**
  Malabsorption, pyloric stenosis, gastrointestinal atresia or malformation, IEM
- **Excessive caloric expenditure**
  Thyroid disease, chronic infection or immunodeficiency, chronic pulmonary disease, congenital heart disease or heart failure, malignancy
- **Excessive output**
  Persistent diarrhea

Clinical presentation

A young infant failing to thrive will be apathetic or crying incessantly, has poor skin turgor, poor muscle tone, (Fig.4) will have decreased urination with a "strong" urine odour, will have infrequent and scanty stools and takes fewer than eight feedings, which are often brief with no evidence of milk-ejection and may also be losing weight.

Findings suggestive of CHD or CHF are recurrent or severe respiratory infections, taking a long time to feed, respiratory distress, murmur and edema. The other red flag signs are prolonged jaundice, recurrent vomiting, diarrhea, dehydration, dysmorphic features, hyperpigmented skin, mucocutaneous lesions, organomegaly, sexual ambiguity and developmental delay.

Usually a careful history and a good targeted examination will clinch the diagnosis. There is no substitute for observation of feeding session. Assessment of feeding must include surveillance of positioning, attachment, swallowing or motor dysfunction, time allowed for feeding, parent-child interaction, method of preparing food and whether the baby is being cuddled during feeds. Developmental assessment should importantly include tone examination. Transient tone abnormalities are relatively common in a growing preterm baby. But persistent abnormal tone definitely affects feeding. Hypotonic infants have weak suck, poor lip closure and frequent slipping off the breast. Infants with hypertonia exhibit extended posture, excessive irritability and strong bite reflex.

Some acute presentations include dehydration, hyperthermia, hypernatremia, shock, dyselectrolytemia, hypoglycemia and superadded infections. These should be

Table II. Some typical patterns of presentation.

S. No	Disease	Presentation	Investigation results
1	Hypernatremic dehydration	Anxious primipara mother, elective LSCS, term baby with problem in latching which was not addressed properly. Noticed to have significant jaundice requiring phototherapy, high temperature, lethargy, poor feeding and vomiting, worsening sensorium, cumulative weight loss more than 15%	Hypernatremia,increased serum osmolality, metabolic acidosis, elevated renal parameters, high urine specific gravity.
2	Congenital adrenal hyperplasia	Two weeks old female neonate with virilization, parental consanguinity, no problems in feeding, passing adequate stools, good urine output, severe dehydration, hyper-pigmented skin, acidosis, shock and hypoglycemia	Hyponatremia, hyperkalemia, elevated serum 17 hydroxy progesterone, low serum cortisol
3	Acyanotic CHD with heart failure	6 weeks old young infant presenting with cough and breathlessness. Suck rest suck feeding cycle. Examination reveals tachycardia, murmur, hepatomegaly and no obvious cyanosis	Structural defects in echocardiography, abnormal flow in Doppler study and cardiac dysfunction
4	Short gut syndrome	A neonate who has not passed meconium even after 24 hours of birth, prsenting with abdominal distension, vomiting and diagnosed to have a surgical problem, requiring resection of intestines and ileostomy. Post operatively he has large volume stools and icterus which could not be attributed to any sepsis. Also showing signs of fat soluable vitamin deficiency	Conjugated hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time, low Vitamin B12 and vitamin D.

identified and corrected prior to proceeding for etiological analysis. Often recognising certain patterns will help to a great extent (Table II).

Investigations

Routine laboratory testing identifies the cause in less than 1% of young infants who are not thriving and is not generally recommended.[5] There should be no fishing investigations.[6] Targeted investigations like stool pathogens, stool fat, cystic fibrosis screening, full biochemistry, detailed metabolic profile, urine screening/culture, thyroid function tests, ECHO and Liver function tests would be useful in specific cases.[7]

Treatment

The importance of nutrition for brain development in the first 2 years of life should be emphasised. Unless corrected earlier, malnutrition can have long lasting detrimental effects on the growing brain. A multidisciplinary approach may be needed for getting good improvement.

Hospitalization vs outpatient care

The advantages of hospitalization include easier observation and control of feeding. It also provides an opportunity to observe the parent-child interaction and medical evaluation can be done easily. The disadvantages of hospitalization include obviously the cost and the different environment which may pose some problems with evaluation.

The compelling indications for hospitalization include hypothermia, bradycardia, hypotension, extreme failure to thrive (weight below birth weight at 6 weeks) and when the distance and transportation issues mean outpatient management is not practical. It is also necessary when outpatient management has failed or when work up is needed.

Nutritional management: Feeding counselling is an important intervention which will ensure adequate intake. Energy need is about 150% of calories required for the expected weight. The normal caloric requirements in 0 to 6 months is at least 110 kcal/kg/d and in 6 to 12 months is around 98 kcal/kg/d. The basal intake of proteins should be 2.2 g/kg/day.[8] Target a weight gain of at least 30 g/d in 0-3 mo, 18 g/d in 3-6 mo, 12 g/d in 6-9 mo, 9 g/d in 9-12 months. The protein gap may be difficult to bridge when the baby is on milk feeds alone. There may be a need to increase the volume of feeds. Some growing preterm babies tolerate upto 200-300 mL/kg/day of milk. If still not thriving well, babies may require human milk fortifiers. Consider nasogastric feeds if no catch up in 4 weeks. Consider gastrostomy if 3 months of nasogastric feeding fails.

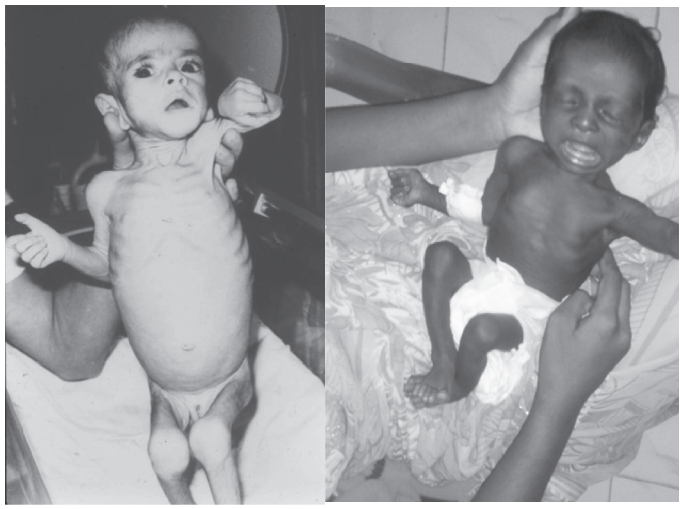

Fig.4. Typical appearance of infants with FTT

Specific therapy: Definitive therapy along with appropriate nutritional management effects better response in an young infant who shows signs of failure to thrive. Some of the specific therapies include fluid resuscitation, correction of dyselectrolytemia, hormone replacement, salt replacement, control of heart failure and infection, surgical intervention and psychological support to the parents.

Follow up

If clinically and socially stable, these infants can be on frequent observational follow up. Even if clear organic cause is evident, one should never forget about psychosocial components - most organic causes have mixed non-organic component. Family should be clearly appraised about seriousness of child's status for ensuring regular follow up visits. Family should be educated on correcting bad cultural practices which are detrimental to growth of the infant. Follow up visits will assess dietary constituents, caloric intake (24 hour recall basis) method of feeding the child and adherence to specific therapy instituted apart from growth monitoring and developmental assessment. All important members of the multidisciplinary team should be involved in assessment and treatment of the infants.[9] Long term follow up should also be encouraged with monitoring of physical growth as well as neurodevelopment achievement both in the psychomotor as well as in the mental components.

Prognosis

Natural history of FTT is gradual improvement over a period but with a lasting deficit. Stunting and low weight are the important long term consequences.Reduced head size is associated with significant developmental delay both in motor and cognitive components. Head growth is maximum in the early infantile period and any disturbance in that can have long term sequelae. These infants have a typical pattern of motor delay more prominent than cognitive delay in the early stages. Early motor development has a strong association with future cognitive outcome according to Piaget's theory. Long term follow up studies on such babies confirm such an association. Even in cases of non-organic failure to thrive, there can be intellectual abnormalities in 15-67%, and behavioural disturbance in 28-48%.[8] They can also have persistent disorders of growth and increased susceptibility to infection.

Points to Remember

- ***Growth monitoring with WHO standards is essential.***
- ***FTT is a sign of under nutrition, which could be of diverse etiologies.***
- ***Look specifically for factors affecting the balance between food intake, utilization, out put and growth.***
- ***Nutritional counseling plays a vital role apart from the nutritional and specific therapies, both at hospital and community level.***

References

1. Olsen EM, Petersen J, Skovgaard AM, Weile B, Jørgensen T, Wright CM. Failure to thrive: The prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child 2007; 92(2):109-114.
2. Failure to thrive. Criteria for determining disability in infants and children summary. Evidence report/technology assessment: Number 72. AHRQ publication no. 03-E019. Rockville, Md.: Agency for Healthcare Research and Quality; March 2003.
3. Frank DA, Zeisel SH. Failure to thrive. Pediatr Clin North Am 1988;35:1187–1206.
4. Shah MD. Failure to thrive in children. J Clin Gastroenterol 2002;35:371-374.
5. Berwick DM, Levy JC, Kleinerman R. Failure to thrive: diagnostic yield of hospitalisation. Arch Dis Child 1982;57:347-351.
6. Sills RH. Failure to thrive. The role of clinical and laboratory evaluation. Am J Dis Child 1978;132:967-996.
7. Stephens MB, Gentry BC, Michener MD, Kendall SK, Gauer R. Clinical inquiries. What is the clinical workup for failure to thrive? J Fam Pract 2008;57(4):264-266.
8. Committee on Nutrition, American Academy of Pediatrics. Failure to thrive. In: Pediatric Nutrition Handbook, 6th edn, Kleinman RE (Ed), American Academy of Pediatrics, Elk Grove Village, IL 2009; p601.
9. Wright CM. Identification and management of failure to thrive: A community perspective. Arch Dis Child 2000; 82: 5–9.

CLIPPINGS

Duration of Pertussis Immunity After DTaP Immunization: A Meta-analysis

Pertussis incidence is increasing, possibly due to the introduction of acellular vaccines, which may have decreased the durability of immune response. We sought to evaluate and compare the duration of protective immunity conferred by a childhood immunization series with 3 or 5 doses of diphtheria-tetanus-acellular pertussis (DTaP).

Eleven of the twelve articles were included from Medline and Embase for meta-analysis. which contained a measure of long-term immunity to pertussis after 3 or 5 doses of DTaP.

There was no significant difference between the annual odds of pertussis for the 3- versus 5-dose DTaP regimens. For every additional year after the last dose of DTaP, the odds of pertussis increased by 1.33 times (95% confidence interval: 1.23–1.43). Assuming 85% vaccine efficacy, it was estimated that 10% of children vaccinated with DTaP would be immune to pertussis 8.5 years after the last dose. Although acellular pertussis vaccines are considered safer, the adoption of these vaccines may necessitate earlier booster vaccination and repeated boosting strategies to achieve necessary "herd effects" to control the spread of pertussis.

Ashleigh McGirr, David N. Fisman. Duration of Pertussis Immunity After DTaP Immunization: A Meta-analysis. Pediatrics *doi: 10.1542/peds.2014-1729.*

IAP-IJPP CME 2014

REFRACTORY ANEMIA

**** Aruna Rajendran***

Abstract: *Iron deficiency anemia refractory to therapy is a frequently encountered problem in pediatric outpatient practice. This article will focus on clinical scenarios answering the common issues such as when to term iron deficiency anemia as refractory to therapy, the possible etiologies and the diagnostic work up required in such cases.*

Keywords: *Refractory anemia, Iron deficiency, Children.*

According to National family health survey (NFHS)-3 data, 70% of Indian children have iron deficiency anemia (IDA).[1] Therefore, IDA is a common issue to be handled in routine pediatric practice. During the treatment of IDA, in a non-responder, it is important to recognize frequently encountered issues like non-compliance of therapy. This will avoid unnecessary and expensive investigations required for evaluation of truly refractory iron deficiency anemia. The following case scenarios will elucidate the evaluation of a child with refractory anemia.

Case 1

A 10-months-old male infant was noted to have pallor in a vaccination visit. The primary care pediatrician did not find hepatosplenomegaly. This is the first born baby to non-consanguineous parents. This baby has been otherwise normal with no history of neonatal jaundice. Complete blood count revealed Hb of 6.5 gm/dL, WBC count of 7600/µL and platelet count of 5,80,000/µL. The mean corpuscular volume (MCV) was low (60 fL) and the red cell distribution width was increased (24%). Peripheral smear confirmed the presence of microcytic hypochromic anemia with anisopoikilocytosis. With the diagnosis of iron deficiency anemia, the pediatrician prescribed iron supplements when the mother volunteered the information that the child is already on iron supplements for last 3 months.

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Initial approach to hypochromic anemia

The common causes of microcytic hypochromic anemia are iron deficiency anemia, and β thalassemia. The rare causes include sideroblastic anemia, lead poisoning and anemia of chronic disease. In children with mild to moderate microcytic anemia without hepatosplenomegaly, the most cost effective treatment is therapeutic trial of iron.[2] In case of poor response to iron therapy, diagnosis of IDA can be ascertained with a low serum ferritin level (<12 ng/mL).[3] In the index case thrombocytosis also favors the diagnosis of IDA.

Refractory iron deficiency anemia

In confirmed iron deficiency anemia, with iron supplements, hemoglobin increases by 1g/dL within 4 weeks of therapy (Fig.1). Refractoriness to oral iron supplementation is defined as failure to respond to therapeutic dose of iron (3-6 mg/kg/day) administered for at least 4 to 6 weeks of treatment.[4] Prior to labelling a child with refractory IDA, three major factors should be checked, i.e., compliance, dose and formulation of iron and diet modification.

Compliance: The most common reason of poor response to iron therapy is poor compliance. Iron supplements at standard doses causes GI intolerance in < 10% of patients. In such situations, the dose can be reduced, frequency decreased to once a day or iron can be administered with food.[5] Similarly intermittent administration (weekly thrice) though inferior to daily iron therapy still helps in treating a rare child with extreme GI intolerance.

Dose and formulation: Therapeutic dose of oral iron is 3-6 mg/kg/day. We generally initiate iron at 3 mg/kg/day (Fig. 1). It is always prudent to check the formulation for elemental iron after procuring the drug to avoid dosing errors. The dose per mL is different for each formulation even in the same brand. For example, a particular brand is available as drops (1mL = 25 mg) and syrups [pediatric (1mL = 16 mg) and adult (1mL=50 mg)]. Parenteral form of iron replacement is less preferred due to fear of anaphylactic reactions.

Ferrous salts have better bio-availability than ferric

salts.[4] Ferrous sulphate with 20% elemental iron remains as the most cost effective form of iron replacement. Other ferrous salts like ferrous fumarate and ferrous gluconate can also be used. Dosing differs with each preparation based on the percentage of elemental iron.

Diet modification: In infants and children, cow's milk consumption causes iron deficiency anemia by the following mechanisms.

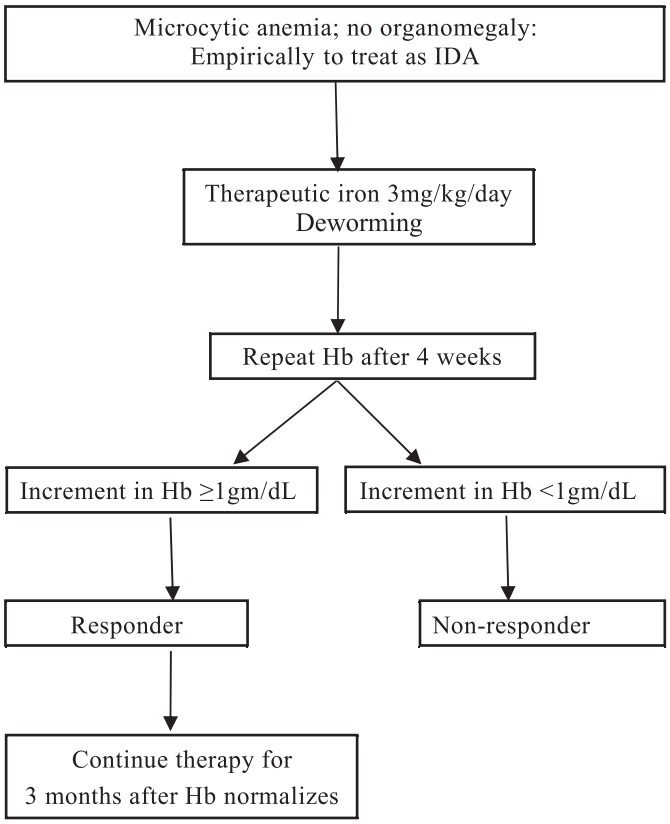


Fig.1.Microcytic hypochromic anemia - an approach

Cow's milk by itself is a poor source of iron, and when consumed in large quantities (>720 mL/day), it will replace iron rich foods in weaning diet. It also induces intestinal blood loss secondary to cow's milk protein induced colitis. Similarly, bottle-fed babies are at more risk to develop IDA than cup-fed ones. Timely introduction of iron rich complementary foods, delayed introduction of cow's milk (after 1 year of age) and cup feeding are essential to prevent and treat IDA.[6]

Index case: The mother was compliant with iron administration. The iron formulation was ferrous fumarate administered in adequate doses. Serum ferritin was 12 ng/mL. The reason for poor response in this child was excess cow's milk consumption. Child was bottle–fed and consumed nearly 1–2 litres/day as a weaning diet. After elimination of cow's milk in diet and with continued iron supplementation, the iron deficiency anemia was resolved.

Case 2

8 year old boy was referred to the hematology clinic as refractory iron deficiency anemia. He was diagnosed to have microcytic anemia 3 months back and was treated with adequate doses of iron. There was an initial response in hemoglobin. It increased from 6 gm/dL to 8 gm/dL within 4 weeks but remained static then onwards. Compliance to therapy was good. The only other remarkable finding was short stature. Serum ferritin was 10 ng/mL.

Underlying diseases causing refractory anemia

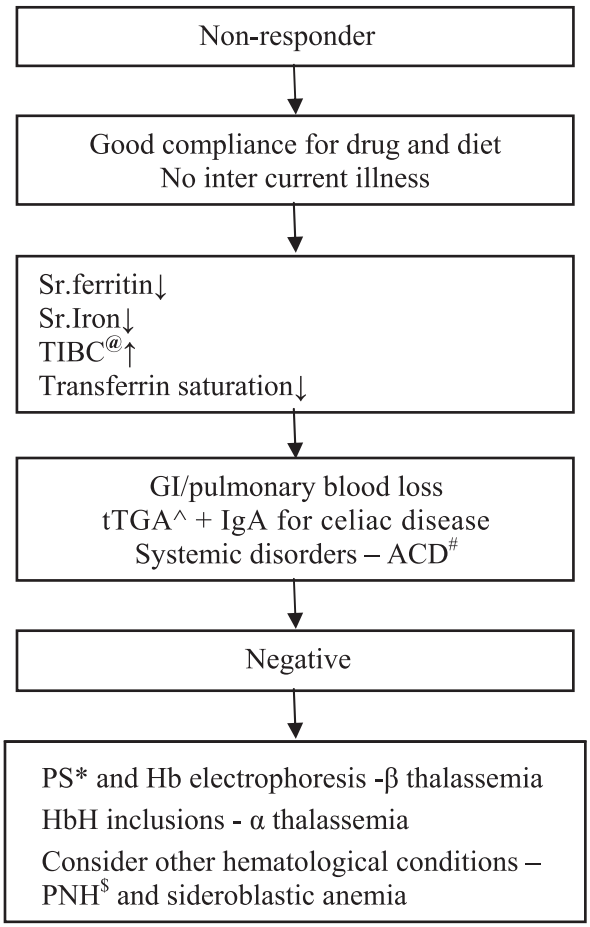
An approach to refractory anemia is delineated in Fig.2. In a non-responder, the following conditions are to be considered.

1. Gut malabsorption: Celiac disease
2. Blood loss: a) GI blood loss: Meckel's diverticulum, cow's milk protein induced colitis, worm infestation and b) Pulmonary blood loss: Pulmonary hemosiderosis
3. Mutations involving iron transport pathway: DMT1 mutation, atransferrinemia
4. Incorrect diagnosis: Thalassemia, sideroblastic anemia, anemia of chronic diseases, chronic renal failure

Index case: Serum tissue transglutaminase antibodies (tTG-IgA) level was raised (100 U/mL). GI endoscopy and small intestinal biopsy revealed crypt hyperplasia with intra-epithelial lymphocytes. Iron deficiency anemia refractory to iron therapy can be the sole manifestation of celiac disease, especially in pediatric patients. Prevalence of celiac disease in patients with refractory IDA is around 20%.[7,8] Investigations for celiac disease are recommended in children presenting with iron deficiency anemia refractory to hematinics and/or growth retardation.[9] Treatment consists of strict elimination of gluten containing diet apart from iron therapy.

Case 3

A 10-year-old girl was brought with complaints of recurrent microcytic anemia requiring two blood transfusions in last 3 years. There was no history of blood in stools. She had not attained menarche. Growth parameters were normal. She gave history of two episodes of pneumonia in last 2 years. Her Hb was 7.9 g/dL, TLC 6500 /mm^3 and platelet count 3.5 lakhs/



@TIBC – Total iron binding capacity

^ tTGA – Tissue transglutaminase

#ACD – Anemia of chronic diseases

*PS – Peripheral smear

$PNH - Paroxysmal nocturnal hemoglobinuria

Fig.2. Approach to a child with refractory iron deficiency anemia

mm³. MCV was low (58 fL) and RDW was increased (28%). Serum ferritin was low (5 ng/mL). She has received iron supplementation on many occasions.

Systematic diagnostic work up of a child with refractory anemia

The low ferritin in this child still favors the diagnosis of iron deficiency anemia. Since it is persisting despite iron supplementation, conditions causing GI malabsorption and blood loses are to be considered. Serum tTGA and IgA levels were normal which will be the screening test for celiac disease. Stool for occult blood was negative. Chest X-ray revealed bilateral heterogenous opacities (Fig.3). Suspecting pulmonary hemosiderosis, gastric aspirates were sent to test for hemosiderin laden macrophages which was positive. The child was having recurrent episodes of pulmonary bleed which were thought to be episodes of pneumonia.

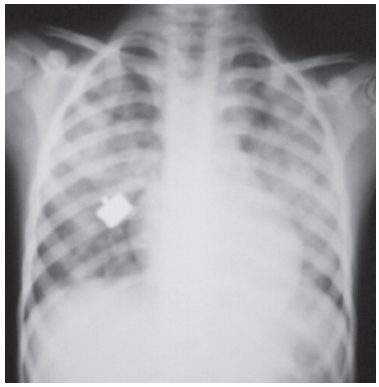


Fig.3. Pulmonary hemosiderosis masquerading as refractory anemia

Idiopathic pulmonary hemosiderosis (IPH): It is characterized by recurrent episodes of alveolar hemorrhage without associated systemic disease like renal or cardiac disorders. Cow's milk sensitivity (Heiner's disease) can lead to pulmonary hemosiderosis in infants and young children. Microcytic hypochromic anemia is a consistent finding in this disorder. Bronchoalveolar lavage and gastric aspirate when stained with Prussian blue will identify haemosiderin-laden macrophages. High index of suspicion is vital to diagnose IPH as in many occasions there will be absence of hemoptysis but non-specific respiratory findings like cough, breathlessness, wheeze in an anemic child.[10]

Case 4

A 10-months-old male infant came with complaints of recurrent anemia requiring 2 blood transfusions in last 3 months. The pre-transfusion hemoglobin was 4 g%. He was born of second degree consanguineous marriage and had moderate hepatosplenomegaly. His CBC revealed Hb of 5.6 gm% TLC of 10,400/cu.mm and platelet of 2.5 lakhs/cu.mm. His MCV was 58 and RDW was 18%. Peripheral smear revealed microcytic hypochromic anemia. Serum ferritin was 460 ng/mL.The last transfusion was given 10 days prior to evaluation.

The presence of hepatosplenomegaly in a child with microcytic hypochromic anemia indicates haemolytic anemia as the underlying disease. β-Thalassemia major was considered upfront. As the child had just received a transfusion, parents' haemoglobin variant analysis was done by HPLC (High Performance Liquid Chromatography). Both parents had high HbA2 indicating thalassemia trait

and this indicates that the index child had thalassemia major. DNA sequencing confirmed the homozygous IVS 1-5 G>C mutation in the index child. Sideroblastic anemia can also have a similar clinical picture but bone marrow examination in this diagnosis will reveal ringed sideroblasts.

Case 5

A 5-year-old female child was brought with complaints of anemia noted since last 3 years. She is born of non-consanguineous marriage. She has not received blood transfusions till date. Her Hb was 7.9 gm%, TLC 6900/ cu.mm and platelet count 4.0 lakhs/ cu.mm, MCV was 55 and RDW was 24%. She has received iron therapy multiple times in adequate doses. Serum ferritin was 240 ng/mL. Thalassemia has been ruled out by gene sequencing. Bone marrow examination has ruled out sideroblastic anemia.

In view of exclusion of other common causes of microcytic anemia and parental consanguinity, a diagnosis of inherited iron refractory iron deficiency anemia (IRIDA) was considered. It belongs to the rare inherited anemias involving iron absorption, transport, recycling and utilization. IRIDA is an autosomal recessive disorder characterized by mutations involving transmembrane serine protease 6 (TMPRSS6) gene encoding Matriptase 2. This protein down regulates expression of hepcidin in the body. Therefore, these children have inappropriately elevated hepcidin levels. This elevated hepcidin suppresses iron absorption from the gut. Unlike iron deficiency anemia, they have normal or high serum ferritin levels. It causes congenital moderate hypochromic microcytic anemia refractory to oral iron and with partial response to parenteral iron therapy. They are treated with intravenous iron therapy. IRIDA should be considered in children after ruling out other known causes of refractory iron deficiency anemia.[4]

Points to Remember

- ***Iron therapy is to a great extent influenced by factors like compliance, diet and drug formulation.***
- ***True iron refractoriness occurs in the setting of ongoing losses due to bleeding, GI malabsorption and genetic disorders.***

References

1. National Family Health Survey (NFHS – 3) 2005-06 Volume 1. International Institute for Population Sciences, Mumbai, India, September 2007.http://dhsprogram.com/pubs/pdf/FRIND3/FRIND3-Vol1AndVol2.pdf (last accessed on 23rd December 2014).
2. Oski FA. Iron deficiency in infancy and childhood. N Engl J Med 1993; 329:190.
3. World Health Organization /UNICEF/UNU. Iron Deficiency Anaemia: Assessment, Prevention, and Control. A Guide for Programme Managers, World Health Organization; Geneva, Switzerland 2001.
4. Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. Blood 2014;123: 326-333.
5. Hershkoa C, Skikneb B. Pathogenesis and Management of Iron Deficiency Anemia: Emerging Role of Celiac Disease, Helicobacter pylori, and Autoimmune Gastritis. Semin Hematol 2009;46:339–350.
6. American Academy of Pediatrics Committee on Nutrition: The use of whole cow's milk in infancy. Pediatrics 1992; 89:1105-1109.
7. Mody RJ, Brown PI, Wechsler DS. Refractory iron deficiency anemia as the primary clinical manifestation of celiac disease. J Pediatr Hematol Oncol 2003; 25:169-172.
8. Economou M, Karyda S, Gombakis N, Tsatra J, Athanassiou-Metaxa M. Subclinical celiac disease in children: refractory iron deficiency as the sole presentation. J Pediatr Hematol Oncol 2004; 26:153-154.
9. Bansal D, Trehan A, Gupta MK, Varma N, Marwaha RK. Serodiagnosis of celiac disease in children referred for evaluation of anemia: a pediatric hematology unit's experience. Indian J Pathol Microbiol 2011; 54:756–760.
10. Susarla S, Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr 2007; 19:314–320.

NEWS AND NOTES

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BLEEDING PER RECTUM IN AN INFANT

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Abstract: *Bleeding per rectum (PR) in infants is a common and disturbing problem encountered in day-to-day practice. The bleeding may present as acute, massive or chronic intermittent bleed. There are several causes of bleeding per rectum in infants, which may be gastrointestinal, hematological, vasculitic or factitious. History plays an important role in diagnosis and helps to choose the appropriate investigation which could be either imaging studies or endoscopy. Depending on the diagnosis, the therapy can vary from simple dietary modification to radiological intervention or surgery.*

Keywords: *Bleeding per rectum, Infants, Imaging, Endoscopy.*

Bleeding per rectum (PR) is a common yet disturbing symptom and indicates passage of blood per rectum which may occur in any age group and presents either as chronic, intermittent small bleed or as acute massive bleed. In majority of patients, the bleeding is usually from the lower GI tract. however, 10% of upper GI bleed (UGIB) may present as bleeding PR. Lower gastrointestinal bleed (LGIB) usually indicates bleeding from sites distal to the ligament of Trietz, whereas upper GI bleed denotes those occurring proximal to it. Bleeding PR can present as hematochezia (passage of frank blood), melena (tarry black stools) or as streaks of blood. Though bleeding PR is an overt manifestation, the site of bleed may be obvious or obscure. Obscure GI bleeding refers to a bleed where the site is not definite even after evaluation by upper gastrointestinal endoscopy, an ileo colonoscopy and a contrast radiological study of the small intestine. Teach and Fleisher have documented that rectal bleeding constituted 0.3% of 40,000 children attending Boston's pediatric emergency department during a ten-month period.[1]

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Etiology of bleeding PR: The common causes of bleeding PR in infants may be gastrointestinal (GI) or non-gastrointestinal. (hematological, vasculitic and factitious).[2,3,4]

I. Gastrointestinal (Table I): This bleeding may occur either from lower GI tract (common or uncommon causes) or from upper GI tract.

.**II. Hematological:** Bleeding disorders, coagulation defects, disseminated intravascular coagulation (DIC) or platelet disorders (dengue, idiopathic thrombocytopenia purpura) can present as bleeding PR.

III. Vasculitic disorders: Henoch Schonlein purpura.

IV. Connective tissue disorders: Ehlers Danlos syndrome and cutis laxa are rare causes of LGI bleed.

V. Factitious bleed: Stool can be colored due to various coloring agents, jelly, beetroot and drugs such as phenolphthalein or rifampicin.

Table I. Gastrointestinal causes of bleeding PR in infants

LGIB: Common	LGIB: Uncommon
Anal fissure	Inflammatory bowel disease:
Colitis: Infective	Ulcerative colitis
Colitis: Allergic, cow milk protein allergy (CMPA)	Intestinal duplication
Intussusception	Segmental enteritis
Meckel's diverticulum	Vascular malformation
Colonic polyp	
UGIB	
Variceal /PHT	
Non- variceal / Peptic ulcer	

Management of bleeding PR

A focused history from parents or caretakers and physical examination of the infant are essential in the initial evaluation of bleeding PR. A meticulous history covering details such as whether bleed was major or minor, with or without colic, acute massive or chronic intermittent, with or without hematemesis, treatment given and associated symptoms are recorded. Information regarding duration, number of episodes, frequency, volume, color, presence of clots or mucus, frank bleed or whether mixed with feces should also be obtained. These notes will help to identify the site and probable etiology of the bleed.

Site of bleed: Hematemesis with bleeding PR is suggestive of UGIB. Similarly melena is more often seen in UGIB whereas hematochezia is more common from the small bowel or colon. Specks or streaks of bright red blood is typically from anorectal region.

Etiology: Acute massive bleed in an infant is commonly due to Meckel's diverticulum, intestinal duplication or AV malformation, whereas chronic intermittent small bleed may be due to fissure in ano, colitis or colonic polyps. Apart from fissure in ano the five common causes of bleeding PR in an infant are infectious colitis, cow's milk protein allergy, intussusception, Meckel's diverticulum and

Table II. Possible etiology of bleeding PR based on symptoms

Bleeding PR + associated symptoms	Possible diagnosis
Crampy abdominal pain and frequent loose stools mixed with mucus and blood	Colitis: infectious, inflammatory or ischemic process
Colicky abdominal pain, vomiting, red currant jelly stool and mass abdomen	Intussusception
Painful defecation with streaks of blood	Fissure in ano
Stools mixed with blood following introduction of bovine milk protein	Cow's milk protein allergy
An infant on exclusive breast milk with normal weight and blood in the stool	Allergic colitis due to transfer of milk protein through breast milk
Passage of large volume, maroon or bright red blood requiring blood transfusions	Meckel's diverticulum, intestinal duplication or AV malformation
Mass prolapsing with bleeding per rectum	Prolapsing polyp, prolapse rectum or an intussusception
Failure to thrive, recurrent infections, bleeding PR	HIV related illness, immune deficiencies
H/o recurrent petechiae, ecchymosis, epistaxis and blood in stool	Hematological disease (DIC, thrombocytopenia, leukemia)
Bloody diarrhea, loss of weight, fever, hypoproteinemia, perianal lesion	Inflammatory bowel disease
History of fever, rash, features of third spacing and bleeding PR	Dengue fever
Family history of bleeding PR requiring surgery	Polyposis coli
Recent antibiotic administration followed by passage of blood and mucus in stools	Pseudomembranous colitis
Bleeding PR-Post bone marrow /liver transplant	Graft versus host disease
History of ingestion of beet or coloring agents	Factitious bleed

colonic polyps.[3] Eliciting certain associated symptoms in the history may also support in ascertaining the various etiology (Table II).

Examination: In children with acute bleeding PR either major or minor, a complete examination including vital signs is necessary. If the infant passes blood during examination or the soiled diaper is available then the volume of blood, color, presence of clots or mucus is also recorded. The presence of petechiae or purpura on the skin may suggest hematological disease. On abdominal palpation splenomegaly would indicate portal hypertension while right upper quadrant mass may indicate a diagnosis of intussusception. Distended abdomen with dilated bowel loops would indicate intestinal obstruction, volvulus, gangrene or segmental enteritis. The presence of anal skin tags, perianal fistula or fissure may be the cutaneous markers of inflammatory bowel disease. A mass prolapsing per rectum could be a polyp, rectal mucosal prolapse or an intussusceptum.

Laboratory studies

Basic investigations such as hemoglobin, total and differential white blood cells, platelet count, bleeding time, clotting time, prothrombin time, blood grouping and Rh typing are included in the investigation panel. A macroscopic examination of the stool is essential before planning sophisticated investigations. Microscopic examination of the stool is done to identify trophozoites and pus cells.

If the stools show more than 10 pus cells/high power field it may indicate an invasive form of colitis. Presence of numerous eosinophils would suggest an allergic colitis such as cow's milk protein allergy. The presence of trophozoites with hemophagocytosis is diagnostic of Entamoeba histolytica infection. If the clinical setting is suggestive of infectious colitis then stool culture for shigella, salmonella, Campylobacter jejuni may be helpful if facilities are available.

Imaging[5] Plain X-ray abdomen is done when there is abdominal colic, bilious vomiting or features of intermittent intestinal obstruction. Supine and upright (or lateral decubitus) views may identify distorted bowel gas pattern indicating mass effect or obstruction, air-fluid levels or pneumoperitoneum. Focal or generalized bowel wall thickening (thumb printing) suggests severe colitis, particularly ischemic colitis. Ultra sonography of abdomen can detect bowel wall thickening or identify features of intussusception such as target sign or pseudo kidney sign. In infants the next choice of investigations depends on whether the infant has acute massive bleed or chronic intermittent minor bleed.

Acute massive bleed

This is usually secondary to Meckel's diverticulum, intestinal duplication, intussusception or rarely arterio venous malformation. Imaging studies therefore play an important role in infants with significant bleeding PR. Radionuclide scintigraphy is useful in the evaluation of children with active LGI bleed of at least 0.1 mL per minute. Technetium-labeled red blood cells (99mTc RBC) identify AVMs and bleeding ulcers. Radionuclide study using Technetium-99m pertechnetate, helps to identify ectopic gastric mucosa within a Meckel's diverticulum or a duplication cyst. It has a sensitivity of 85%, specificity of 95% in the diagnosis of Meckel's diverticulum. Air contrast or saline contrast enema is done when intussuception is suspected. It helps not only to confirm the diagnosis but also reduce ileo colonic intussuception. Cross-sectional imaging with CT or MR is generally reserved for evaluation of mass lesions or complex vascular anomalies.

Chronic intermittent bleed

Ileo colonoscopy is recommended whenever mucosal lesions of the colon such as colitis, polyps, nodular lymphoid hyperplasia are considered. An upper GI endoscopy should always be performed along with ileo colonoscopy, since 10% of upper GI bleed can present as bleeding per rectum. Ileo colonoscopy is a safe diagnostic modality for identifying the source of rectal bleeding even in infants. Early colonoscopy helps both in diagnosis and therapy. The overall yield ranges from 69%-80%. Bowel preparation is safely achieved in children using a standard oral polyethylene-glycol electrolyte solution (25mL/kg/h) given over a period of 2 hours as infusion through naso gastric tube. The preparation is done about 4-6 hours before the procedure. The majority of mucosal lesions such as allergic colitis, nodular lymphoid hyperplasia, polyps, IBD, rectal varices and portal colopathy can be diagnosed. Biopsy of the mucosal lesions will help in confirming the etiology.

Special procedures

Triple visceral arteriography: This is rarely necessary in infants with bleeding PR. It is however useful in obscure small bowel bleed if there is active bleeding of at least 0.5 mL/minute. The advantage of arteriography in obscure LGIB is that it helps both in localization and embolization of the lesion.

Rarely magneticoresonance enteroclysis, enteroscopy or intraoperative enteroscopy may be included in the protocol for evaluating infants with bleeding PR.

Intra-operative enteroscopy: During intra-operative enteroscopy, an endoscope can be negotiated through an operative enterotomy and the small bowel visualized. It is useful in detecting more than 85% of obscure small bowel bleeding lesions. The surgeon guides the intestine over the scope and examines the bowel both by palpation and visualizing the trans-illuminated segment while the endoscopist visualizes the mucosa.

Capsule endoscopy is not feasible in infants because of its size and is not recommended for very young children with obscure bleeding.

Management of bleeding PR in infants

When the bleed is significant the first step is to resuscitate the infant before further evaluation. The specific management then depends on the underlying condition and may range from dietary modification, antimicrobials, radiological intervention, air enema, endotherapy or surgery.

Common case scenarios

The five common case scenarios of bleeding PR in infants seen in day to day practice have been outlined.

Case scenario 1: A one year old infant presented with two day history of frequent loose stools of 10-15 times/day mixed with blood and mucus. Child strains and cries before defecation. The infant weighed 8.7 kgs and was peevish. Abdomen was soft not distended, liver and spleen not palpable. Investigations revealed Hb 9.8 gm/dL, CRP 48 mg/dL, WBC total 16,000, DC N75%, L13%, stab forms 12%. Result of stool examination was reported as mucoid with blood, 20-30 pus cells/HPF and numerous RBCs, EH cyst was also seen. In view of the short duration of illness, frequent stools with blood and mucous and feces examination showing many pus cells a diagnosis of acute infectious colitis possibly a bacterial infection was considered. Since EH cyst was seen in the stool examination amebic colitis had to be excluded in the diagnosis.

Infectious colitis: This type of colitis is usually referred to as acute self-limiting colitis. There are several causes of infectious colitis (Box 1) in infants but the most important is the Shigella species which is to be considered in developing countries. The majority of children respond to antimicrobials administered in the correct dosage for the recommended duration. In India, it is acceptable to treat infectious colitis as for shigella dysentery. The therapy for admitted children is parenteral IM/IV Ceftriaxone (100mg/kg) once daily for 5 days. Children attending outpatient services are prescribed oral antibiotic which are effective for Shigella (e.g. Cefixime, Quinolone). Zinc supplement as for watery diarrhea is essential.

Box 1. Etiology of infectious colitis

Shigella	Clostridium difficile
Shiga toxin producing Esch.coli	Cytomegalo inclusion virus
Salmonella	HIV
Entero invasive Escherichia coli.	Entamoeba histolytica
Enteroaggregative E coli	Aeromonas spp
Entero hemorrhaghic E coli	Noncholera vibrio spp
Campylobacter jejuni	Enterotoxigenic Bacteroides fragilis
Yersinia enterocolitica	

Amebic colitis: Even in India amebic colitis is not a common problem in children. In this infant even though EH cyst was reported in the stool examination amebicidal drugs such as metronidazole need not be given since the cysts of Entamoeba histolytica resemble those of Entamoeba dispar, a non-pathogenic intestinal commensal. The IMNCI guidelines state that the infection should be treated as amebiasis with oral metronidazole 10mg/kg, 3 times a day for 5 days only if microscopic examination of fresh feces carried out in a reliable laboratory reveals trophozoites of E histolytica with hemophagocytosis or two different antibiotics, which are usually effective for shigella have been given without clinical improvement.[6]

Case Scenario 2: A 6-months-old male infant presented with diarrhea since the 30th day of life. The stools were loose, 7 to 8 times/day, yellow in color with occasional streaks of blood. The infant had been hospitalized twice and received antibiotics. There was no history of fever, seizures or respiratory symptoms. A red evanescent rash had been noticed by the mother on the cheeks and forearms. The birth weight was 3.2 kg and the present weight was only 4.3 kg. Infant has been on supplemental top feeds since birth and three different cow's milk based commercial formulae have been tried but not helpful. Breast milk was completely stopped since 30th day of life. There was no response to withdrawal of lactose. Infant was lethargic, sick looking with rash on cheek and forearm and had mild perianal excoriation. The abdomen was soft with mild distension and liver was palpable 3 cms below right costal

margin. Stool examination showed positivity for both occult blood and reducing substance and Hb was 9 gm/dL. Serum total IgE was elevated and the level of IgE-specific antibody to cow's milk protein was also high. Colonoscopy showed multiple tiny nodules 2-4 mm in diameter with some of them showing central brownish black spots suggestive of nodular lymphoid hyperplasia (Fig.1). Biopsy showed features of colitis with more than 20 eosinophils per HPF suggestive of allergic colitis.

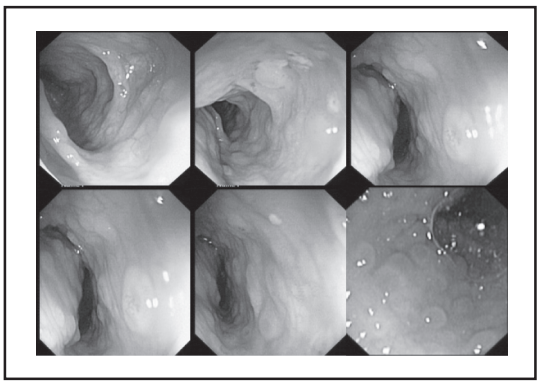

Fig.1. Colonoscopy showing features of nodular lymphoid hyperplasia

A diagnosis of cow's milk protein allergy (CMPA) was considered as the infant was symptomatic since one month of age and on supplemental feeds since then. The clinical presentation of skin rash, loose stools with occasional blood streaks and colonoscopy biopsy showing eosinophilic colitis was suggestive of GI and skin manifestation to a food protein allergen. Since cow's milk protein is the most common food allergen to which infants are exposed, CMPA is most likely. Elevated IgE with increased cow's milk protein-specific antibody support the diagnosis but may not be always high in CMPA.

Cow's Milk Protein allergy[7]: This is the most common food allergy in infants. The incidence ranges from 2% to 3 % and occurs in 0.5% of breast-fed infants. The immune reaction could be either IgE-mediated (rash, urticaria, angioedema of lips) or T cell-mediated (diarrhea, FTT, anemia and hypoproteinemia) or both. The clinical manifestations may be gastrointestinal seen in 50%-60%. Symptoms may range from mild to severe. The various presentations are proctocolitis manifesting as blood and mucus in stools and anemia which is seen in the first few months of life, enteropathy which presents as diarrhea, vomiting, failure to thrive, abdominal distension, anemia and hypoproteinemia with onset in infancy; enterocolitis which is more severe than enteropathy and manifests as vomiting, diarrhea, dehydration and lethargy and shock-like reaction with metabolic acidosis is the severe form called 'food protein induced enterocolitis syndrome'; Skin manifestions such as atopic dermatitis, urticaria, contact rash and angioedema and respiratory symptoms like rhinitis, asthma, cough, chronic pulmonary disease (Heiner syndrome) and systemic anaphylaxis. The diagnosis of CMPA is by the clinical presentation and confirmed by IgE-specific antibody or colonoscopy and histopathology. Bleeding PR in an infant with CMPA is managed by avoiding cow's milk, its products and other unmodified animal milk proteins such as goat, sheep, buffalo and donkey' milk. If the infant is more than 6 months old and the disease is mild then soy protein may be substituted instead of cow's milk; however in severe disease presenting as failure to thrive, anemia and bleeding PR as in this infant extensively hydrolysed formula or amino acid-based formula may be required.

Case scenario 3: A 10-months-old male infant was brought to the ER with one episode of bleeding PR which was large in volume and maroon in color. There was no history of colic, diarrhea, medications or fever. Child was pale and restless. Abdomen was soft there was no mass or hepatomegaly. Since the infant was pale with Hb of 6.7 gm/dL, he was transfused with packed red blood cells. Radionuclide scan using Technetium 99m pertechnetate was done which showed an area of ectopic gastric mucosa in the right lower quadrant at the same time of stomach uptake. This infant presented with massive bleeding PR which warranted exclusion of Meckel's diverticulum or intestinal duplication.[8,9] Radionuclide scan was diagnostic of Meckel's diverticulum.

Meckel's diverticulum: This is the most common congenital anomaly of small intestine and is the remnant of the vitelline (omphalo mesentric) duct. The famous 'rule of two' describes the clinical features. It is seen in 2% of population in infants less than 2 years of age in a male female ratio 2:1. The diverticulum is 2 feet from ileocaecal junction, 2 inches long, 2 cms diameter, with 2 types of mucosa (gastric, pancreatic) with 22% presenting as GI bleed. The bleeding occurs because of the acid secreting ectopic gastric mucosa which causes necrosis of the tissue. Radionuclide studies using Technetium 99m pertechnetate help in identifying the lesion and the sensitivity may be increased by administering ranitidine or pentagastrin. The treatment for Meckel's diverticulum is surgical resection.[8]

Case scenario 4: A 10-months-old infant presented to the ER with one day history of intermittent bleeding PR, small in amount, like 'red currant jelly'. The mother had noted that the infant was lethargic and had severe intermittent abdominal pain. During these episodes, the infant would

scream and then quieten down. The infant was lethargic and crying intermittently. Abdomen was mildly distended with a vague mass right hypochondrium. The stools were red and shiny without fecal matter. This infant was diagnosed as having intussusception based on the severe abdominal colic, bleeding PR and mass right hypochondrium. This was confirmed by ultrasound of the abdomen which showed the classical 'target sign' of intussusceptions (Fig.2).

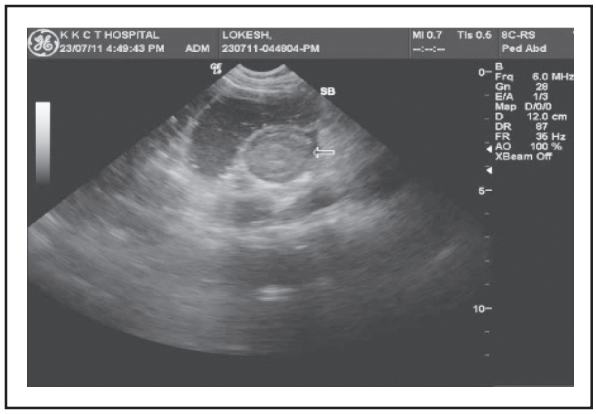

Fig 2: Ultrasound of abdomen showing target sign of intussusception

Intussusception in infants: In developed countries, the incidence of intussusception varies from 0.5 to 4.3 cases per 1,000 live births or 0.7–1.2 cases per 1,000 children aged less than one year. The male-to-female ratio is 3:1, 60% are younger than 1 year and the peak age of presentation is 5 to 10 months. In most infants and toddlers the etiology of intussusception is not clear and there is a rarely a lead point as seen in older children. The possible explanation for the common occurrence of an ileo-colonic intussusception may be the enlarged Peyer's patch which is seen following viral infection. The classic clinical presentation comprises of two symptoms abdominal colic and vomiting and two signs 'sausage'-shaped abdominal mass and bleeding per rectum of a 'red currant jelly'-like material. Imaging studies will support the diagnosis: a plain X-ray abdomen has an accuracy of 25% to 50% and may reveal 'pincer sign' or target sign while the ultrasound of abdomen is more diagnostic and may show donut, pseudo-kidney or target sign. Non-operative reduction of intussusception using fluoroscopy or ultrasound -guided air enema with graded and guided air pressure is preferred (Figs.3,4). The procedure is quick and clean with a high reduction rate (73%–95%). Compared to barium enema there is lesser peritoneal contamination and smaller perforations seen with air enema.[10,11] The contraindications for air enema reduction of intussusception are if the infant is younger than 3 months and older than 3 years of age, presents with shock, ,hematochezia, perforation with peritonitis and is symptomatic for more than 48 hours.

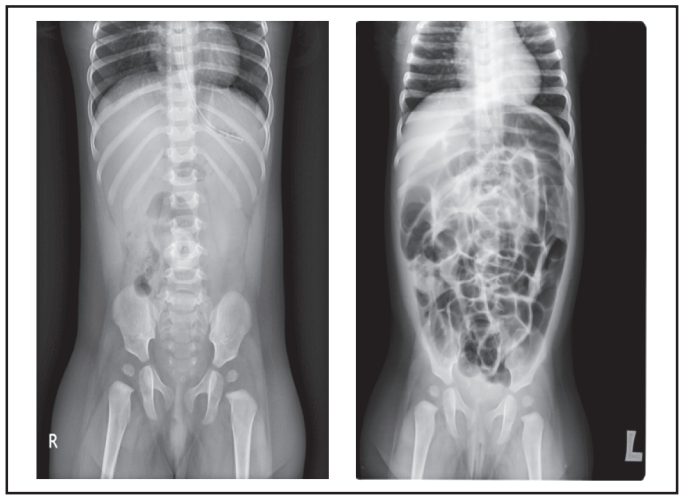

Fig. 3,4. Pre and post air enema reduction for intussusception

Case Scenario 5: A 8/12 old female infant was brought with h/o bleeding PR of 3 days duration. The infant was passing stools once or twice a day, soft without any difficulty. The blood was bright red in color which was either mixed with stools or occurred at the end of defecation. Mother had been diagnosed to have colonic polyps in childhood. The infant was cheerful without any cutaneous markers. The abdomen was soft and there was no hepatosplenomegaly. Hb was 10.2 gm/dL, prothrombin time was 14 secs and control was 14 secs and other basic investigations were normal. Colonoscopy showed a multilobulated polyp at 8 cms from the anal verge and several polyps distributed through out the colon,(Fig.5). Biopsy was done which was reported as hamartomatous polyp. The presentation of painless bleeding PR in an infant with normal frequency of stools and family history of colonic polyps was suggestive of polyposis coli. Colonoscopy confirmed the diagnosis of polyps and endoscopic polypectomy was performed. The mother had pigmentation of the buccal mucosa and thus a diagnosis of Peutz Jegher Syndrome was made.

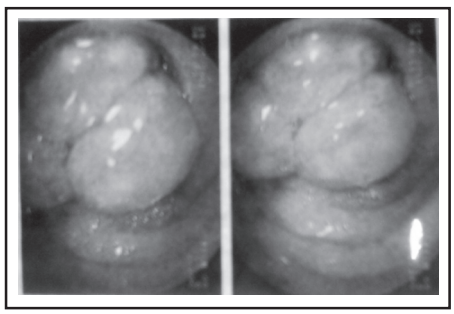

Fig.5.Colonoscopy showing multilobulated colonic polyp.

Colonic polyps[12]: These are a common cause of bleeding PR in children. Polyps may be hamartomatous or adenomatous. They may be solitary or part of the polyposis syndrome as in Peutz Jegher's syndrome, familial adenomatous polyposis and juvenile polyposis coli (JPC). In children juvenile polyp (JP) or hamartomatous is the most common type of colonic polyp which may present with bleeding, anemia, intussusception or rarely mucorrhea. Juvenile polyps are usually rectal, cherry red in color (Fig. 6) and solitary and are not classified as premalignant.

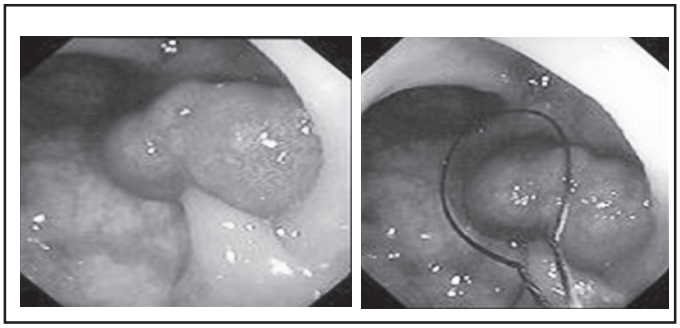

Fig 6 & 7. Colonoscopy: Cherry red juvenile polyp & Colonoscopic polypectomy

However if there are more than 5 juvenile polyps in the colon, it is called as juvenile polyposis coli which is premalignant. The management of colonic polyps presenting with bleeding per rectum is endoscopic polypectomy (Fig.7).

Points to Remember

- ***Bleeding PR is a common problem in infants.***
- ***The diagnosis is made by history, clinical examination, stool examination, USG abdomen, radio nuclide studies and endoscopy (UGI and LGI).***
- ***Obscure bleeds requiring laparotomy/ laparoscopy or operative enteroscopy is rare in infants.***
- ***Management of bleeding PR in an infant may be with simple medications, dietary modification, endotherapy, interventional radiology or surgery.***

References

1. Leung Alexander KC, Wong AL. Lower gastrointestinal bleeding in children. Pediatr Emeg Care 2002:18:319-323.
2. Fox VL. Gastrointestinal bleeding in infancy and Childhood. Gastroenterol Clin N Am 2000; 29: 36-64.
3. Vinton NE. Gastrointestinal bleeding in infancy and childhood. Gastroenterol. Clin N Am 1994; 23(1): 93-188.
4. Khurana AK, Saraya A, Jain N, Chandra M, Kulshreshta R. Profile of lower gastrointestinal bleeding in children from a tropical country. Trop Gastroenterol 1998; 19:70-71.
5. Strate LL. Lower GI bleeding:epidemiology and diagnosis. Gastroenterol Clin N Am 2005; 34:643-664.
6. Recommendations for management of common childhood conditions. Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. World Health Organisation 2012. Switzerland.
7. Koletzko S,Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S.Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children:ESPGHAN GI Committee Practical Guidelines. J Pediatr Gastroenterol Nutr 2012;55: 221–229.
8. Brown RL, Azizkhan RG: Gastrointestinal bleeding in infants and children: Meckel's Diverticulum and Intestinal Duplication. Semin Pediatr Surg 1999; 8:202-209.
9. Pandey S, Srivastava A, Lal R, Yachha SK, Poddar U. Enteric duplication cysts in children: A target in algorithm for evaluation of lower gastrointestinal bleeding. Indian J Gastroenterol 2014; 33:285-288.
10. Jen HC, Shew SB. The impact of hospital type and experience on the operative utilization in pediatric intussusception: a nationwide study. J Pediatr Surg 2009; 44(1):241-246.
11. Ramachandran P, Gupta A, Vincent P, Sridharan S. Air enema for intussusception: is predicting the outcome important? Pediatr Surg Int 2008; 24:311-313.
12. Poddar U, Thapa BR, Vaiphei K, Singh K. Colonic Polyps: Experience of 236 children. Am J Gastroenterol 1998; 93: 619-622.

NEWS AND NOTES

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INFANTILE WHEEZE

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Abstract: *Many medical and surgical conditions produce wheeze in infants. Viral infections, aspiration syndrome, phenotypes of asthma and structural airway anomalies are the main causes. In children with recurrent wheeze, several phenotypes are identified, of which episodic viral wheeze (viral-induced) and multiple-trigger wheeze (due to multiple allergens) are the important ones from the management point of view though they need further validation. Structural anomalies and foreign body aspiration should be considered when unexplained wheeze or cough persists in infants. Avoidance of smoke particularly that of tobacco, appropriate treatment of respiratory infections and encouragement of breast feeding may reduce the incidence of wheeze and development of asthma especially in high-risk children.*

Keywords: *Wheeze, Infants, Asthma phenotypes, Airway anomalies.*

Wheezing in infants can present as medical emergency and the situation makes both the parents and the treating doctor anxious. Acute bronchiolitis is the standard diagnosis in a previously healthy infant presenting with a first episode of wheezing. If an infant presents with recurrent wheeze, thorough evaluation is mandatory.

Small caliber of the peripheral airways (contributing up to 50% of the total airway resistance), compliant chest wall and immaturity of immunologic system make infants prone to wheeze. In addition to medical conditions many surgical conditions also do produce wheeze in infants. Since precise etiological diagnosis of infantile wheeze is some times not possible, management may be difficult. Revisiting this subject will improve our understanding and contribute to effective management of infants with wheeze.

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Wheeze and respiratory sounds

Respiratory sounds are due to partial obstruction of respiratory passage at various levels. The common respiratory sounds include snuffles, grunt, snoring, stridor and wheezing.

Nasal sounds in normal young infants due to nose block (mucus collection) are termed as snuffles, which are harmless. Expiration through a partially closed glottis results in grunt, a compensatory mechanism that occurs in an attempt to increase the functional residual capacity and oxygenation status in diffuse parenchymal lung diseases. Grunt may be an early sign of impending respiratory failure.

Snoring is produced due to respiratory compromise at the naso/oropharyngeal level. Stridor is a harsh, vibratory sound of variable pitch that occurs due to partial obstruction of larynx and upper trachea. Since both snoring and stridor are produced due to partial obstruction of the extrathoracic airway, they get exaggerated during inspiration.

Wheeze is a continuous high-pitched sound that occurs during the expiratory phase due to partial obstruction of the intrathoracic airways (lower trachea and bronchi). When wheeze exists in combination with other sounds (chest rattling, noise due to secretions in the respiratory tract) it can confuse the issue and localization may be difficult.

Monophonic wheeze, also referred to as homophonous wheeze, is produced in the central airways in conditions like tracheomalacia. It is uniform in tone and pitch and is heard throughout the chest, though the amplitude may differ. Polyphonic wheeze, also referred to as heterophonous wheeze occurs due to widespread narrowing of the airways as seen in asthma or bronchiolitis. It may evince changes in pitch and tone because of the obstruction that occurs at multiple levels.[1]

History and evaluation

Generally, parents differ in the understanding of the meaning of wheeze. Due to social stigma they may be reluctant to use the word wheeze. Mimicking the respiratory sounds during history elicitation will help the parents to express their complaints more effectively. The clinical history should focus on the age at which the first attack of

Table I. Infantile wheeze: Co-morbid conditions and probable etiology

Co-morbid condition	Probable etiology
Early onset of symptoms after birth	Structural anomalies
Feeding difficulties, with vomiting	Gastroesophageal reflux
Nocturnal symptoms	Respiratory allergy
H/o daycare exposure	Viral respiratory infection
Environmental pollution /smoking	Asthma
Family history	Asthma
Cooking and biofuel	Respiratory allergy
Repeated hospitalizations/Intubation	Structural anomalies
Multifocal infection	Immunodeficiency
Failure to thrive, malabsorption	Cystic fibrosis
Eczema, flexural dermatitis	Atopy

wheeze occurred, its temporal relationship with feeding and the associated aggravating factors. Environmental exposure to respiratory irritants particularly parental smoking should be elicited. In Indian scenario the type of cooking, the biomass used and the living area also matter a lot (Table I).

Repeated elicitation of family history of asthma and atopic diseases is also important. History of perennial allergy is invariably due to indoor allergens such as dust mites, animal dander, and mold spores whereas seasonal allergy is constantly linked with outdoor allergen exposure such as pollen from trees, grasses and weeds.

Allergic markers like eczema, flexural dermatitis should be looked for. Examination of ears, eyes, nose and skin may give a clue about the underlying disease. Auscultation of heart to rule out murmurs and thorough examination of other systems should also be routinely done.

Common conditions which can cause recurrent wheeze in infants are recurrent viral infections, aspiration syndrome, phenotypes of asthma and missed foreign body aspiration. Though recurrent respiratory infection is the usual presentation, conditions like congenital airway anomalies, cystic fibrosis, ciliary disorders, immunodeficiency and congenital heart diseases, may also present with wheeze.

Plain chest X-ray may be a useful modality to rule out structural abnormalities. Increased IgE (>100 IU/mL before 6 years of age) is considered as a non-specific marker of allergy. Fractional concentration of exhaled nitric oxide (FeNO) measurement may be used in the diagnosis if available but needs further validation.

Imaging studies and fiberoptic bronchoscopy play a major role in the diagnostic work up. A battery of lung function tests like infant raised-volume rapid thoracic compression, specific airway resistance, forced oscillation, the interrupter technique and multiple-breath washout are under research for the diagnostic evaluation of recurrent wheeze in infants; however, a simple test is yet to be available for common practice.[2]

Repeated viral infections

Some babies are prone to repeated viral infections (rhinovirus, respiratory syncytial virus, coronavirus, human metapneumovirus, parainfluenza virus and adenovirus) and it has been argued that altered innate or adaptive immune responses are the cause. Repeated infections with these pathogens occur because of the large number of distinct serotypes of each virus. Genetic predisposition to develop bronchial hyperresponsiveness predisposes some of them to get frequent wheezy attacks. Mannose-binding lectin deficiency with impaired innate immunity may be associated with an increased incidence of 'colds' in children.[3]

Some data suggest that viral infections interact with atopy in infancy to promote the development of asthma later, suggesting contribution from both classes of inflammatory insults to disease pathogenesis.

Protection of 'high-risk' children against the effects of severe respiratory infections during infancy may represent an effective strategy for primary asthma prevention.

Contradictory to this, it has also been argued (hygiene hypothesis) that infections during early life direct the maturing immune system toward Th1, (which counterbalances proallergic responses of Th2 cells) and its reduction results in unrestrained Th2 response that allows an increase in allergy.

Aspiration syndrome

There are many anatomical (gastroesophageal reflux disease) or neuromuscular conditions (oropharyngeal incoordination) that predispose to aspiration in infants.

Gastroesophageal reflux disease (GERD) is the most common condition which predisposes infants to recurrent respiratory disease and wheeze. The recurrent aspiration of gastric contents results in airway inflammation leading to wheezing and cough. A careful history may reveal associated symptoms such as vomiting, crying, arching soon after feeding. GERD can produce wheeze by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration or microaspiration) or by other refluxive interactions between the esophagus and respiratory tract.[4]

To confirm GERD, investigations like barium esophagogram, video fluoroscopic swallowing study, 'milk' scintiscan, fiberoptic endoscopic evaluation, quantitation of lipid-laden alveolar macrophages from bronchoalveolar lavage and esophageal pH monitoring are used. A therapeutic trial of proton pump inhibitors may be justified to confirm the diagnosis when clinical suspicion is strong and when the above investigations are available.

Phenotypes of wheezing in children

Asthma is a heterogenous disease and based on the longitudinal studies conducted on its natural history, researchers have identified many clinical phenotypes particularly in children below five years. Tucson birth cohort study identified three phenotypes of childhood wheezing namely transient early wheezing, non-atopic wheezing and persistent 'atopic' wheezing.[5]

The best way to discriminate phenotypes in young children is yet to be found as phenotypes are not mutually exclusive. Again it has been argued that these phenotypes are determined by retrospective parental report at the start of the study that was not predictive of phenotype during the study year.[6]

There is poor agreement on definitions of different phenotypes of preschool wheezing disorders. An evidence-based approach (there is no prospective validation) proposed two phenotypes namely episodic wheeze (EW) to describe children who wheeze intermittently and are well between episodes and multiple-trigger wheeze (MTW) for children who wheeze both during and outside discrete episodes.[7]

Episodic wheeze is usually caused by viral infections (viral wheeze) and the affected children are well between episodes. Usually personal or family history of atopy may be absent. In addition to β -agonists, montelukast is used for the treatment of frequent EW and it can be started when symptoms of a viral infection develop.

Children with MTW more frequently and often remain symptomatic between the attacks. Apart from viral infections many triggers like allergens, mist and exercise can precipitate wheezy attacks and they may be associated with personal or family history of atopy. The individual wheezy attacks can be treated with inhaled β-agonists. A trial of inhaled corticosteroids is recommended for MTW.

When associated with personal or family history of atopy, a significant proportion of MTW may develop into asthma and hence this group needs closer attention. During the follow-up, qualifying features of asthma should be repeatedly asked for.

Early childhood wheezing phenotypes and asthma are heterogeneous disorders and both represent the ends of the common spectrum. Thus, attempting to make a correct diagnosis results in effective management avoiding unnecessary therapy. Though it is difficult to diagnose, recurrent wheeze frequently precedes the diagnosis of asthma and it is estimated to occur in more than 20% of infants. Mother's atopic-related disease history is an independent risk factor for recurrent wheezing and asthma.[8]

Avoidance of smoke, particularly of tobacco smoke has positive effect on reduction of wheeze. Since breast feeding seems to reduce the development of asthma and eczema especially in high-risk children breast feeding should be encouraged.[9]

Airway malacias and wheeze

Airway malacias include tracheomalacia, bronchomalacia and tracheobronchomalacia. Tracheomalacia is characterized by flaccidity of the tracheal

support cartilage which leads to tracheal collapse (Fig.1) especially when there is increased airflow demand.[10]

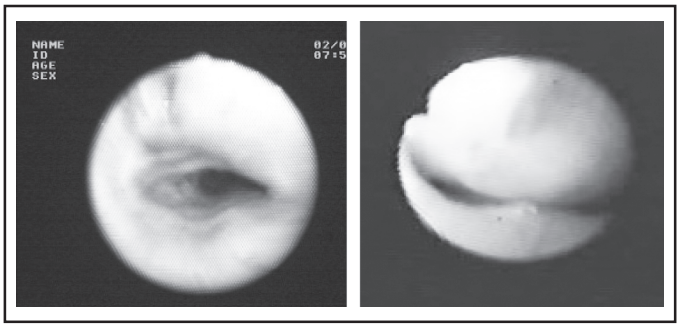

Fig.1.Bronchoscopic views of tracheomalacia and bilateral bronchomalacia

Tracheomalacia should be considered when unexplained symptoms of wheeze or cough are present in young infants, especially if the symptoms start four to eight weeks after birth and persist without signs of viral infection. Unlike the polyphonic wheezing that is heard in bronchiolitis, in infants with airway malacia, low-pitched monophonic wheezing is demonstrated over the central airways. In a child with tracheomalacia, the monophonic wheeze is loudest over the trachea.[10] Fibreoptic bronchoscopy done under local anesthesia is the gold standard for the diagnosis of dynamic airway anomalies.[11]

Due to defective cartilage support, in airway malacias the contour of airways is maintained by the bronchial smooth muscle tone. Infants with congenital airway malacias presenting with wheeze may not improve with β_2-agonist nebulization as β-agonists relax the bronchial smooth muscle. In fact, repeated use of β_2-agonists can actually aggravate the wheeze in these situations by reducing the muscle tone further.[12] Since β-adrenergic agents can exacerbate poor airway tone, they should be avoided and nebulized ipratropium bromide may be used. Some authors are of the opinion that inadequate lung function with β_2-receptor agonist administration in wheezy infants seems to be due to the negative effect of bronchodilation on airway stability[13] but in our opinion this group of infants may have associated airway malacias. Children with airway malacias, particularly tracheomalacias, often have difficulties with retained secretions. Impaired drainage of secretions caused by these disorders results in accumulation of secretions which may be responsible for the parenchymal lung lesions. Postural drainage can help with the clearance of retained secretions. Early diagnosis of airway malacias will prevent unnecessary use of antibiotics or â$_2$-receptor agonists, which are often abused to treat these children.[14]

Other causes of infantile wheeze

Foreign body aspiration can present in many ways. If respiratory distress with wheeze does not improve with adequate therapy, foreign body in the airway should be suspected. Since foreign body history is obtained only in one-third of cases, unexplained (sudden onset) and poorly responding wheeze warrants fibreoptic bronchoscopic evaluation. When there is definite history of foreign body aspiration, rigid bronchoscopy is advised.

Cystic fibrosis (CF) may manifest as failure to thrive with recurrent cough and wheeze accompanied by steatorrhea. Of late, many mild CF genotypes are identified which explains their variable presentation. High index of suspicion and early diagnosis may postpone the lung infection which ultimately increase the longevity of life for these patients. Occurrence of multifocal infections in a wheezy infant gives a clue about the underlying immunodeficiency. Congenital heart disease with failure may cause dyspnea (pulmonary edema) and wheezing (bronchospasm). Whenever an infant presents with atypical symptoms in addition to wheeze, a thorough evaluation is important.

Conclusion

Majority of cases of wheeze during infancy are due to viral infections, aspiration syndrome and wheezing phenotypes. Eighty percent of children who wheeze during the first year of life do not wheeze after the age of three years, hence parental reassurance is the most important aspect which may allay their anxiety. Avoidance of smoke, particularly tobacco smoke has positive effect on the reduction of wheeze. Breast feeding may have a role in reducing the development of asthma and eczema, especially in high-risk infants. Poor response to â$_2$-agonist nebulization and repeated hospitalization suggest the suspicion of possible underlying airway anomalies that need to be investigated.

Points to Remember

- ***The causes of infantile wheeze are multifactorial and a methodical approach is important.***
- ***Phenotypes of wheezing in young children (early wheezers) are grouped as episodic viral wheeze and multiple-trigger wheeze.***
- ***Aspiration syndrome, structural anomalies and non-opaque foreign body are considered when unexplained symptoms of wheezing or coughing persist in infants.***

- ***Avoidance of smoke particularly tobacco smoke, severe respiratory infections and encouragement of breast feeding may reduce the development of asthma especially in high-risk children.***

References

1. Needleman JP. Assessment and approach to common problems. In: Panitch HB,: Pediatric pulmonology: The requisites in pediatrics. Panitch, HB (Ed). Mosby An imprint of Elsevier, Philadelphia, 2005; pp 1-11.
2. An official American thoracic society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. Annals ATS 2013; (10):S1-11.
3. Turner RB, Hayden GF. The Common Cold.In: Kliegman RM, Stanton BF, Joseph W, Duke JB, Schor NF(eds). Nelson Textbook of Pediatrics, 19th Edn. Saunders, Philadelphia, 2011; pp 1434-1436.
4. Khan S, Orenstein S R. Complications of Gastroesophageal Reflux Disease. In: Kliegman RM, Stanton BF, Joseph W, Duke JB, Schor NF. Nelson Textbook of Pediatrics, 19th Ed. Saunders, Philadelphia 2011;pp1269-1270.
5. Martinez FD. Development of wheezing disorders and asthma in preschool children. Pediatrics 2002; 109(2)(Suppl):362-367.
6. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souëf PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. Acta Paediatr 2010; 99(1):56-60.
7. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008; 32(4): 1096-110. doi: 10.1183/09031936.00002108
8. Reis GG,Miranda VM, Cardoso RA, Sole D,Barral A, Nascimento-Carvalho CM, et al. Prevalence and risk factors for wheezing in Salvador, Brazil: a population-based study. Q J Med; 2015;108:213-218.
9. Fredriksson P, Jaakkola N, Jouni JK. Breastfeeding and childhood asthma: a six-year population-based cohort study. BMC Pediatrics 2007; 7:39 doi: 10.1186/1471-2431-7-39.
10. Carden KA, Boiselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. Chest 2005; 127:984-1005.
11. Austin J, Ali T. Tracheomalacia and bronchomalacia in children: Pathophysiology, assessment, treatment and anesthesia management. Pediatr Anesth 2003; 13:3-11.
12. Vijayasekaran D, Kalpana S,Vivekanandan VE. Tracheobronchomalacia presenting as infantile wheeze. Indian Pediatr 2011;48: 903–904.
13. Tiddens HAWM, Hofhuis W, Bogaard JM, Hop WCJ, Bruin HH, Willems LNA et al. Compliance, hysteresis, and collapsibility of human small airways. Am J Respir Crit Care Med 1999; 160:1110–1118.
14. Yalcin E, Dogru D, Ozcelik U, Kiper N, Aslan AT, Gozacan A. Tracheomalacia and bronchomalacia in 34 children: clinical and radiologic profiles and associations with other diseases. Clin Pediatr 2005; 44:777-781.

NEWS AND NOTES

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ACUTE ENCEPHALITIS SYNDROME

***Sangeetha Y**

Abstract: *Encephalitis in children is a potentially devastating neurological syndrome. The etiological spectrum for acute encephalitis in children is expanding due to better neuroimaging modalities and improved diagnostic methods. Encephalitis due to infectious or immune-mediated etiology occurs in children. Clinical presentation includes flu-like syndrome, altered sensorium, seizures, pyramidal signs, cerebellar and extrapyramidal involvement with or without the involvement of spinal cord. Treatment of children with encephalitis has also improved in recent years due to the availability of antiviral agents, immunomodulatory therapies, advances in the neurocritical care and rehabilitation facilities. Early identification and appropriate management will improve the outcome by reducing the morbidity and mortality.*

Keywords: *Encephalitis, Viral, Immune-mediated.*

Encephalitis in children is a potentially devastating neurological syndrome caused either by an infectious agent or a non-infectious cause. Various terms including acute febrile encephalopathy, acute encephalitis syndrome and infectious encephalitis have been commonly used in clinical practice.

Terminologies

Encephalitis

Encephalitis refers to the inflammation of brain parenchyma and is manifested by the presence of neurologic dysfunction. Neurological dysfunction includes altered mental status, behaviour or personality changes, motor or sensory deficits, and speech or movement disorders.[1] Encephalitis is characterized by the pathological findings in grey matter such as direct infection of neural cells, perivascular inflammation, neuronal destruction, neuronophagia and tissue necrosis.[2]

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Encephalopathy

Encephalopathy refers to disruption of brain function in the absence of a direct inflammatory process in brain parenchyma. The causative factors include metabolic disturbances, hypoxia, ischemia, drugs, toxins, organ dysfunction or systemic infection.

Acute encephalitis syndrome

World Health Organization defines acute encephalitis syndrome as "acute onset of fever and a change in mental status and/or new onset of seizures in a person of any age at any time of the year".[3] It has been clearly stated that this definition excludes febrile seizures.

Etio-pathogenesis

Etiology of acute encephalitis can be broadly classified as infectious (viral, bacterial, fungal, protozoal or helminthic) and non-infectious (immune-mediated, toxic, metabolic).[4] In up to two-thirds of the patients with encephalitis-like presentation, no specific infectious etiology was identified.[5] Acute encephalitis is caused by viral agents in a majority of cases with infectious etiology. Various viral pathogens and non-viral pathogens causing encephalitis are summarized. (Box 1 and Box 2)

Acute disseminated encephalomyelitis (ADEM) is an inflammatory disorder frequently involving white matter of brain and spinal cord and has lesser involvement of grey matter of brain. Para- or post-infectious ADEM can be triggered by infection with any of the following organisms: Enterovirus, Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Human Herpes Virus-6 (HHV-6), Hepatitis A, Influenza A/B, Parainfluenza, Measles, Rubella, Coronavirus, Coxsackie virus, Varicella Zoster Virus (VZV), West Nile Virus (WNV), Rotavirus, Mycoplasma pneumoniae, Borellia burgdorferi, Bartonella henselae, Chlamydia, Leptospira, Rickettsia or Streptococcus.ADEM can also be triggered by immunization with diphtheria, pertussis, tetanus toxoid vaccine (DPT), measles, mumps, rubella vaccine (MMR), rabies, Japanese B encephalitis, hepatitis B, influenza or meningococcal vaccines.[6]

Immune-mediated encephalitis also includes autoimmune encephalitis without cancer association,

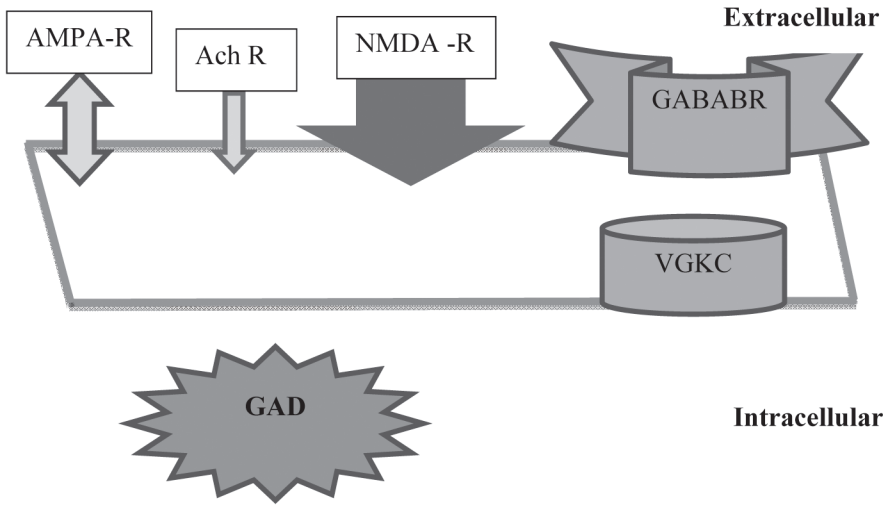

Fig.1. Neuronal transmembrane receptors

AMPAR: Alpha Amino 3 Hydroxy 5 Methyl 4 Isoxazole Propionic Acid receptor, NMDAR: N Methyl D Aspartate receptor, GABABR: Gamma Amino Butyric Acid receptor, VGKC: Voltage Gated Potassium Channel receptor, Ach R: Acetyl Choline receptor, GAD: Glutamic Acid Decarboxylase

Box. 1. Acute encephalitis - Viral

DNA viruses

Herpes viruses

- Herpes virus type 1, 2
- Epstein Barr virus
- Cytomegalovirus
- Human herpes virus 6
- Varicella zoster virus

Adenoviruses

RNA viruses

Picorna viruses

- Polio virus 1,2,3
- Non-polio enteroviruses 70, 71

Toga viruses

- Eastern and western equine encephalitis viruses
- Venezuelan equine encephalitis virus
- Rubella virus (non-arthropod-borne)

Flaviviruses

- Japanese and St. Louis encephalitis viruses
- West Nile virus

Bunyaviruses

La Crosse encephalitis virus

Reoviruses

- Colorado tick fever virus
- Rotavirus

Paramyxoviruses

- Mumps and measles viruses
- Parainfluenza virus
- Respiratory syncytial virus

Orthomyxoviruses

Influenza viruses

Rhabdoviruses

Rabies virus

Arenaviruses

Lymphocytic choriomeningitic virus

Retroviruses

- Human T-cell lymphotropic virus type 1
- Human immunodeficiency virus type 1

Box 2. Non-viral pathogens causing acute encephalitis

Bacterial

Mycoplasma pneumoniae, Mycobacterium tuberculosis, Listeria monocytogenes, Bartonella spp, Coxiella burnetti, Rickettsia rickettsiae, Ehrlichia chaffeensis, Treponema pallidum

Fungal

Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides spp, Candida spp

Parasitic

Toxoplasma gondii, Plasmodium falciparum, Naegleria fowleri, Acanthamoeba spp, Balamuthia mandrillaris, Taenia solium, Baylis ascaris procyonis, Gnathostoma spinigerum

paraneoplastic encephalitis and systemic vasculitis. Autoantibodies against N-methyl D aspartate receptor (NMDAR), voltage gated potassium channel (VGKC), α-amino 3-hydroxy 5-methyl 4-isoxazole propionic acid (AMPAR), γ-amino butyric acid receptor (GABABR) can occur with or without cancer association. Neuronal receptors which are targeted by these autoantibodies are demonstrated in the Fig.1.

Epidemiology

Epidemiological data on encephalitis in India is inadequate because of the lack of concrete case definition and differences in the surveillance systems. Worldwide data found an incidence of up to 16/100000 and the highest incidence is found in children aged less than 1 year.[2] In neonates, encephalitis is often caused by HSV-2, Enterovirus (EV), CMV, Listeria monocytogenes, T pallidum, and Toxoplasma gondii.

A systematic review on acute encephalitis syndrome in India found that outbreak or surveillance studies published before 2000 identified Japanese encephalitis (JE) as the leading cause and studies published after 2000 identified Enterovirus, Chandipura and Nipah viruses as common agents.[7] A hospital-based study of 526 patient from eastern states of India identified viral etiology in 91 cases and the identified viruses were HSV I or II in 16.1%, measles in 2.6%, JE virus in 1.5%, Dengue virus in 0.57%, VZV in 0.38% and EV 0.19%.[8] Another hospital-based study of more than 1500 patients from northern states of India had identified JE in 16.2%, dengue virus, HSV, measles, mumps (each contributing 8%-10%) and VZV (4.4%).[9]

California encephalitis project enrolled 1570 patients of all ages from 1998 to 2005, performed an extensive microbiologic evaluation and found that no etiology was identified in 63% of cases.[5] A confirmed or probable infectious etiology was identified in 16% (69% viral and 20% bacterial) and a possible infectious etiology was identified in 13%, and a non-infectious etiology was identified in 8%. The most commonly isolated viruses were enterovirus and herpes simplex virus type 1. Another cohort of immunocompetent subjects of age between 6 months to 30 years with encephalitis was enrolled between September 2007 and February 2011. This cohort revealed that anti-NMDAR encephalitis was identified 4 times as frequently as HSV-1, WNV or VZV.[10]

In children presenting with encephalitis, etiological diagnosis is essential for treatment options, prognosis, potential prophylaxis, counseling of parents and public health interventions. Epidemiologic clues for identifying the pathogen include season, geographic area, prevalence of disease in the local community, travel history, recreational activities, occupational exposure, insect contact, animal contact, vaccination history and also the immune status of the patient. Clinical and radiological clues may also help the physicians in considering specific etiologies.

Clinical presentation

Clinical presentation includes flu-like syndrome, altered sensorium, seizures, pyramidal signs, cerebellar, extrapyramidal involvement with or without the involvement of spinal cord. In children with encephalitis, up to 80% had fever, seizures (79% focal and generalized in remaining), focal neurological signs and up to 50% had low Glasgow coma scale score.[11] Clinical presentation in encephalitis of varying etiology are summarized in Table I.

Diagnosis

Pediatricians should be aware of the common pathogens causing encephalitis in their locality, diagnostic evaluation and the surveillance system in case of epidemics. After sending the samples for diagnostic testing, supportive care and prompt empirical therapy with acyclovir must be initiated. Neuroprotective care is important to prevent ongoing brain damage and to improve the outcome.

Table I. Clinical presentation in encephalitis of varying etiology[14]

Pathogen	Clinical features
Mycoplasma pneumoniae	Prodrome of respiratory symptoms, seizures, focal motor deficits, ataxia and increased intracranial pressure
Herpes virus	Fever, behavioural changes, seizures, altered sensorium
Epstein Barr virus	Encephalitis, ADEM, encephalopathy, acute cerebellar ataxia
Japanese B virus	Fever, impairment of consciousness and meningeal irritation signs,
West Nile virus	Extrapyramidal signs: rigidity, tremor, parkinsonism
Influenza virus	Reye syndrome, acute necrotising encephalopathy of infants, hemorrhagic shock and encephalopathy syndrome
Dengue virus	Fever, bleeding diathesis, shock, seizures, focal deficits
Chikungunya virus	Prodromal symptoms, behaviour changes, extrapyramidal involvement, myeloneuropathy
Enterovirus	Fever, coryza, headache, altered sensorium, seizures
Chandipura virus to deep coma and death	Reye-like presentation, vomiting followed by LOC, rapid progression
Cytomegalovirus	Diffuse encephalitis, ventriculo-encephalitis, transverse myelitis in immunosuppressed
Nipah virus	High grade fever, altered sensorium, respiratory symptoms, seizures, dystonia

ADEM - Acute disseminated encephalomyelitis; LOC - Loss of consciosness

Investigations: This includes complete blood count, urea, creatinine, electrolytes, calcium, glucose, liver function tests, prothrombin time, activated partial thromboplastin time, C-reactive protein, urine ketones, arterial blood gases, lactate, ammonia, peripheral smear for malarial parasite, chest X-ray, blood culture, peripheral smear study and screening for HIV.

Lumbar puncture is mandatory in all children with acute encephalitis, unless there are absolute contraindications. Cerebrospinal spinal fluid should be analyzed for cell count, protein, sugar (concurrent blood sugar recording is essential), bacterial culture and sensitivity, latex agglutination, Gram stain, smear for acid fast bacilli, polymerase chain reaction (PCR) for Mycobacterium tuberculosis, PCR for viral pathogens (HSV 1 and 2; enterovirus; adenovirus; cytomegalovirus; Epstein Barr virus; Varicella zoster virus; HHV 6; influenza; Chandipura virus), CSF and blood Ig M antibodies for Japanese B encephalitis, India ink for cryptococcus, wet mount for acanthamoeba, fungal culture and CSF for IgM and IgG antibodies in suspected toxoplasmosis. If clinico-radiological findings and EEG findings suggest probable HSV encephalitis but PCR testing is negative for HSV, a repeat PCR analysis should be done 3-7 days after the initial testing.

Testing for dengue virus by IgM antibody detection in CSF, measles by measles specific IgM antibody in CSF, HHV-6, rickettsial infections and meningococci should be considered in children presenting with acute febrile encephalopathy and rash. It is also mandatory in case of outbreak of these infections.

Electroencephalography (EEG) is mandatory in all children with unexplained encephalopathy and in children with altered sensorium after a convulsive status to rule out an ongoing non-convulsive status. Presence of periodic lateralized epileptiform discharges (PLEDs) in EEG suggests the possibility of herpes encephalitis. In children with encephalitis, slowing of background and poorly formed sleep markers only suggest the possibility of diffuse encephalopathy irrespective of etiology.

Table II. Neuroimaging clues for underlying etiology in children with acute encephalitis

Etiology	Imaging findings
ADEM	Multiple large lesion, poorly defined margins, mass effect usually slight or completely absent, subcortical and deep white matter signal changes, usually asymmetrical but symmetrical deep grey involvement in 1/3rd cases;MR contrast: patchy or ring enhancement or non-enhancing lesions
Anti NMDA-R encephalitis	Normal in 50% of patients; remaining may have T2 or FLAIR signal hyperintensity seen in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem and infrequently, the spinal cord[13]
Herpes encephalitis	T2 or FLAIR signal hyperintensity in temporal lobe, insular cortex, orbital surface of the frontal lobe and cingulate gyrus; Non-temporal location may be present in HIV infected children
EBV encephalitis	Normal or non-specific signal changes; T2 or FLAIR signal hyperintensity in the gray or white matter of the cerebrum and cerebellum, basal ganglia, brainstem involvement and brain atrophy[15,16]
Varicella	Diffuse cerebellar swelling and bilateral, symmetrical areas that are hypodense on CT and T2 or FLAIR signal hyperintensity in the gray matter of cerebellum; basal ganglia infarcts. MRA may show narrowing of the common carotid artery and of proximal branches of the anterior or middle cerebral artery[17,18]
Japanese B encephalitis	T2 or FLAIR signal hyperintensity in thalami, substantia nigra, basal ganglia
Influenza encephalitis	T2 or FLAIR signal hyperintensity in the cerebral cortex, adjacent white matter; symmetrical thalamic lesions[19,20]
Enterovirus 71	T2 or FLAIR signal hyperintensity in the dorsal pons, medulla, midbrain, and dentate nuclei of the cerebellum; anterior horn cells of spinal cord in patients with acute flaccid paralysis
West Nile virus	T2 or FLAIR signal hyperintensity in deep gray matter and brainstem; white matter lesions

ADEM- Acute disseminated encephalomyelitis, NMDAR- N methyl D Aspartate Receptor, CT- Computerized tomography, FLAIR- Fluid attenuated inversion recovery, EBV- Epstein Barr Virus, MR- Magnetic resonance, HIV - Human immunodeficiency virus

Neuroimaging is essential in all children with acute encephalitis. MRI brain with diffusion weighted images and gadolinium contrast is preferred over CT brain except in children where MRI cannot be performed and non-availability of MRI brain in resource limited settings. MRI findings in children with encephalitis of different etiologies are summarized in the Table II. Fig. 2 and 3 depict the neuroimaging findings seen in patients with herpes simplex and Japanese encephalitis respectively.

Brain biopsy

Brain biopsy is rarely performed in clinical setting of children with encephalitis. Brain biopsy should be considered in children who succumb during an outbreak of encephalitis, if no pathogen is identified after a comprehensive diagnostic evaluation. Brain biopsy specimens can be used for smear examination, viral antigen detection, tissue culture, electron microscopy and detection of virus by PCR method.

Other tests

Thyroid antibodies, vasculitis markers, anti-NMDA receptor antibodies, anti-VGKC antibodies and other onconeural antibodies panel testing should be considered in children with encephalitis, if infectious screen results are

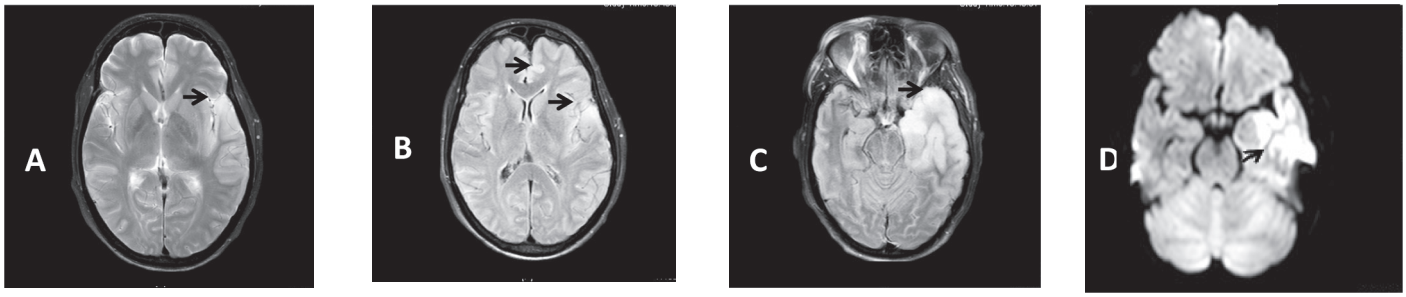

Fig. 2. MRI in Herpes simplex encephalitis

2A. T2 Weighted axial image

2B & 2C. T2 Fluid attenuated inversion recovery image (FLAIR). Arrows show hyperintense signal changes in cingular cortex, perinsular, left temporal lobe, hippocampus

2D. Diffusion weighted images: Arrow show restriction of diffusion in left temporal & cingulate cortex.

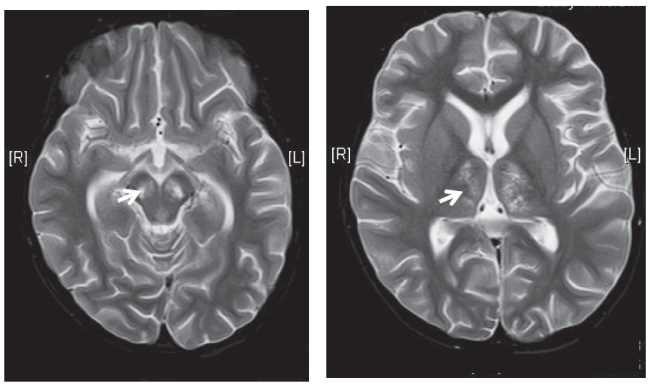

Fig.3(A & B). MRI in Japanese encephalitis

T2 axial images: Arrows show signal hyperintensity in bilateral thalami and substantia nigra of mid brain

negative. In children with autoimmune encephalitis, tumor surveillance is also essential. Basic metabolic profile such as blood tandem mass spectrometry, urine gas chromatography mass spectrometry, blood ammonia, arterial blood gases, arterial lactate and CSF lactate are recommended in children with encephalitis-like presentation with suspected underlying metabolic disorder.

Treatment

Managing airway, breathing and circulation must be the priority in all children with acute encephalitis. Maintain euthermia and euglycemia. Correct acid-base abnormalities and dyselectrolytemia, if detected. In those children with status epilepticus, management of seizures as per the standardized protocols will improve the outcome. Consider the following efforts to manage children with raised intracranial pressure: 30º elevation of head end; ventilation targeting low normal PCO_2; adequate analgesics and sedation; therapy with 3% normal saline and mannitol.

Encephalitis- infectious etiology

Empirical therapy with acyclovir should be initiated and continued in all children with acute encephalitis till diagnostic test reports are available. Treatment of immune-mediated encephalitis is outlined in Table III. In addition, therapy with specific antiviral, anti-microbial, anti-protozoal and anti-fungal agents should be considered as depicted in the Tables IV, V, VI and VII in appropriate settings.

Outcome in children with encephalitis

A study on analysis of the morbidities among 71 children who survived from acute encephalitis found that more than half reported persistent symptoms such as emotional symptoms, personality changes, cognitive disturbances, motor disabilities, speech dysfunction and epilepsy. Mortality varies depending upon the causative agent.[12] Reported mortality in HSV encephalitis was upto 10% and in Japanese encephalitis was upto 40%. Outcome is variable in arbovirus encephalitis. Most children with immune-mediated encephalitis make a near complete recovery and reported mortality in anti NMDAR encephalitis was less than 5%.[13] Early rehabilitation to prevent contractures and adequate nutrition will improve the outcome. Psychosocial support should be provided to these children and their families.

Prevention

Surveillance studies during an epidemic are essential to understand the disease burden, utilization of resources, framing of public health policies and initiating public health interventions. Public health measures such as sanitation, avoidance of man-vector contact and vector control play vital role in preventing outbreaks of encephalitis. Universal

Table III. Management of non-infectious encephalitis

Encephalitis	Diagnosis	Treatment
ADEM	MRI brain with contrast ± MRI spine	Intravenous pulse methyl prednisolone 30mg/kg for 5 days. If no improvement, repeat pulsing of steroids or IV IG 2gm/kg. If residual deficit, oral steroids 1 mg/kg for 3 weeks
Anti- NMDAR encephalitis[13]	MRI brain Serum and CSF anti-NMDAR antibodies MRI pelvis for tumor surveillance	Concurrent IV IG and methyl prednisolone infusion or plasma exchange. Tumor removal if present If no improvement, rituximab ± cyclophosphamide If improvement occurs, chronic immunosuppression with mycophenolate mofetil or azathioprine and yearly tumor surveillance

ADEM - Acute disseminated encephalomyelitis; IVIG - Intravenous immunoglobulin; CSF - Cerebro spinal fluid; MRI - Magnetic resonance image; NMDAR- N methyl D Aspartate Receptor

Table IV. Antiviral agents in encephalitis [21]

Virus	Anti-viral agents
Herpes	Acyclovir (A-I)
Varicella Zoster	Acyclovir (B-III) Ganciclovir as an alternative (C-III) Adjunctive corticosteroids (C-III)
Cytomegalovirus	Ganciclovir + foscarnet (C-III)
Epstein Barr virus	Acyclovir - Not recommended Corticosteroids (C-III)
Human Herpes Virus -6	Ganciclovir or foscarnet in immunocompromised patients (B-III) Immunocompetent patients (C-III)
Influenza virus	Oseltamavir (C-III)
Measles virus	Ribavirin (C-III)
Nipah virus	Ribavirin (C-III)
West Nile virus	Ribavirin not recommended
Japanese B encephalitis	IFN á not recommended
Human Immunodeficiency Virus	HAART (A-II)

IFN - Interferon; HAART - Highly active anti-retroviral therapy

(Strength of recommendation: A- Good evidence, B-Moderate evidence, C-Poor evidence)

Quality of evidence: I- Evidence from ≥1 randomized controlled trials, II- Evidence from ≥1 non-randomized trials, case control or cohort studies, III- Evidence from opinion based on clinical experience, descriptive studies, or reports of expert committees

Table V. Anti-bacterial agents in encephalitis[21]

Bacteria	Anti- microbial agents
Bartonella henselae	Doxycycline or azithromycin, with or without rifampin (C-III)
Bartonella bacilliformis	Chloramphenicol, ciprofloxacin,doxycycline, ampicillin, or trimethoprim-sulfamethoxazole (B-III)
Borrelia burgdorferi	Ceftriaxone, cefotaxime or penicillin G (B-II)
Listeria monocytogenes	Ampicillin plus gentamicin (A-III); In patients with penicillin allergy, trimethoprim-sulfamethoxazole (A-III)
Mycobacterium tuberculosis	4-drug antituberculoustherapy (A-III); adjunctive dexamethasone in patients with meningitis (B-I)
Mycoplasma pneumoniae	Azithromycin, doxycycline, or a fluoroquinolone (C-III)
Treponema pallidum	Penicillin G (AII); ceftriaxone (B-III)
Rickettsial infection	
Anaplasma phagocytophilum	Doxycycline (A-III)
Ehrlichia chaffeensis	Doxycycline (A-II)
Rickettsia rickettsii	Doxycycline (A-II); Chloramphenicol as an alternative (C-III)
Coxiella burnetii	Doxycycline plus a fluoroquinolone plus rifampicin (B-III)

Table VI. Anti-protozoal agents in encephalitis

Protozoal	Treatment
Acanthamoeba	Trimethoprim- sulfamethoxazole plus rifampin plus ketoconazole (C-III) or fluconazole plus sulfadiazine plus pyrimethamine (C-III)
Naegleria fowleri	Amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered (C-III)
Toxoplasma gondii	Pyrimethamine plus either sulfadiazine or clindamycin (A-I); trimethoprim sulfamethoxazole alone (B-I) and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone (B-III)
Plasmodium falciparum[22]	Artesunate 2.4 mg/kg IV then at 12 and 24 hours, then once a day for a total of 7 days. Change to oral preparation once the child is able to swallow.* OR Artemether 3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily for 6 days. Change to oral preparation once the child is able to swallow.* OR Quinine salt 20mg salt/kg (loading dose) diluted in 10mL of isotonic fluid/kg by infusion over 4 hours and 12 hours later give a maintenance dose of 10mg salt/kg over 2 hours. Maintenance dose should be repeated every 8 hours and once the child tolerates orally, give quinine tablets, 10mg salt/kg 8-hourly to complete a 7-day course of treatment.*

*Tetracycline or doxycycline or clindamycin is added as soon as the patient can tolerate orally and should be continued for 7 days.

IV - Intravenous; IM - Intramuscalar

Table VII. Anti-fungal agents in encephalitis[21]

Fungi	Anti-fungal agents
Cryptococcus neoformans	Amphotericin B deoxycholate plus flucytosine (A-I); oral lipid formulation of amphotericin B plus flucytosine (A-II)
Coccidioides species	Fluconazole (AII); Itraconazole (B-II); voriconazole (B-III), and amphotericin B (C-III).
Histoplasma capsulatum	Liposomal amphotericin B followed by itraconazole (B-III)

precautions must be followed by all health care workers. Adequate immunization coverage for measles, mumps, rubella, varicella, influenza and post exposure prophylaxis for rabies is essential. In geographic areas endemic for Japanese encephalitis, mass vaccination strategies against JE virus should be done as per Government policy.

Points to Remember

- ***In children with encephalitis, the pathogen is identified in less than half of the cases and most commonly identified pathogens are viruses.***
- ***Differential diagnosis includes immune-mediated or non-infectious disease process.***
- ***Detailed history, clinico-radiological findings, cerebrospinal fluid analysis and epidemiological clues guide in etiology work up.***
- ***Provide supportive care and start empirical acyclovir awaiting definitive diagnosis.***
- ***Public health interventions should be considered in epidemics.***

References

1. Bronstein DE, Shields WD, Glaser CA. Encephalitis and meningoencephalitis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th edn, Cherry JD, Harrison GJ, Kaplan SL, et al. (Eds), Elsevier Saunders, Philadelphia 2014; p492.
2. Johnson RT. Acute encephalitis. Clin Infect Dis 1996; 23:219-224.
3. Solomon T, Thao TT, Lewthwaite P, Ooi MH, Kneen R, Dung NM, et al. A cohort study to assess the new WHO Japanese encephalitis surveillance standards. Bull World Health Organ 2008; 86:178-186.
4. Thompson C, Kneen R, Riordan A, Kelly D, Pollard AJ. Encephalitis in children. Arch Dis Child 2012; 97: 150-161.
5. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 2006; 43:565-577.
6. Panicker JN. Acute disseminated encephalomyelitis. Ann of Indian Acad Neurol 2007; 10:137-144.
7. Joshi R, Kalantri SP, Reingold A, Colford JM Jr. Changing landscape of acute encephalitis syndrome in India: a systematic review. Natl Med J India 2012; 25: 212-220.
8. Rathore SK, Dwibedi B, Kar SK, Dixit S, Sabat J, Panda M. Viral aetiology and clinico-epidemiological features of acute encephalitis syndrome in eastern India. Epidemiol Infect 2014; 142:2514-2521.
9. Jain P, Jain A, Kumar A, Prakash S, Khan DN, Singh KP, et al. Epidemiology and etiology of acute encephalitis syndrome in North India. Jpn J Infect Dis 2014;67(3): 197-203.
10. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 2012;54:899-904.
11. Kolski H, Ford-Jones EL, Richardson S, Petric M, Nelson S, Jamieson F, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995. Clin Infect Dis 1998; 26:398-409.
12. Fowler A, Stödberg T, Eriksson M, Wickström R. Long-term outcomes of acute encephalitis in childhood Pediatrics 2010;126:e828-835.
13. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63-74.
14. Shoji H, Azuma K, Nishimura Y, Fujimoto H, Sugita Y, Eizuru Y. Acute viral encephalitis: the recent progress. Intern Med 2002; 41:420-428.
15. Angelini L, Bugiani M, Zibordi F, Cinque P, Bizzi A. Brainstem encephalitis resulting from Epstein-Barr virus mimicking an infiltrating tumor in a child. Pediatr Neurol 2000; 22:130-132.

16. Shian WJ, Chi CS. Epstein-Barr virus encephalitis and encephalomyelitis: MR findings. Pediatr Radiol 1996; 26:690-693.

17. Darling CF, Larsen MB, Byrd SE, Radkowski MA, Palka PS, Allen ED. MR and CT imaging patterns in post-varicella encephalitis. Pediatr Radiol 1995; 25:241-244.

18. Silverstein F, Brunberg J. Postvaricella basal ganglia infarction in children. AJNR Am J Neuroradiol 1995; 16: 449-452.

19. Tsuchiya K, Katase S, Yoshino A, Hachiya J. MRI of influenza encephalopathy in children: value of diffusion-weighted imaging. J Comput Assist Tomogr 2000; 24: 303-307.

20. Fujimoto Y, Shibata M, Tsuyuki M, Okada M, Tsuzuki K. Influenza A virus encephalopathy with symmetrical thalamic lesions. Eur J Pediatr 2000; 159:319-321.

21. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008; 47:303-327.

22. Kundu R, Ganguly N, Ghosh TK. Infectious Diseases Chapter. Indian Academy of Pediatrics, Management of malaria in children: update 2008. Indian Pediatr 2008; 45: 731-735.

CLIPPINGS

As required versus fixed schedule analgesic administration for postoperative pain in children.

Acute postoperative pain occurs as a result of tissue damage following surgery. Administering the appropriate analgesia to children is a complex process and it is unclear whether children's postoperative pain is more successfully treated by using 'as required' (when pain occurs -PRN) or irrespective of pain around the clock (ATC).

Aim: To assess the efficacy of as required versus fixed schedule analgesic administration for the management of postoperative pain in children under the age of 16 years

Three RCTs (four reports) of 246 children aged under 16 years undergoing tonsillectomy were included. Children were given weight-appropriate doses of the study medication, either PRN or ATC, by a parent or carer at home for up to four days following surgery. Mean pain intensity scores decreased over time, as did medication use. However, children were still reporting pain at the final assessment, suggesting that no administration schedule provided adequate analgesia. There were no significant differences in pain intensity scores at any time point. The studies reported adverse events that may have been related to the study medication, such as nausea, vomiting and constipation, but no statistically significant differences were noted between the groups. There were too few data from only three small studies and meta-analysis was not possible. One study reported that a higher amount of analgesics was consumed in the ATC group compared with the PRN group: it would have been helpful to show that the higher volume in the ATC group led to better analgesia but was not able to demonstrate the same.

Authors' conclusions: There was limited evidence available to draw any conclusions about the efficacy of PRN versus ATC analgesic administration for the management of postoperative pain in children.

Anna Hobson, Philip J Wiffen, Joy A Conlon. As required versus fixed schedule analgesic administration for postoperative pain in children. First published: 26 February 2015. Assessed as up-to-date: 2 July 2014. Editorial Group: Cochrane Pain, Palliative and Supportive Care Group. DOI: 10.1002/ 14651858.CD011404.pub2.

NEWS AND NOTES

Neonatal and Paediatric Ventilation Workshop, New Delhi
Date: 4th & 5th April, 2015
Course Director: Dr Praveen Khilnani.

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IAP-IJPP CME 2014

PEDIATRIC CARDIAC EMERGENCIES – GUIDELINES FOR MANAGEMENT

**** Sasidaran K***

Abstract: *Cardiac conditions leading to emergencies fall under three main categories, namely: undiagnosed congenital heart diseases (CHD) with decompensation, CHDs with complications due to interventions and acquired heart diseases. A systematic approach to acute heart failure, dysrhythmias, hypercyanotic spells and hypertensive crisis which are the common cardiac emergencies is dealt with in this article.*

Keywords: *Cardiac emergencies, Acute heart failure, Dysrhythmias, Hypercyanotic spell, Hypertensive crisis, Children.*

Cardiac conditions presenting as acute emergency are not uncommon in pediatric practice. Three groups of pediatric population can present with acute cardiac conditions to the emergency room(ER) viz.,

a) Undiagnosed congenital heart diseases presenting in acute decompensation; b) Diagnosed congenital heart disease presenting to emergency due to disease related or intervention (surgical procedure) related complications and c) Acquired heart diseases and toxicological emergencies presenting as cardiac emergency (Table I).

Independent of the primary etiology, the presenting problems would be acute heart failure, dysrhythmia, cyanotic spell or hypertensive emergency (Fig. 1). The purpose of this article is to provide a comprehensive review about the diagnosis and emergency management guidelines for the above mentioned common cardiac problems in the pediatric emergency room.

Acute heart failure in children

Heart failure in children can be defined as the failure of heart to supply blood to either systemic or pulmonary circulation at an appropriate rate of flow, or to receive venous return at an appropriate filling pressure, resulting in adverse effects on the heart, the circulation, and the patient. Clinical presentation of acute decompensated heart failure is known as 'cardiogenic shock'.

Assessment of child presenting to ER with suspected acute heart failure

Children presenting with symptoms and signs of heart failure (Table II) require an urgent and rapid assessment

Table I. Clinical conditions presenting as acute heart failure

Structural heart disease	Acquired heart disease
(a) Volume overload lesions	Myocarditis, Cardiomyopathy
	Coronary artery disease
ASD	ALCAPA,
VSD/AVSD	Kawasaki disease
PDA	Rhythm and conduction
Arterio-venous malformation	disturbance
	Post-cardiopulmonary
Aortopulmonary window	bypass
	Anemia
Aortic regurgitation	Arteriovenous fistula
	Hypoxic ischemia
(b) Pressure overload lesions	Hypertension
	Sepsis,
	Toxic myocarditis
Aortic stenosis	Hypocalcemia,
Pulmonary stenosis	Hypoglycemia
Coarctation of aorta	Endocrinopathies
Systemic hypertension	

ASD: Atrial septal defect
VSD: Ventricular septal defect
AVSD: Atrioventricular septal defect
PDA: Patent ductus arteriosus
ALCAPA: Anamalous origin of left coronary artery from pulmonary artery

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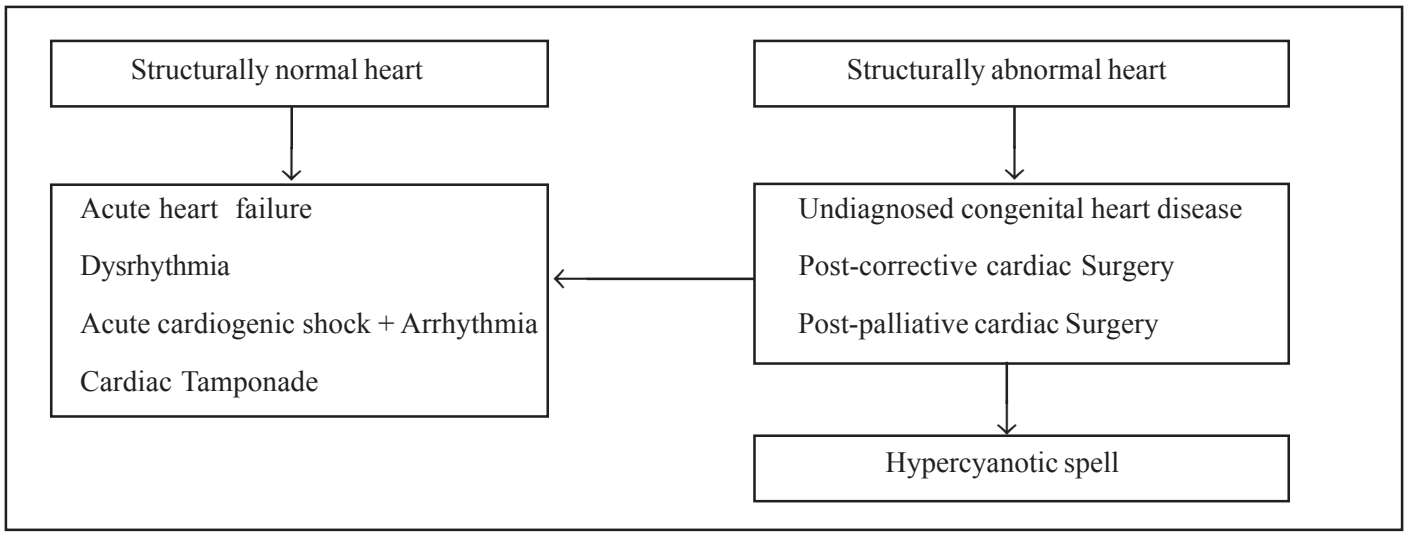


Fig. 1. Clinical spectrum of pediatric cardiac emergencies

to establish the physiologic state of the hemodynamics and identify any reversible causes of heart failure. At this juncture, two most important questions are to be answered, (a) Are there features of congestion? (b) Are there features of low perfusion?

Low perfusion is identified by hypotension or tachycardia with narrow pulse pressure, cool extremities. Congestion is clinically defined by hepatomegaly, tachypnea, orthopnea, facial/dependent edema, and ascites. Finding answers to these questions would help to classify the child's hemodynamics into one of the four recognized patterns of acute decompensated heart failure:[1] (a) Warm and dry, (b) warm and wet, (c) cold and dry and (d) cold and wet (Fig. 2).

Table II. Presenting symptoms of heart failure in children

Age	Common symptoms	Less common symptoms
Infants and young children	Tachypnea Feeding difficulty Diaphoresis Pallor	Cyanosis Palpitations Syncope Facial edema Dependent edema Ascites
Older children and adults	Fatigue Effort intolerance Dyspnea Orthopnea Abdominal pain Nausea Vomiting	Palpitations Chest pain Dependent edema Ascites

Investigations

Chest X-ray is indicated as first line investigation in children with suspected heart failure apart from electrolytes (Na, K, Cl, and Ca), glucose, acid–base status, urea, creatinine, hepatic transaminases, thyroid hormone levels and complete blood count. Cardiomegaly on chest X-ray is highly predictive of ventricular dilatation on echocardiography with high specificity and negative predictive value.[2] However, the sensitivity and positive predictive value are low. Electrocardiogram is routinely done in such children, remains non-specific but frequently abnormal.

Management of acute heart failure

In the diagrammatic representation, Class B, C and D are the states of decompensated heart failure or cardiogenic shock (Fig. 2). Basic steps in managing these categories are given in Table III and Fig. 3.

Children presenting in hypotensive cardiogenic shock [Class C] may require a slow fluid bolus of 10 mL/kg. Repeated fluid boluses may worsen the clinical status as they usually fail to improve the stroke index in presence of cardiac dysfunction. These children [Class C at presentation] may be benefitted by early initiation of noninvasive positive pressure oxygen administration (NP-CPAP High flow nasal cannula oxygen therapy).

Vasoactive drugs in cardiogenic shock

It is essential to know the basic characteristics of commonly used vasoactive agents to select the appropriate one for the given hemodynamic status. The basic properties of commonly used vasoactive agents are summarized (Table IV).[3]

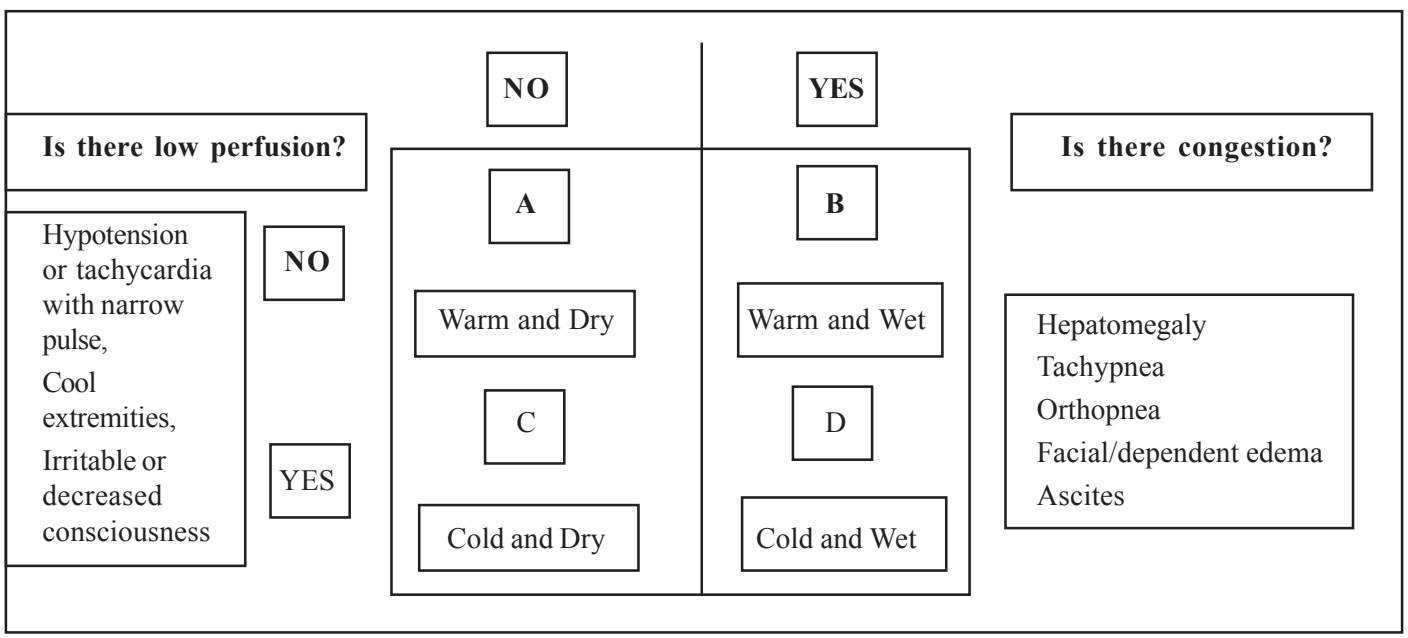
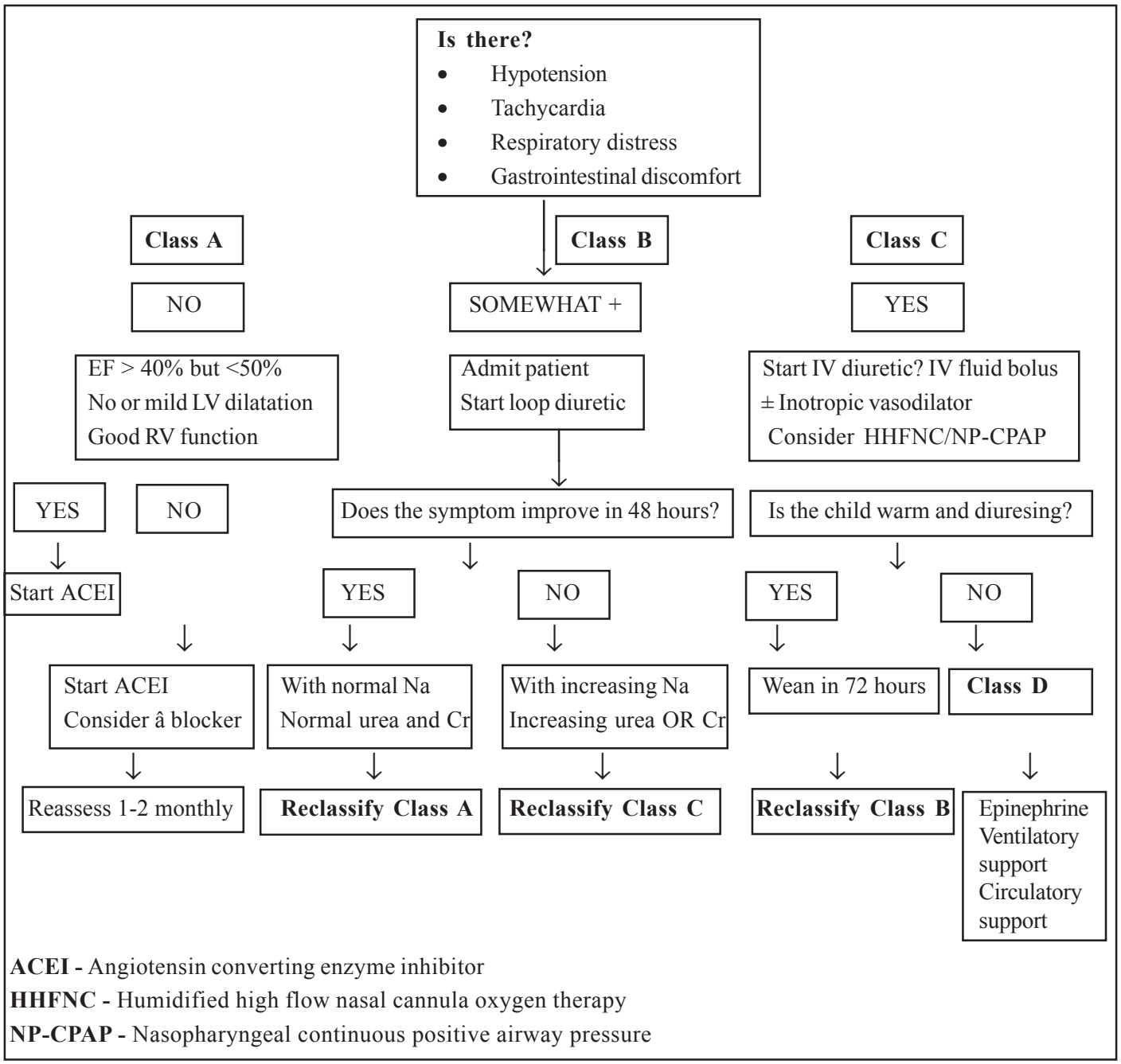


Fig. 2. Recognized patterns of acute heart failure.

Table III. Stepwise management in cardiac failure

Warm and dry (A): Optimization of oral medication

Warm and Wet (B)	Cold and Dry (C)	Cold and Wet (D)
Avoid fluid bolus	Fluid bolus 10 mL/Kg	Inotropic medication
Afterload reduction	Inotropic medications	Slow fluid bolus
Reduce myocardial O_2 consumption	Reduce myocardial O_2 consumption	Afterload reduction
Improve myocardial Contractility	Afterload reduction	Reduce myocardial O_2 consumption
Fluid restriction	Fluid restriction	Fluid restriction



ACEI - Angiotensin converting enzyme inhibitor
HHFNC - Humidified high flow nasal cannula oxygen therapy
NP-CPAP - Nasopharyngeal continuous positive airway pressure

Fig. 3. Approach to acute heart failure management

Table IV. Properties of vasoactive agents

Drugs	Properties
Epinephrine	Inotropy + Chronotropy; Receptor effects dose dependent; Receptor down regulation with longer use < 0.1 μg Beta (β) effect
Norepinephrine	Predominant α agonist; Increases peripheral vascular resistance; Increases after load
Dobutamine	Hypotension due to α_2 effect; Reflex tachycardia
Dopamine	At higher dose α action
Milrinone	Increases cardiac output; Reduces filling pressures; Reduces after load

Though dobutamine and milrinone are stated as preferred vasoactive agents in cardiogenic shock, it is advisable to start low dose epinephrine (0.1-0.2 μg/kg/minute) in children who are presenting in wet and cold shock to stabilize the systemic BP and improve the inotropy before initiating potentially afterload reducing vasodilator therapy.

Management of dysrhythmia

Children presenting in bradyarrhythmias or tachyarrhythmias (Fig. 4 and 5) constitute one of the most challenging clinical scenarios in pediatric emergency room. With the help of pediatric advanced life support (PALS) training, management of these children using time sensitive algorithmic management protocol has improved.

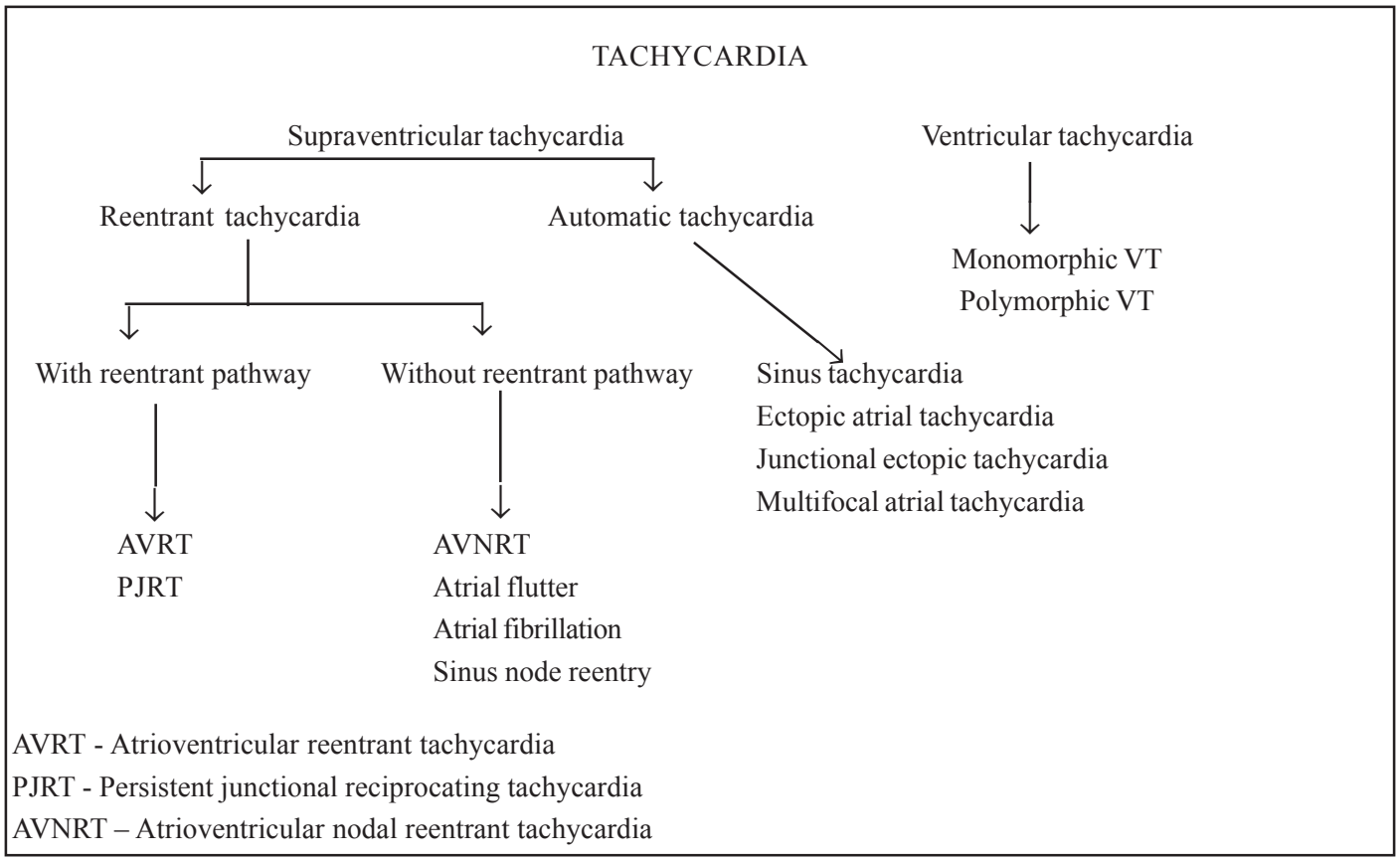


Fig.4. Common types of pediatric tachyarrhythmia

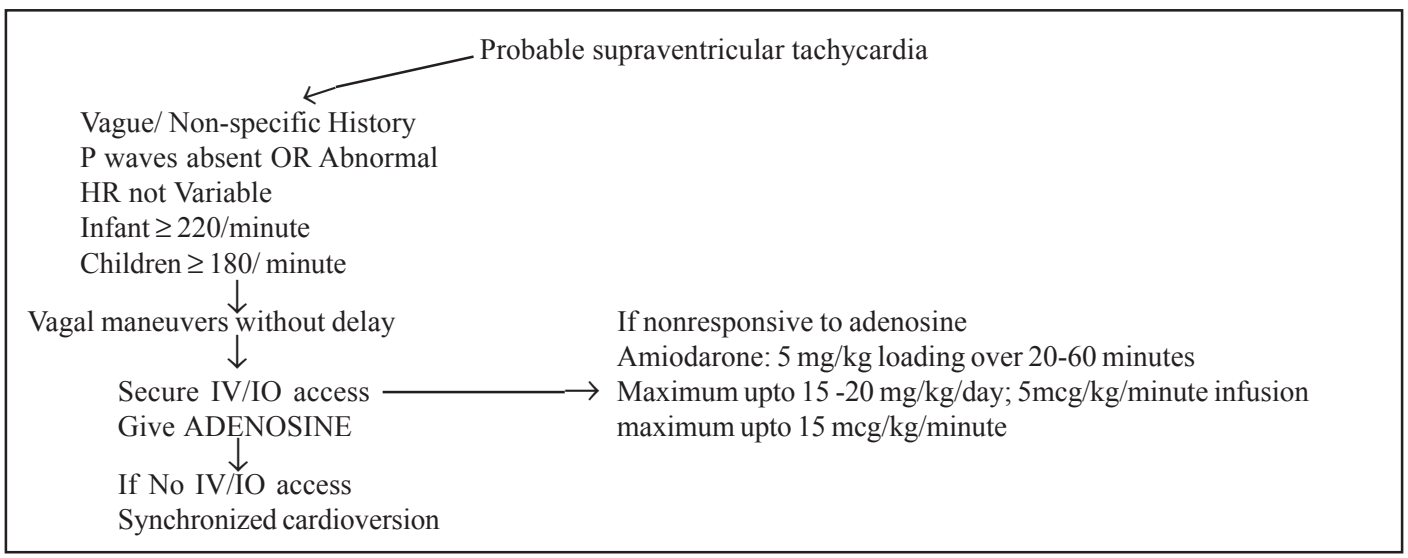


Fig.5. Diagnosis and management of supraventricular tachycardia in children

Reversible causes of tachyarrhythmias

In every child presenting with tachyarrhythmia, identification and treatment of underlying disease is an important step. We may need to look for 6Hs (hypovolemia, hypoxia, hydrogen ion (acidosis), hypoglycemia, hypo/hyperkalemia, hypothermia) and 5Ts (tension pneumothorax, tamponade – cardiac, toxins, coronary thrombosis, pulmonary thrombosis) in each step while proceeding with the treatment protocol and most of the time, refractoriness to therapy may be due to one of these unidentified predisposing factors.[4]

Hypercyanotic spell

Hypoxic spell also known as hypercyanotic spell occurs in young infants with tetralogy of Fallot. It consists of rapid and deep respiration, worsening cyanosis and disappearance or reduced intensity of the heart murmur. Any event (i.e., crying, defecation, increased physical activity) that suddenly lowers the systemic vascular resistance (SVR) or produces a large right to left ventricular shunt may initiate the spell.[5] The management of hypercyanotic spell is given in Box 1.

Diagnosis and management of hypertensive emergencies

Hypertension is uncommon in children, but often goes unrecognized for long time. It is defined as systolic and/or diastolic BP being ≥ 95th percentile for ≥ 3 occasions. Severe hypertension (when there is threat to life and function of vital organs) is considered when BP is > 99th percentile. Cardiac sequelae of childhood hypertension are uncommon, but acute severe forms (malignant hypertension) can result in ventricular dysfunction and congestive heart failure. Long standing hypertension can result in diastolic dysfunction with increased filling pressures.[6]

Presenting features of systemic hypertension

These children may be asymptomatic and detected coincidentally. Symptoms of primary etiology (Cardiac, Reno-vascular, Endocrine, Drug related) may be seen sometimes. Epistaxis may be seen in some children. Headaches and visual disturbances may occur when there is an acute rise in BP. Encephalopathy indicates hypertensive

Box 1. Steps in the management of cyanotic spell

- Knee chest position – increases the SVR by reducing arterial blood flow through femoral arteries. This may help by trapping the systemic venous blood in the legs thereby temporarily decreasing the systemic venous return.
- Intravenous (IV) morphine suppresses respiratory center and reduces hyperpnea
- IV sodium bicarbonate corrects acidosis and eliminates the respiratory center stimulating effect of acidosis
- Administration of oxygen to improve arterial oxygen saturation (though the effect is less)
- Vasoconstrictors like phenylephrine
- Ketamine increases the SVR and sedates the patient.
- Propranolol may reduce the spasm of right ventricular outflow tract and slow down the heart rate.

Box 2. Basic principles in managing hypertensive emergency

- Administer short acting parenteral antihypertensive along with meticulous blood pressure monitoring
- BP decreased by 25%-30% in first eight hours, 25%-30% over next 24-36 hours and the remaining over 48-72 hours. A quicker reduction is safe if the BP rise is of very recent onset.
- There are no absolute recommendations regarding preferences of pharmacological agents.
- Sodium nitroprusside, labetolol, nitroglycerine and nicardipine are commonly used parenteral antihypertensives

emergency. (The basic principles of managing hypertensive emergency is given in Box 2).

Points to Remember

- ***Congenital heart diseases, acquired heart diseases and toxins affecting heart can present as cardiac emergencies.***
- ***Acute heart failure, dysrhythmias, hypercyanotic spells, hypertensive crisis are important cardiac emergencies.***
- ***Judicious fluid management with vasoactive agents is the mainstay of treatment in acute heart failure.***
- ***Care to treat underlying cause is important in managing dysrhythmias.***
- ***Stepwise management of hypercyanotic spell will be ideal.***
- ***Hypertensive emergencies should be managed with short acting parenteral antihypertensives to bring down the BP gradually with close monitoring.***

References

1. Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. Canadian J Cardiol 2013; 29(12):1535-1552.
2. Satou GM, Lacro RV, Chung T, Gaureau K, Jenkins KJ. Heart size on chest X-ray as a predictor of cardiac enlargement by echocardiography in children. Pediatr Cardiol 2001; 22: 218-222.
3. Thakur V, Fouran JC, Merttens L, Jeggi ET. Diagnosis and management of heart failure. Canadian J Cardiol 2013;29:759-767.
4. Escudero C, Carr RP, Sanatani S. The medical management of Pediatric arrhythmias. Current treatment options in cardiovascular medicine 2012; 14: 455-472.
5. Craig NV, Aaron LZ. Emergency Management of Hypercyanotic Crises in Tetralogy of Fallot. Ann Emerg Med 1995; 25(2):256-258.
6. Singh D, Akingbola O, Yosypiv I, El-Dahr S. Emergency management of hypertension in children. Int J Nephrol 2012; 2012:420-447.

CLIPPINGS

Rapid Normalization of Vitamin D Levels: A Meta-Analysis.

Vitamin D deficiency may represent a modifiable risk factor to improve outcome in severe illness. The efficacy of high-dose regimens in rapid normalization of vitamin D levels is uncertain.

A systematic review of pediatric clinical trials administering high-dose vitamin D to evaluate 25-hydroxyvitamin D (25[OH]D) response and characteristics associated with final 25(OH)D levels was done by using Medline, Embase, and the Cochrane Central Register of Controlled Trials. Uncontrolled and controlled trials reporting 25(OH)D levels after high-dose (≥1000 IU) ergocalciferol or cholecalciferol were selected.

We identified 88 eligible full-text articles. Two of 6 studies that administered daily doses approximating the Institute of Medicine's Tolerable Upper Intake Level (1000–4000 IU) to vitamin D–deficient populations achieved group 25(OH)D levels >75 nmol/L within 1 month. Nine of 10 studies evaluating loading therapy (>50 000 IU) achieved group 25(OH)D levels >75 nmol/L. In meta-regression, baseline 25(OH)D, regimen type, dose, age, and time factors were associated with final 25(OH)D levels. Adverse event analysis identified increased hypercalcemia risk with doses >400 000 IU, but no increased hypercalcemia or hypercalciuria with loading doses <400 000 IU (or 10 000 IU/kg). Few studies in adolescents evaluated loading dose regimens >300 000 IU.

Rapid normalization of vitamin D levels is best achieved by using loading therapy that considers disease status, baseline 25(OH)D, and age (or weight). Loading doses >300000 IU should be avoided until trials are conducted to better evaluate risk and benefit.

J. Dayre McNally, Klevis Iliriani, Supichaya Pojsupap, Margaret Sampson, Katie O'Hearn, R Kin, Lauralyn McIntyre, et al. Rapid Normalization of Vitamin D Levels: A Meta-Analysis. Pediatrics doi: 10.1542/peds.2014-1703.

IAP-IJPP CME 2014

POINT OF CARE TESTING IN PEDIATRIC EMERGENCIES

*** Radhika R**

Abstract: *Point of care testing (POCT) is near-patient testing wherein diagnostic tests are performed near the patient. Specimen drawn from the patient is tested immediately and results are displayed instantly on the point of care device. Point of care testing evolved due to the need for a high-quality, efficient, timely laboratory testing at a reasonable cost. In an emergency situation, with an urgent need for rapid diagnosis and therapy, this provides a lot of supplemental information and is invaluable in patient management. POCT is accomplished at the bedside through the use of transportable, portable devices and test kits. Quantity of sample required is very minimal and results are obtained in a very short period of time at or near the location of the patient. Although only a limited number of investigations can be performed using a POCT and errors are prone to occur, newer tests are increasingly becoming available and it has been found to improve patient care.*

Keywords: *Point of care testing, Emergency, Children.*

Laboratory estimation of various parameters in the pediatric emergency can provide a lot of supplemental information and is often invaluable in patient management. In the past, except for bedside glucometry all other tests by and large were performed in a central laboratory. The point of care testing (POCT) evolved due to the need for a high-quality, efficient, timely laboratory testing at a reasonable cost at entry. Diagnostic tests being performed near the patient is called POCT and it involves conducting tests immediately on the specimen drawn from the patient without pre- or post-processing of the specimen. Results that are obtained are displayed at once on the point of care device.

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Usefulness of POCT

POCT is extremely useful in areas with an urgent need for rapid diagnosis and therapy as it reduces the arrival-to-treatment time or therapeutic turnaround time (TAT) which is calculated from the time of the request for a particular testing to the time when therapeutic or patient management action was taken. Often in a sick child this translates to the time before the onset of irreversible cellular damage of vital organs. POCT brings the test to the patient's bedside without delay thereby helping the physician, and the emergency care team receives the results quicker, which expedites clinical management decisions.

POCT devices, sampling and results

POCT is often accomplished through the use of transportable, portable and handheld instruments (e.g., blood glucose meter device) and test kits. Small bench analyzers or fixed equipment can also be used when a handheld device is not available–the goal is to collect the specimen and obtain the results in a very short period of time at or near the location of the patient so that the treatment plan can be adjusted as necessary before the patient leaves emergency services. Many POCT test systems use membrane-based test strips which are very easy to use, requiring only a single drop of whole blood, urine or saliva. Moreover, they can be performed and interpreted by medical personnel within minutes. Either a single test or a cluster of tests can be performed using a POCT using a drop of blood drawn from a vein or finger stick. POCTs are generally performed by doctors or nurses. Laboratory personnel performing a bedside POCT is not advantageous as multiple tests may be required in various areas of a hospital and the feasibility to provide laboratory technicians at various areas in a hospital is laborious. Results from a POCT are displayed on the devices and can be easily interpreted. Data generated by a POCT however cannot be discarded and needs to be transferred and stored at the laboratory information system and the hospital information system for later retrieval.

An ideal POCT

An ideal POCT equipment should be easily portable so that it does not require permanent dedicated space. Testing time should be rapid and at the same time provide

accurate results that are reliable and easy to perform in real time. A cost effective POCT that is available round the clock is ideal.

POCT tests available for pediatric patients

Blood gas, electrolytes, glucose, hematocrit, total bilirubin, complete CO-oximetry and drug assays can be performed from a single sample. Many more tests are available but need to be validated in pediatric patients.

POCT in the emergency setting

Emergency interventions rely on accurate laboratory test results and time cannot be wasted waiting for a retest to confirm a laboratory result. POCT results in the emergency setting must be of the highest quality, without compromise on the accuracy of the test as clinical action will be taken immediately based on the test results.

POCT in the pediatric ER

Some of the following tests have undergone trials and have been validated; however before embarking on use of a POCT all evidences pertaining to its use in an individual situation have to be ascertained. Recommendations for using a POCT in the emergency department exist for complete blood count, prothrombin time, HbA1c and blood ketones. Urine dipstick for urinary tract infection is a POCT which can be used to initiate therapy in suspected UTI while awaiting urine culture result. Rapid dengue test and serum electrolytes are other tests which are under trial and have to be validated for use in the emergency room.

POCT USG in the emergency setting

Bedside USG is a point of care testing in the pediatric emergency setting with a wide range of applications which improve patient care. The cardiovascular status of the patient can be evaluated thereby helping in fluid resuscitation and decisions on ionotropes. It is a very useful non-invasive adjunct as it improves the accuracy of diagnosis in emergencies. In a child who has sustained trauma, bedside USG helps to identify organ injury, bleed in the abdominal or pleural spaces, raised intracranial pressure, pneumothorax, etc. Emergency procedures such as thoracostomy, lumbar puncture and intubation can be guided by a bedside USG.

Advantages of POCT

Due to the rapid data availability, immediate decision making is possible which translates to rapid response to critical values and a decreased turnaround time. Accuracy of diagnosis is improved as the information obtained supplements the clinical diagnosis with less chances of inappropriate treatment. Chances of preanalytical error using a POCT is minimal and there is the added advantage of blood conservation through small blood samples which is an asset for neonatal and pediatric patients especially in the ICU, where the patient's condition often requires multiple blood sampling. The disposal of samples after processing is made easy as it requires just a few drops of the specimen.

Limitations of POCT

All tests performed in a laboratory cannot be performed using a POCT and the list of tests is limited. Errors can occur due to improper handling of the sample or due to the operator especially due to multitasking or performance failures of the instrument The need for repeated instrument calibration and a strict quality control cannot be overemphasized. Data generated has to be recorded, stored and requires resources and is prone to transcriptional errors. Unit cost of testing using a POCT can be quite high in comparison to conventional methods. Unauthorized testing which is bound to occur as the POCT appears to be simple enough to be performed with very little training is a limitation and can influence the outcome of tests performed.

As POCT is performed by medical or paramedical personnel, it adds to workload. Duplication of instruments or methods can occur. POCT does not eliminate the need for a laboratory as specialized tests still have to be performed in a central laboratory and the laboratory information system will store all the data pertaining to POCT performed in a hospital. Policies for functioning of POCT have to be strictly followed and compliance with the policies is mandatory. Problems with licensing are bound to occur, as licensing is a must for using POCT.

General recommendations to be followed for performing POCT

The staff at every hospital and critical care unit must decide which bedside tests or cluster of tests are indicated for their given patient population. To determine this, other factors must be considered, including advantages, disadvantages, accuracy, clinical impact and cost–benefit ratio of the tests. There are some guidelines to be followed before deciding on a POCT. Foremost of all, the clinical need for a POCT should be clearly identified and evaluated and the POCT equipment should be evaluated for its analytical performance. A POCT committee should be established to coordinate and monitor all POCT activities. Standard operating procedures for training, quality assurance control and safety policy must be strictly adhered to. There

are many 'official' and professionally based standards and guidelines which define the manner in which POC testing should be implemented, managed and the performance quality checked and maintained. Clear and comprehensive record keeping and documentation of POCT results is mandatory.

Advances in POCT

Smaller, faster and user-friendly analysers that are more accurate using smaller blood samples eliminating the need for centrifugation are recent advances. Enhancements in automation with fewer analytical steps have been introduced, thereby increasing the speed of functioning. Newer POCT devices have automated calibration, quality control and enhanced features for security which have improved application of POCT in the emergency setting.

New generation POCTs

A portable centrifuge for measurement of hematocrit in low resource settings and a novel technology for 5-part differentiation of leukocytes point-of-care are new developments in this rapidly expanding field.

Future of POCT

POCTs which are under research might add to the present armamentarium in the near future. These include rapid immunochromatography, microbiological tests especially MRSA identification, endocrine testing, sepsis markers, stroke markers and DNA testing.

Conclusion

It must be understood that providers of medical care are under pressure to provide care more quickly and many see POCT as a solution to remove bottlenecks. Faster is often understood to mean better outcomes. Because a POCT test is available it does not mean it is a recommendation for its use. Increasing use of POCT and its validation, can provide evidence-based guidelines for application in clinical settings, more so in the emergency department.

Points to Remember

- ***POCT is an invaluable adjunct to clinical examination and treatment in the pediatric emergency department.***
- ***POCT is a rapidly advancing bedside technology with a wide array of applications.***
- ***Limitations pertain to user expertise, calibration and logistics.***

Bibliography

1. Stellan L, Inger J, Magnus N, Elin J, Tomas J. A Novel Technology for 5-Part Differentiation of Leukocytes Point-of-Care Point of Care: Near-Patient Testing and Technol 2014; 13(2): 27-30.
2. Pai NP, Vadnais C, Denkinger C, Engel N, Pai M. Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries. Published: September 04, 2012 DOI: 10.1371/journal.pmed.1001306.
3. Fiallos MR, Hanhan UA, Orlowski JP. A randomized trial to assess the efficacy of point-of-care testing in decreasing length of stay in a pediatric emergency department. Pediatr Clin N Am 2001;48(3):589-600.
4. Christopher P. Price Point of care testing. Br Med J 2001; 322(7297):1285-1288.

NEWS AND NOTES

GENERAL ARTICLE

SURFACTANT REPLACEMENT THERAPY

*Karthikeyan AG

Abstract: *Surfactant administration has reduced the mortality and morbidity of respiratory distress syndrome in preterm neonates. Despite being a widely available intervention, there is no clear evidence regarding the timing of surfactant administration, indications of surfactant in conditions other than respiratory distress syndrome in preterm neonates and dosing of different surfactant preparations. Newer synthetic surfactants are available which are effective in early human trials. InSurE (intubate, surfactant, extubate) technique is being widely used to administer surfactant for babies managed on continuous positive airway pressure (CPAP). Newer methods of surfactant administration using minimally invasive and non-invasive methods are being studied currently.*

Keywords: *Respiratory distress syndrome, Surfactant, Surfactant administration, InSurE technique.*

Surfactant therapy is one of the most studied and widely used interventions in neonatology. Surfactant therapy has become a standard of care in managing preterm neonates with respiratory distress syndrome (RDS).[1] Meta-analysis of randomized trials have shown that surfactant reduces mortality and incidence of air leak in preterm neonates with RDS.[1] This article discusses the indications, timing and method of administration of surfactant in neonates.

Indications for surfactant therapy

The indications for surfactant therapy with proven efficacy in neonates is respiratory distress syndrome while potential benefits are seen in meconium aspiration syndrome, pulmonary hemorrhage, pneumonia, pulmonary hypoplasia and congenital diaphragmatic hernia.[2]

When to administer surfactant?

There is no clear consensus on the timing of surfactant administration. A practical way of deciding the timing is given below.

Prophylactic: Surfactant is given at less than 30 minutes of life even before babies develop signs of respiratory distress syndrome. Baby has to be resuscitated and stabilized first before surfactant is administered. Prophylactic surfactant administration is generally reserved for babies less than 28 weeks gestation who are very likely to develop RDS. Prophylactic surfactant has been shown to reduce mortality and incidence of air leaks in preterm neonates in multiple randomized trials.[3]

Early rescue: Surfactant is usually administered less than 2 hours of life when signs of RDS develop. This approach is considered more practical in India due to its cost effectiveness and also due to a large number of babies being delivered outside level III neonatal intensive care units.[4] Increasingly, antenatal steroids are given to mothers which reduces the need for surfactant in some preterm babies.[5] Hence, a policy of prophylactic surfactant for all preterm babies below 28 weeks would not be cost effective and currently not recommended in Indian setting.[4]

Late rescue: Surfactant is administered after 2 hours of life when signs of RDS develop. Surfactant can be given to babies with RDS admitted in the first 24–48 hours of life beyond which endogenous production should take over.

Types of surfactant preparations

Surfactant preparations are of two types a) Natural surfactants b) Synthetic surfactants. Natural surfactants are considered more effective than the synthetic type.[6] The effectiveness of surfactant is mainly due to the presence of phospholipids (phosphatidyl glycerol, phosphatidylcholine) and surfactant protein B (SP-B). While phospholipids contribute to the surface lowering properties of surfactant, SP-B is necessary for the spread of surfactant in the alveoli. The currently available synthetic surfactants lack surfactant protein B which makes them less effective than the natural surfactants. Newer synthetic surfactants like lucinactant (contains sinapultide which mimics SP-B) and venticute (contains recombinant form of surfactant protein c) seem promising in early human trials.[7] Table I gives the doses of current commercially available natural surfactants in India. Fig. 1 illustrates the

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different types of natural and synthetic surfactant preparations that are available.

Method of surfactant administration

The equipment required for surfactant administration are: vial of surfactant, nasogastric (NG) tube 5F, sterile scissors/blade, sterile gloves and gown, sterile needle and 5mL syringe

1. The surfactant is to be stored in a refrigerator at 2°-8° C. Surfactant is warmed by keeping in room temperature for about 20 minutes. Do not heat by artificial methods. Do not shake the vial.
2. Prior to starting the procedure: Confirm endotracheal tube (ETT) is in the trachea, position the infant supine, assess the infant for equal air entry, ensure resuscitation equipment is ready.
3. Under aseptic precautions, cut the NG tube to about 1 cm shorter than the length of ETT by using the sterile scissors/blade.
4. Aspirate the required dose of surfactant from the vial. The dose of surfactants currently available in the market is shown in Table I. Add some air into the syringe and connect to the NG tube.
5. Disconnect the baby from ventilator.
6. Instil surfactant in one or two aliquots with neonate on supine position with head in midline and neck in neutral position. There is no need to change the position of head during the procedure.
7. Monitor the baby's oxygen saturation and heart rate during administration of surfactant. There may be a transient desaturation and bradycardia during or just after administration. This will usually resolve post-procedure.
8. After administration of each aliquot, hand ventilate the baby for 30 seconds. Use a flow controlled pressure limited mechanical device like a T-piece resuscitator to monitor the peak inspiratory pressure (PIP) and peak end expiratory pressure.This minimizes inadvertent delivery of high pressures to the neonate.
9. Do not attempt to suction the ETT for about 4 hours after administering the surfactant. A partial ETT block can be managed by increasing the pressures delivered.

Table I . Recommended and licensed doses for natural surfactants

		Dose of surfactant (mg/kg)			
Name of surfactant	**Trade name**	**Initial dose**	**Repeat doses**	**Dose (mL/kg)**	**Dose interval**
Beractant	Survanta	100	100	4	6 hourly
Poractant alfa	Curosurf	200	100	Initial 2.5 Repeat 1.25	6-12 hourly
BLES*	Neosurf	135	135	5	6 hourly

*Bovine Lipid Extract Surfactant

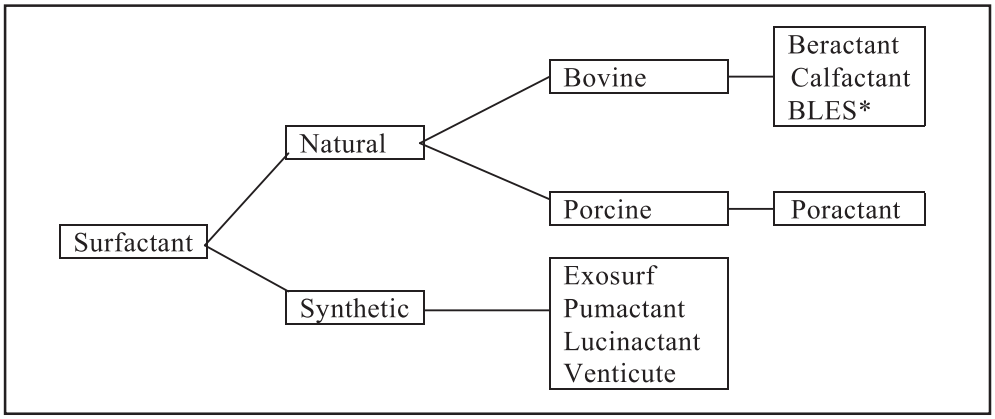

Fig.1. Different types of surfactant preparations available.

10. After completing the surfactant administration, reconnect the baby to the ventilator. Do not walk away from the baby! As the lung compliance improves with surfactant, there will be a need to decrease the FiO_2 and PIP delivered. Monitor the baby closely for the next hour including blood gas and change ventilation accordingly.

Repeat doses of surfactant

Obtain a CXR if not obtained earlier. Assess the need for repeat dose of surfactant 6-8 hours after the first dose by assessing oxygen requirement and chest X-ray findings. Second dose of surfactant is indicated if there are signs of RDS in CXR and/or oxygen requirement exceeds 30%-40%.[1] A third dose of surfactant may be tried if the baby continues to show signs of RDS in CXR and oxygen requirement exceeds 30-40%. There is no evidence to show that more than three doses of surfactant is useful in clinical practice.[8]

Administering surfactant for babies on continuous positive airway pressure (CPAP)

A large number of randomized trials have shown that many babies who have RDS need not be mechanically ventilated. A number of these babies can be managed with CPAP alone. Early rescue therapy with surfactant is indicated in these babies with respiratory distress when their oxygen requirement is greater than 30%-40%.

Use InSurE (intubate, give surfactant, extubate to CPAP within 3-5 minutes) approach to administer surfactant in babies who are likely to need CPAP or already managed on CPAP. InSurE approach has been shown to reduce the need for mechanical ventilation, reduce the duration of respiratory support, possible decrease in bronchopulmonary dysplasia and airleak syndromes.[9] Intubate the baby and administer surfactant as described above in steps 1 to 10. Hand ventilate the baby for about 1 to 2 minutes. Assess baby's respiratory effort and if good, remove ETT and commence on CPAP.

Emerging methods of administering surfactant

Newer methods of administering surfactant are under trial. They include minimally invasive surfactant therapy and non invasive surfactant therapy.

Minimally invasive surfactant therapy (MIST)

a) Surfactant is administered to posterior pharynx immediately after delivery of head before the first breath. This has not been evaluated in well-designed clinical trials although the approach seems to be feasible, effective and safe in small observational studies.[10]

b) Laryngeal mask airway (LMA): shown to be effective in administering surfactant in preterm babies larger than 1200 grams although further trials are required to evaluate the effectiveness of this technique in various gestational age groups.[11]

c) Nasogastric (NG) feeding catheter: A feeding tube can be placed endotracheally using Magill's forceps under direct laryngoscopy. The feeding tube is left for a few minutes until surfactant is administered. CPAP can be continued during this procedure.[12]

d) Vascular catheter: An alternative to NG feeding catheter is using a stiff vascular catheter (Angiocath 16G) to intubate the trachea directly using a laryngoscope without the need for using Magill's forceps (Hobart method).[13] CPAP can be continued during the procedure. Further controlled trials are being conducted to evaluate this procedure further (OPTIMIST- A and –B trials). This method seems more practical and less traumatic to babies than using the other methods mentioned above. Complications include coughing episodes and transient bradycardia post-procedure. Transient bradycardia post procedure is managed with positive pressure breaths using a mask.

Non-invasive surfactant therapy (NIST)

Aerosolized surfactant administration is difficult because of challenges in delivering the surfactant to the distal alveoli of the lungs. Aerosolized lucinactant (synthetic surfactant) delivery has been shown to be safe and feasible in neonates.[14] Currently a large trial (Cure Neb Trial) is underway looking at efficacy and safety of aerosolized porcine surfactant in the first hour of life in preterm neonates.

Side effects of surfactant therapy

(a) Transient hypoxia and bradycardia at the time of surfactant administration due to transient ETT block with surfactant. This can be minimised by administering the surfactant slowly, increasing the FiO2 or the peak pressures delivered.

(b) Rapid improvement in ventilation leading to pneumothorax or pulmonary interstitial emphysema.

(c) Alterations in cerebral blood flow resulting in intraventricular hemorrhage.

(d) Pulmonary hemorrhage which is probably more common following natural surfactant administration than in synthetic surfactants.

Surfactant is not effective in a neonate after more than 48 hours of life and in congenital cyanotic heart disease without RDS. Side effects of surfactant administration are not contraindications but subsequent doses should be administered by an experienced clinician. Lethal congenital malformation is a contraindication to surfactant administration.

Points to Remember

- ***Surfactant should be administered as an early rescue therapy in babies with RDS.***
- ***The ideal way of administering surfactant is by the endotracheal tube in ventilated babies and using the InSurE approach in babies managed on CPAP.***
- ***Emerging methods of surfactant administration include the minimally invasive and non-invasive surfactant therapy.***
- ***Repeat dose(s) of surfactant can be given as per predefined criteria at a dosing interval of 6-12 hours.***
- ***Rapid improvement in lung compliance occurs after surfactant is given necessitating decrease in FiO2 and peak inspiratory pressures.***

References

1. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2009, Issue 1. Art No.:CD000141. DOI:10.1002/14651858.CD000141.pub2.
2. Lacaze-Masmonteil. Expanded uses of surfactant therapy in newborn. Clin Perinatol 2007; 34:179-189.
3. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD000510. DOI: 10.1002/14651858.CD000510.pub2.
4. Surfactant replacement therapy.Clinical Practice Guidelines 2010, National Neonatology Forum, India.
5. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2006, Issue 3. Art No.: CD004454. DOI: 10.1002/14651858. CD004454.pub2.
6. Soll R, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD000144. DOI: 10.1002/14651858. CD000144.
7. Gautham K. Suresh, Roger F. Soll. Current surfactant use in premature infants. Clinics in Perinatology 2001;28(3):671-694.
8. Zola EM, Gunkel JH, Chan RK, Lim MO, Knox I, Feldman MPHBH, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. J Pediatr. 1993; 122: 453-59
9. Lopez E, Gascoin G, Flamant C, Merhi M, Tourneux P, Baud O. Exogenous surfactant therapy in 2013. What is next? Who, when and how should we treat newborn infants in the future? BMC Pediatrics 2013, 13:165.
10. Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. Cochrane Database Syst Rev 2011, 3, CD008311.
11. Trevisanuto D, Grazzina N, Ferrarese P, Micaglio M, Verghese C, Zanardo V. Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. Biol Neonate 2005, 87:217-220.
12. Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet 2011, 378:1627-1634.
13. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed 2011, 96:F243-248.
14. Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv 2010, 23:303-309.

DRUG PROFILE

EVIDENCE-BASED USE OF SYSTEMIC STEROIDS IN PEDIATRIC PRACTICE

**** Jeeson C Unni***

Abstract: *Systemic corticosteroids have become essential in various inflammatory and autoimmune disorders. This article deals with the individual conditions under various specialities where these drugs are indicated with their dose, route, frequency, duration, and so on in detail, with justification.*

Keywords: *Systemic corticosteroids, Indications, Children.*

Corticosteroids were discovered in the 1940s. These drugs have since become essential in the treatment of various inflammatory and autoimmune ailments in medicine. Physiological doses are used in replacement therapy as in adrenal insufficiency. Higher doses may be administered in the treatment of various other disorders. Specialties that often require systemic steroid therapy include respiratory and allergic disorders, hemato-oncology, nephrology, dermatology, rheumatology, endocrinology, gastroenterology, neurology, organ transplantation and ophthalmology. An attempt is made to review studies on its use in these specialties.

The commonly used systemic steroids and their anti-inflammatory doses, relative potencies and duration of action are shown in Tables I, II and III.

Respiratory system

Moderate to severe asthma: Systemic corticosteroid therapy is recommended for children with moderate to severe acute asthma or if there is incomplete response to β_2-agonists.[1,2] Initial administration of 1 mg/kg prednisolone (maximum, 50 mg) orally is suggested and this may be repeated every 12-24 hours, depending on response. While a course of three days is generally sufficient, in more severe cases a prolonged course (with tapering) may occasionally be indicated. The need for recurrent systemic corticosteroid therapy for acute episodes is an indication for reassessment of the child's interval therapy.

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Croup: Parenterally or orally administered dexamethasone (0.15-0.6mg/kg) is the mainstay of treatment with addition of nebulized epinephrine only in cases of moderate-to-severe croup.[2,3] Evidence suggests that corticosteroids may decrease the intensity of viral croup symptoms irrespective of their severity on presentation.

Rare indications for systemic steroids in respiratory illnesses in children include hypersensitivity pneumonitis,[4] interstitial lung disease[5] and chronic eosinophilic pneumonia.[6] Evidence does not support use of systemic steroids in nasal allergy or nasal polyps.[7]

Allergic disorders

Acute and recurrent urticaria: There may be a role for a short course of systemic steroids in addition to allergen detection,prevention and anti-H1-histamines.[8] They are not recommended for treatment of anaphylaxis[9] and there is insufficient evidence for its use in food and drug allergies.

Dermatology

The mainstay of therapy of pemphigus in pediatric patients is oral corticosteroids.[10] Methylprednisolone 1-2mg/kg/day may be given initially.

Systemic steroids are not recommended for atopic dermatitis[11] and it was not even mentioned as an option in the recent 'Guidelines of care for the management of atopic dermatitis' of the American Academy of Dermatology.[12] The role of systemic steroids in Stevens Johnson syndrome and toxic epidermal necrolysis is controversial. However, they may be used in children with early active disease or when erythema reappears during the recovery phase.[13,14]

Hematology

I**diopathic thrombocytopenic purpura:** For children requiring treatment, a single dose of IVIg (0.8 to 1 g/kg) or a short course of corticosteroids may be used as first-line treatment, after a bone marrow aspiration has been performed. High-dose dexamethasone may be considered for children or adolescents with ITP who have significant

ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids. High-dose dexamethasone may also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy.[15]

Acute lymphoblastic leukemia: Prednisolone or dexamethasone, along with vincristine, with or without L-asparginase, and an anthracycline (daunorubicin or doxorubicin), cytarbine, cyclophosphamide, methotrexate, 6-mercaptopurine or etoposide is recommended for inducing remission.[16]

Table I. Systemic steroids based on route of administration

Oral route	Prednisone, prednisolone, dexamethasone, betamethasone
Parenteral	Hydrocortisone, dexamethasone, methyl prednisolone (MPS), triamcinolone

Table II. Anti-inflammatory effect of systemic steroids

Prednisolone 1mg	Betamethasone 150mcg
	Deflazacort 1-2mcg
	Dexamethasone 150mcg
	Hydrocortisone 4mg
	MPS 800mcg
	Triamcinolone 800mcg

Source : British National Formulary for children 2014-2015, page 376.

Table III. Relative potencies and duration of action

Compound	**Relative glucocorticoid activity**	**Relative mineralocorticoid activity**	**Duration of effect[a] (Alcohol form)**
Cortisol	1	1	S
Prednisone	5	0.8	I
Prednisolone	5	0.8	I
Methylprednisolone	5	0.5	I
Fludrocortisone	10	125	I
Triamcinolone	5	0	I
Triamcinolone acetonide	30	0	I
Dexamethasone	25	0	L
Betamethasone	25	0	L

[a]S=short (~12hr), I=intermediate (~24hr), L=long (~48-72hr)

Rheumatology

Systemic-onset juvenile idiopathic arthritis: Glucocorticoids have been the mainstay of treatment for many years in systemic-onset juvenile idiopathic arthritis (SOJIA), causing important side effects and some difficulties in the management of this disease. Nowadays, biologic agents, such as the interleukin-1 inhibitors, anakinra and the more recent canakinumab, or the interleukin-6 inhibitor tocilizumab, have improved the prognosis of this debilitating disease. Glucocorticoids still have to be considered at the onset of disease when a non-steroidal anti-inflammatory drug therapy fails or when there are life-threatening complications such as severe anemia or pericarditis, or macrophage activation syndrome.[17]

SLE: Mild SLE may be treated with NSAIDs, analgesics, low dose steroid, topical therapies and antimalarials for symptom relief. Major organ involvement: Neuropsychiatric SLE, lupus nephritis, hemolytic anemia, severe thrombocytopenia and interstitial lung disease require high doses of steroids and immunosuppressives like azathioprine (AZA), cyclophosphamide (CYC) or mycophenolate mofetil (MMF). The usual regime is pulsed methylprednisolone 30mg/kg/day IV for 3 days, followed by high-dose 0.6-1 mg/kg daily oral prednisolone or equivalent.[18]

CNS involvement in pediatric rheumatic diseases: High dose steroid and cyclophosphamide (oral or intravenous) are first choice drugs in the treatment; plasmapheresis, IVIG, thalidomide and intrathecal treatment may be valuable in treatment-resistant and serious cases.[19]

Juvenile dermatomyositis/polymyositis: Initial treatment recommendation is prednisolone orally or pulsed methylprednisolone.[20,21]

Nephrology

Nephrotic syndrome: The initial drug of choice for steroid sensitive minimal change disease is oral prednisolone.[22,23] Treat for at least three months; an increase in benefit being demonstrated with regards to less relapses if treatment is extended up to seven months. Children with frequent relapses and those who develop steroid dependency/ resistance would require alternative treatment.

Endocrinology

Adrenocortical insufficiency[24] : Hydrocortisone IV 100 mg/m^2 followed by 100 mg/m^2/day 6 hourly in divided doses - 10 mg for infants, 25 mg for toddlers, 50 mg for older children and 100 mg for adolescents; every 6 hours for 24 hours. High doses of hydrocortisone given during emergencies will temporarily provide mineralocorticoid activity to a lesser extent. Following stabilization, the dose of hydrocortisone can be tapered:

Day 2 - Decrease hydrocortisone to 75mg/m^2/day; decrease fluids

Day 3 - Decrease hydrocortisone to 50mg/m^2/day; add fludrocortisone

Day 4 - Decrease hydrocortisone to 25mg/m^2/day

At discharge: Hydrocortisone (15 mg/m^2/day) and fludrocortisone (0.1 mg/day) are given.

Long term glucocorticoid replacement therapy for autoimmune addison's disease:

Oral hydrocortisone tablets: 10 mg/m^2/24 hours in 2 doses, preferably with the early morning dose being higher than the evening dose, mimicking the physiological circadian rhythm of cortisol secretion. Other glucocorticoid preparations like prednisolone and dexamethasone should be avoided in children due to disproportionate growth suppressing effects. Chronic overdose will result in obesity, hypertension, osteoporosis and short stature.

Dosage adjustments need to be made for stress in these children (Table IV). For minor illness, two-fold daily doses are given for 2-3 days. For moderate illness, three-fold daily doses are given for a few days with gradual reversal to regular dose. If higher dose is given for 72 hours or less, tapering to regular dose is not required. For major surgery, high intravenous doses will be required as for acute adrenal insufficiency (Table IV). In absolute and relative adrenal insufficiency in children with systemic inflammatory response syndrome and vasopressor-dependent shock steroids produce a significant reduction in vasopressor duration and dosage.[25]

Congenital adrenal hyperplasia[26] (21-Hydroxylase Deficiency): Hydrocortisone treatment serves as glucocorticoid replacement. It also suppresses excess androgen production and its effects such as acceleration of growth, skeletal maturation and virilization. The usual dose of hydrocortisone is 10 - 20 mg/m^2/24 hours given in 2-3 divided doses. Two to 3 fold the daily doses are required in stress situations such as infection or surgery. For neonates presenting with shock an IV bolus of hydrocortisone 25 mg followed by 15 mg IM every 6 hours may be started. The dose is then tapered over the next few days by monitoring serum electrolytes; later changed to oral dose of 2.5 mg twice a day (25mg/m^2/day). Studies suggest that the deleterious

Table IV. Glucocorticoid dose in stress situations

Stress	Example	Glucocorticoid dose
Mild	Low grade fever, viral infection	No change
Moderate	Vomiting, diarrhea	Increase to three times
Severe	Pneumonia, meningitis	Increase to five times
Very severe	Surgery, shock	100 mg/m^2/day

effects on pubertal growth can be reduced, in both sexes, if hydrocortisone dose does not exceed 17 mg/m^2.[27]

Gastroenterology

Ulcerative colitis: Oral 5-ASAs and systemic steroids are the mainstay of treatment in patients with new-onset ulcerative colitis.[28] However, steroids should not be continued for long periods.[29]

Crohn's diasease: Corticosteroids are effective for induction of remission in Crohn's disease, particularly when used for more than 15 weeks.[30]

Further studies are required to determine a) optimal duration of therapy and schedules for tapering medication b) phenotypes that produce better results with steroid therapy and c) preferred route of administration.

Autoimmune hepatitis: Early diagnosis and treatment with steroids and azathioprine could achieve full remission and halt progression of liver disease.[31]

Central nervous system

Chronic inflammatory demyelinating polyneuropathy (CIDP): Prognosis for children is far better than for adults with 80-100% functional recovery with standard treatments using steroids, IVIg and/or plasmapheresis.[32]

Corticosteroids were previously used to treat pediatric Guillain-Barre Syndrome, but current data indicate they provide little benefit.

Infantile spasms: Adrenocorticotropic hormone (ACTH) and corticosteroids are the usual first-line treatment options for infantile spasms. On the basis of the available evidence, the efficacy of high-dose corticosteroids is similar to low-dose ACTH and inferior to high-dose ACTH, the current standard treatment.[33]

Bacterial meningitis: The initial enthusiasm to start dexamathasone before or at the time of initiating antibiotics for bacterial meningitis to reduce complications is being re-evaluated. A review from developed countries suggests that it may prevent hearing loss in Hib meningitis. However, it needs a re-look in pneumococcal meningitis; it may not be as effective in children whose treatment is delayed and it may be unfavourable in cephalosporin-resistant pneumococci meningitis. Further, there was no evidence to recommend the use of corticosteroids in meningococcal meningitis.[34]

Tuberculous meningitis: Corticosteroids should be routinely used in HIV-negative patients with tuberculous meningitis to reduce death and disabling residual neurological deficit amongst survivors.[35,36] However, there is not enough evidence to support or refute a similar conclusion for those who are HIV positive. A study of the appropriate dose of steroid for tuberculous meningitis found that 4mg/kg/day prednisolone for 1 week followed by 2mg/kg/day for 3 weeks was associated with fewer tuberculomas and infarcts but a higher incidence of hearing loss. A prolonged period of high dose steroids increased the risk of optic atrophy and hydrocephalus. A dose of 2mg/kg/day was associated with lower risk of mental retardation and spasticity.[37]

Severe sepsis and septic shock

The role of corticosteroid in treating severe sepsis and septic shock remains controversial.[38]

It seems to improve systemic BP but contradictory reports on its effect on mortality and possible adverse effects of high dose corticosteroids has made it difficult to recommend as evidence based guideline for its use in this condition at this point of time.

Conclusion

Systemic steroids have their role in management of pediatric illnesses but their use must be evidence-based.

Points to Remember

- *Role of systemic steroids have emerged as vital in various inflammatory and autoimmune disorders.*
- *They are indicated as curative as well as replacement therapy.*
- *Recommendation corticosteroids to be judicious is based on current evidence available.*

References

1. Van Asperen PP, Mellis CM, Sly PD. Thoracic Society of Australia and New Zealand. The role of corticosteroids in the management of childhood asthma. Med J Aust 2002; 176(4):168-173.
2. Kilic A, Unuvar E, Sutçu M, Suleyman A, Tamay Z, Yildiz I, et al. Acute obstructive respiratory tract diseases in a pediatric emergency unit: Evidence-based evaluation. Pediatr Emerg Care 2012; 28(12): 1321-1327.
3. Petrocheilou A, Tanou K, Kalampouka E, Malakasioti G, Giannios C, Kaditis AG. Viral croup: diagnosis and a treatment algorithm. Pediatr Pulmonol 2014; 49(5): 421-429.
4. Griese M, Haug M, Hartl D, Teusch V, Glöckner-Pagel J, Brasch F. National EAA Study Group. Hypersensitivity pneumonitis: lessons for diagnosis and treatment of a rare entity in children. Orphanet J Rare Dis 2013; 8: 121.
5. Paul K, Klettke U, Moldenhauer J, Müller KM, Kleinau I, Magdorf K, et al. Increasing dose of methylprednisolone pulse therapy treats desquamative interstitial pneumonia in a child. Eur Respir J 1999; 14(6): 1429-1432.
6. Tassinari D, Di Silverio Carulli C, Visciotti F, Petrucci R. Chronic eosinophilic pneumonia: A paediatric case. BMJ Case Rep. 2013; 2013. Epub 2013 Apr 25. pii: bcr 2013008888. doi: 10.1136/bcr-2013-008888.
7. Mygind N, Dahl R, Nielsen LP, Hilberg O, Bjerke T. Effect of corticosteroids on nasal blockage in rhinitis measured by objective methods. Allergy 1997; 52(40 Suppl): 39-44.
8. Novembre E, Cianferoni A, Mori F, Barni S, Calogero C, Bernardini R, et al. Urticaria and urticaria related skin condition/disease in children. Eur Ann Allergy Clin Immunol 2008; 40(1): 5-13.
9. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69(8): 1026-1045. doi: 10.1111/all.12437. Epub 2014 Jun 9.
10. Gürcan H, Mabrouk D, Razzaque Ahmed A. Management of pemphigus in pediatric patients. Minerva Pediatr 2011; 63(4): 279-291.
11. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol 2014; 133(2): 429-438. doi: 10.1016/j.jaci.2013.07.049. Epub 2013 Oct 24.
12. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014; 71(2): 327-349. Epub 2014 May 9.
13. Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: a retrospective study of causative drugs and clinical outcome. Indian J Dermatol Venereol Leprol 2008; 74(3): 238-240.
14. Singalavanija S, Limpongsanurak W. Stevens-Johnson syndrome in Thai children: a 29-year study. J Med Assoc Thai 2011; 94 Suppl 3:S85-90.
15. Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117(16): 4190-4207.
16. Acute lymphoblastic leukemia. In: IAP Drug Formulary. Eds Jeeson C Unni, Menon PSN, Nair MKC, Bansal CP Eds. Publication of IAP. Edn 4. Pixel Studio. 2015;pp151-157.
17. Vannucci G, Cantarini L, Giani T, Marrani E, Moretti D, Pagnini I, et al. Glucocorticoids in the management of systemic juvenile idiopathic arthritis. Paediatr Drugs 2013; 15(5): 343-349.
18. Systemic lupus erythematosus. In: IAP Drug Formulary. Eds Jeeson C Unni, Menon PSN, Nair MKC, Bansal CP. Publication of IAP. Edition 4. Pixel Studio. 2015;pp203-205.
19. Duzova A, Bakkaloglu A. Central nervous system involvement in pediatric rheumatic diseases: current concepts in treatment. Curr Pharm Des 2008; 14(13): 1295-1301.
20. Kishi T, Miyamae T, Hara R, Nakajima S, Imagawa T, Mori M, et al. Clinical analysis of 50 children with juvenile dermatomyositis. Mod Rheumatol 2013; 23(2): 311-317. doi: 10.1007/s10165-012-0647-4. Epub 2012 Apr 22.
21. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008; 371(9631): 2201-2212.
22. Van Husen M, Kemper MJ. New therapies in steroid-sensitive and steroid-resistant idiopathic nephrotic syndrome. Pediatr Nephrol 2011; 26(6): 881-892. doi: 10.1007/s00467-010-1717-5.
23. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2004; (2): CD001533.
24. Adrenocortical insufficiency. In: IAP Drug Formulary. Eds Jeeson C Unni, Menon PSN, Nair MKC, Bansal CP, 4th Edn, Publication of IAP. Pixel Studio. 2015;pp126-127.

25. Hebbar KB, Stockwell JA, Leong T, Fortenberry JD. Incidence of adrenal insufficiency and impact of corticosteroid supplementation in critically ill children with systemic inflammatory syndrome and vasopressor-dependent shock. Crit Care Med 2011; 39(5): 1145-1150.
26. Congenital Adrenal Hyperplasia. In: IAP Drug Formulary. eds Jeeson C Unni, Menon PSN, Nair MKC, Bansal CP, 4th edn. Publication of IAP. Edition 4. Pixel Studio 2015; p127.
27. Bonfig W, Pozza SB, Schmidt H, Pagel P, Knorr D, Schwarz HP. Hydrocortisone dosing during puberty in patients with classical congenital adrenal hyperplasia: an evidence-based recommendation. J Clin Endocrinol Metab 2009; 94(10): 3882-3888. doi: 10.1210/jc.2009-0942.
28. Richter JM, Kushkuley S, Barrett JA, Oster G. Treatment of new-onset ulcerative colitis and ulcerative proctitis: a retrospective study. Aliment Pharmacol Ther 2012; 36(3): 248-256.
29. Tomomasa T, Kobayashi A, Ushijima K, Uchida K, Kagimoto S, Shimizu T, et al. Working Group of the Japanese Society for Pediatric Gastroenterology, Guidelines for treatment of ulcerative colitis in children. Hepatology and Nutrition.Pediatr Int 2004; 46(4): 494-496.
30. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008; (2): CD006792.
31. Vergani D, Mieli-Vergani G. Pharmacological management of autoimmune hepatitis. Expert Opin Pharmacother 2011; 12(4): 607-613.
32. Vanasse M, Rossignol E, Hadad E. Chronic inflammatory demyelinating polyneuropathy. Handb Clin Neurol 2013; 112: 1163-1169. doi: 10.1016/B978-0-444-52910-7.00037-4.
33. Arya R, Shinnar S, Glauser TA. Corticosteroids for the treatment of infantile spasms: a systematic review. J Child Neurol 2012; 27(10): 1284-1288.
34. Esposito S, Semino M, Picciolli I, Principi N. Should corticosteroids be used in bacterial meningitis in children? Eur J Paediatr Neurol 2013; 17(1): 24-28.
35. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23; (1):CD002244.
36. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009; 59(3):167-187.
37. Shah I, Meshram L. High dose versus low dose steroids in children with tuberculous meningitis. J Clin Neurosci 2014; 21(5): 761-764.
38. Patel GP, Balk RA. Systemic steroids in severe sepsis and septic shock. Am J Respir Crit Care Med 2012; 185(2): 133-139. doi: 10.1164/rccm.201011-1897CI.

CLIPPINGS

Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants.

Lactoferrin, a normal component of human colostrum and milk, can enhance host defense and may be effective in the prevention of sepsis and necrotizing enterocolitis (NEC) in preterm neonates.

Objective was to assess the safety and effectiveness of oral lactoferrin in the prevention of sepsis and NEC in preterm neonates.

Randomized controlled trials (RCTs) evaluating oral lactoferrin at any dose or duration to prevent sepsis or NEC in preterm neonates were included.

Oral lactoferrin with or without probiotics decreased fungal sepsis but not chronic lung disease or length of hospital stay (from one study, low-quality evidence). No adverse effects were reported. Long-term neurological outcomes or periventricular leukomalacia was not evaluated.

Evidence of moderate to low quality suggests that oral lactoferrin prophylaxis with or without probiotics decreases late-onset sepsis and NEC stage II or greater in preterm infants without adverse effects. Completion of ongoing trials will provide evidence from more than 6000 preterm neonates and may enhance the quality of the evidence. Clarifications regarding optimum dosing regimens, type of lactoferrin (human or bovine), and long-term outcomes are still needed.

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DERMATOLOGY

CHILDHOOD ERYTHRODERMA – DIAGNOSTIC OUTLINE

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Abstract: *Childhood erythroderma, is a challenge to both pediatricians and dermatologists as they pose difficulty in diagnosis due to overlapping clinical features and life threatening nature. Although the initial management is similar in all cases of erythroderma, specific management is necessary to achieve remission. This review outlines the approach to diagnosis of a child presenting with erythroderma.*

Keywords: *Child, Erythroderma, Dermatological emergency.*

The term erythroderma, first described by Hebra in 1868, is used to describe a reaction pattern characterized by scaling and erythema involving more than 90% of the body surface area. It is largely a secondary process, and necessitates intensive management due to the accompanying metabolic and systemic complications, more so in pediatric age group. Hence, early diagnosis and differential diagnosis by both pediatricians and dermatologists is imperative.

Clinical features

Apart from diffuse erythema and scaling, the most common presenting complaints are burning and itching, besides the symptoms specific to the cause.

Erythroderma is a dermatological emergency because of accompanying systemic complications which include fever, tachycardia, pedal edema, septicemia, hypoalbuminemia, hyperpyrexia and metabolic complications that could be potentially life threatening.

Etiology

In a study conducted by Sarkar, et al in a tertiary centre in Delhi, the causes identified were infections (40%), ichthyosiform erythroderma (25%), atopic dermatitis (15%), infantile seborrheic dermatitis (10%) and unidentified (10%).[1] In another study of childhood erythroderma, drugs (29%) followed equally by genodermatoses, psoriasis and staphylococcal scalded skin syndrome (SSSS) were found to be the etiological factors.

Causes of erythroderma in children have been listed in Table I. The differential diagnosis and treatment in brief of the common dermatological conditions leading to erythroderma have been presented here. General care in erythroderma has been dealt towards the end of article.

Inflammatory

Seborrhoeic dermatitis: Infantile seborrhoeic dermatitis typically begins with inflammatory, greasy yellowish, scaling on the scalp (cradle cap) with involvement of the skin folds of the intertriginous areas, most commonly neck, groin and axilla. It can manifest as erythroderma rarely.

Treatment: Low potency corticosteroids such as hydrocortisone or desonide can be used if there is clinical evidence of inflammation. Topical ketoconazole / other antifungals like selenium sulphide and zinc pyrithrone in lotion/ shampoo twice weekly for 4 weeks with a contact period of about 15-20 minutes is recommended followed by review.

Atopic dermatitis: Atopic dermatitis in pediatric age group characteristically involves the cheek, flexural creases (may involve extensors in children less than 2 years) with sparing of napkin area. Family history of atopy and vesicular and exudative primary lesions, itchy after 3 months of age point in favour of atopic dermatitis.

Treatment: Lukewarm soaking bath with neutral pH soap/ syndets, wet dressings or moisturizers, low potent steroids, calcineurin inhibitors like tacrolimus/ pimecrolimus with systemic antihistamines followed by review.

Psoriasis: Erythrodermic psoriasis is rare in pediatric age group. Congenital erythrodermic psoriasis carries a bad prognosis.[2] Positive family history and absence of ectropion differentiates it from non-bullous ichthyosiform

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Table I. Causes of erythroderma in children

Inflammatory	Infections	Infestation	Immuno deficiency	Metabolic diseases	Ichthyosis	Miscellaneous
Atopic dermatitis Seborrheic dermatitis Psoriasis Pityriasis rubra pilaris Cutaneous mastocytosis Miliaria rubra	Staphylococcal skin scalded syndrome Toxic shock syndrome Scarlet fever Cutaneous candidiasis Herpes simplex Syphilis	Scabies	Leiner syndrome Omenn syndrome Hyper IgE syndrome DiGeorge syndrome Graft vs host disease Wiskott Aldrich syndrome Hypo - gammaglobulinemia	Multiple carboxylase deficiency Essential fatty acid deficiency Acrodermatitis enteropathica Maple syrup urine disease	Bullous ichthyosiform erythroderma Non – bullous ichthyosiform erythroderma Lamellar ichthyosis Harlequin ichthyosis Netherton syndrome KID syndrome Sjogren Larsson syndrome Conradi Hunerman syndrome Tay syndrome Chanari Dorfman syndrome	Drugs Sarcoidosis Kawasaki disease Pemphigus foliaceous

erythroderma (NBIE). Scalp, palms and soles may show diffuse scaling and characteristically involves diaper region due to Koebner's phenomenon.

Treatment: Narrow band ultraviolet light therapy, topical emollients, topical corticosteroids (daily or weekend therapy), systemic immunosuppressants like cyclosporine, methotrexate, systemic retinoids for recalcitrant cases under proper monitoring.

Pityriasis rubra pilaris (PRP): PRP is characterized by erythematous and scaly plaques with follicular hyperkeratosis and interspersed islands of normal skin (napes claires) with yellowish palmoplantar keratoderma (PRP sandal).

Treatment: Topical emollients, keratolytics (salicylic acid, urea), topical steroids, systemic retinoids (acitretin/ isotretinoin), high dose vitamin A.

Cutaneous mastocytosis: Doughy and thickened skin with or without orange papules can be the presenting feature of neonatal mastocytosis and blisters may develop within 2-3 years of life. Diffuse forms present as erythroderma. Systemic symptoms like diarrhea, vomiting, wheezing, pruritus and rise of temperature accompany the condition. Darier's sign (appearance of urticarial wheal on minor pressure/rubbing) is positive.

Treatment: It tends to remit spontaneously. Only symptomatic treatment with antihistamines needs to be

given. Non-responders can be given a short course of systemic steroids.

Infections

Staphylococcal scalded skin syndrome: Erythrodermic SSSS is seen in children below 5 years of age and is very acute in onset (within 1-2 days). Macular rash is followed by erythroderma which is followed by a more definite and specific phase of blister formation, erosions, crusting and exfoliation. There is increased skin tenderness and presence of constitutional symptoms like fever, irritability in all stages. Nikolsky sign is positive, which can be elicited by applying a tangential pressure to the intact skin around the blister that leads to peeling of superficial epidermis. There is often periorificial accentuation.

Treatment: First and second generation cephalosporin, clindamycin or vancomycin (MRSA).

Scarlet fever: Caused by group A beta-hemolytic streptococci,it presents as transient erythroderma. Skin eruption follows pharyngitis by 1-2 days and appears in caudal distribution involving extremities but sparing palms and soles and accompanied by constitutional symptoms. Accentuation along the skin folds, perioral pallor and linear petechial eruption differentiate it from TSS.

Treatment: The drug of choice for treatment of scarlet fever is penicillin V. Although amoxicillin or ampicillin is frequently used, they have no microbiologic advantage over penicillin. In penicillin-allergic patients, erythromycin or another macrolide (i.e., clarithromycin or azithromycin) is indicated.

Toxic shock syndrome: TSS as erythroderma presents like scarlet fever with rash, followed by desquamation within 1-2 weeks accompanied by constitutional symptoms like fever, hypotension and involvement of 3 or more systems.

Treatment: Combination of antibiotics (preferably including clindamycin), IVIg in non-responding cases.

Cutaneous candidiasis: It could be either intrauterine or post-natal infection. Preterm infants are prone to develop disseminated cutaneous candidiasis and can show diffuse burn-like erythema. Discrete skin lesions like macules, papules and satellite pustules become confluent to give rise to erythroderma. Nappy area and oral cavity are spared in congenital forms. Pustules over palms and soles are present. KOH mount is used for diagnosis.

Treatment: Topical antifungals like azoles for 4 weeks followed by review, systemic antifungals if associated with organ system involvement.

Infestation

Norwegian scabies: Norwegian scabies is a highly contagious variant of scabies and presents with crusting which may or may not be itchy. Crusted scabies may involve the entire body, including the head and the scalp and may progress to cause erythroderma.

Treatment: 5% permethrin cream two applications, one week apart (>2 months age), 2.5% precipitated sulphur, Ivermectin (>5years, 200 μg/kg per dose given orally for 2 doses, 2 weeks apart).

Immunodeficiency

Immunodeficiency syndromes like Omenn syndrome, Leiner's disease, Job's syndrome, Graft Vs host disease, Digeorge syndrome can progress to erythroderma. Usually they are associated with recurrent infections, failure to thrive, mostly chronic diarrhoea with other specific cutaneous, systemic symptoms and laboratory anomalies.

Treatment is essentially symptomatic with antibiotics, systemic cyclosporine for eosinophilia (in Omenn's), and intravenous immunoglobulin. Only definitive treatment is bone marrow transplant (thymus transplant for DiGeorge syndrome).[4]

Metabolic diseases

Multiple carboxylase deficiency: Holocarboxylase deficiency presents within 1 week of age with sharply marginated dermatitis over scalp, eyebrows and eyelashes and characterized by ketoacidosis, dehydration and coma, whereas bioitinidase deficiency manifests later with hypotonia, hearing loss, ataxia and seizures. Immediate treatment needs to be initiated with oral biotin 5-10 mg/day (upto 40mg).

Essential fatty acid deficiency: Rare condition presenting with erythroderma with dry, thickened, erythematous desquamating plaque with periorificial accentuation associated with fat malabsorption and correction of deficiency reverses this condition.

Maple syrup urine disease: Scaling eruption presents in the periorificial region, followed by acrodermatitis enteropathica like distribution and subsequently erythroderma within days of initiating diet. Child feeds poorly with vomiting, lethargy and seizures.

Treatment: Withdrawal of branched chain amino acids with intravenous glucose administration (5-8 mg/kg/min).

Acrodermatitis enteropathica: Acrodermatitis

enteropathica due to impaired intestinal absorption of zinc in which the initial lesions are vesiculobullous, crusted or psoriasiform usually in the perioral and perianal areas accompanied by diarrhea, failure to thrive, alopecia, recurrent infection, photophobia and irritability.

Treatment: Zinc supplementation 5-10 mg/kg/day.

Ichthyosis

Syndromic and non-syndromic ichthyosis is associated with erythroderma. The most common non-syndromic ichthyosis is lamellar ichthyosis which presents with fish-like scales and harlequin ichthyosis presenting with armor-like scales with ectropion and deformities.

Amongst syndromic ichthyosis, bullous characterized by appearance of superficial blisters and non-bullous ichthyosiform erythroderma (presents as colloidon baby with ectropion, fissure and contracture) are most common associations. Other miscellaneous syndromes include Netherton syndrome (ichthyosis, bamboo hair and atopy), KID syndrome (keratitis, ichthyosis and sensorineural deafness with palmoplatar keratoderma and follicular hyperkeratosis) and Sjogren Larsson syndrome with neurological and skeletal defects.

Treatment: Topical emollient, topical keratolytics (Salicylic acid, urea, alpha hydroxyl acid), systemic Retinoids (acitretin and isotretinoin) under proper monitoring.

Drugs

Erythroderma is most commonly associated with ceftriaxone and vancomycin, but can also be seen with penicillin, boric acid poisoning, antiepileptic (phenobarbitone, phenytoin), sulphonamide, antitubercular drugs, aminoglycoside and ampicillin.[3] Historically, 'red baby' was used to describe erythroderma caused by vancomycin, but is now used as an umbrella term to involve erythrodermic neonate. Histopathologically it is characterized by vascular changes and nectrotic keratinocytes.

Treatment: Immediate withdrawal of offending drug, short course systemic corticosteroids to tide over the crisis.

Diagnosis of erythroderma

(a) History and clinical examination

(b) Laboratory investigation

Investigations include baseline complete blood count, liver function tests and renal function tests. Specific tests like Gram stain, KOH scraping, patch test, urine routine, genetic testing (SPINK5 mutation in Netherton syndrome), assays for zinc, alkaline phosphatase, essential fatty acids, amino acids, and biotinidase for diagnosis of specific causes of childhood erythroderma are also done.

Histopathology: More often than not, serial histopathology can be diagnostic on the cause of erythroderma. Simultaneous biopsies need to be taken from minimum 3 sites.[4] All erythroderma on histopathological examination may show non specific features of dermatitis. It is particularly useful in cases of immunodeficiency, where lymphocytic infiltration is seen and differentiating between ichthyotic etiologies.

Treatment

Childhood erythroderma is a dermatological emergency, the child should be hospitalized and provided optimum temperature and appropriate fluid and electrolyte infusion along with correction of metabolic, hematologic and biochemical imbalance.[5] The supplementation of protein and calorie in neonates with erythroderma must meet the demands of hypermetabolic state and requirements of normal growth and development.[6] Topical application of bland emollients such as petrolatum or white soft paraffin helps in maintenance of barrier function of stratum corneum. Tepid water bath or 2-3 hourly wet dressing maybe soothing. Systemic corticosteroids can be used to tide the acute crises and systemic antibiotics could be administered to prevent secondary bacterial infections, especially S. aureus. Further treatment should be undertaken according to underlying etiology.

Conclusion

Childhood erythroderma with its varying etiologies, can be life threatening. Immediate inpatient care and timely diagnosis with the aid of clinical, laboratory and histopathological aids can improve the prognosis to a great extent by provision of specific treatment.

Points to Remember

- ***Childhood erythroderma is a dermatological emergency.***
- ***Immediate inpatient care is necessary.***
- ***Although the initial management of all erythroderma cases are similar, etiology needs to be identified to administer specific treatment.***
- ***Clinical, laboratory and histopathological correlation can usually identify the cause of erythroderma.***

References

1. Sarkar R, Garg VK. Erythroderma in children. Indian J Dermatol Venereol Leprol 2010; 76:341-347.
2. Sarkar R, Sharma RC, Koranne RV, Sardana K. Erythroderma in children: A clinico-etiological study. J Dermatol 1999; 26:507-511.
3. Sehgal VN, Srivastava G. Erythroderma / generalized exfoliative dermatitis in pediatric practice: An overview. Int J Dermatol 2006; 45:831-839.
4. Sarkar R. Neonatal and infantile erythroderma: "The Red Baby". Indian J Dermatol 2006; 51:178-182.
5. Dhar S, Banerjee R, Malakar R. Neonatal erythroderma: Diagnostic and therapeutic challenges. Indian J Dermatol 2012; 57:475-478.
6. Ragunatha S, Inamadar AC. Neonatal dermatological emergencies. Indian J Dermatol Venereol Leprol 2010; 76:328-340.

CLIPPINGS

Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: A systematic review and prospective multicentre external validation study

Background: Several clinical prediction rules for diagnosing group A streptococcal infection in children with pharyngitis are available. This study done in France was aimed to compare the diagnostic accuracy of rules-based selective testing strategies in a prospective cohort of children with pharyngitis.

Methods: Clinical prediction rules were identified through a systematic search of MEDLINE and Embase (1975–2014), which were then validated in a prospective cohort involving French children who presented with pharyngitis during 1-year period (2010–2011). Group A streptococcus infection was diagnosed by using two throat swabs: One obtained for a rapid antigen detection test (StreptAtest, Dectrapharm) and the other for culture (reference standard). Rules-based selective testing strategies were validated as follows: Low risk of group A streptococcal infection, no further testing or antibiotic therapy needed; intermediate risk of infection, rapid antigen detection for all patients and antibiotic therapy for those with a positive test result; and high risk of infection, empiric antibiotic treatment.

Results: Eight clinical prediction rules were identified, 6 of which could be prospectively validated . Sensitivity and specificity of rules-based selective testing strategies ranged from 66% (95% confidence interval [CI] 61–72) to 94% (95% CI 92–97) and from 40% (95% CI 35–45) to 88% (95% CI 85–91), respectively. Use of rapid antigen detection testing following the clinical prediction rule ranged from 24% (95% CI 21–27) to 86% (95% CI 84–89). None of the rules-based selective testing strategies achieved the diagnostic accuracy target aimed in the study (sensitivity and specificity > 85%).

Interpretation: Rules-based selective testing strategies did not show sufficient diagnostic accuracy in this study population. The relevance of clinical prediction rules for determining which children with pharyngitis should undergo a rapid antigen detection test remains questionable.

Jérémie F. Cohen, Robert Cohen,Corinne Levy, Franck Thollot, Mohamed Benani,Philippe Bidet, et al. Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: a systematic review and prospective multicentre external validation study First published December 8, 2014,doi:10.1503/cmaj.140772 at www.cmaj.ca/lookup/doi/10.1503/cmaj.140155.

SURGERY

MANAGEMENT OF VESICO URETERIC REFLUX

* ***Ramesh Babu S***

Abstract: *Guidelines for the management of vesico ureteric reflux have been undergoing constant revision based on published studies. The interventions aim to reduce the frequency of urinary infections and prevent renal scarring. Recently, the long term benefits of various practice guidelines have been questioned. This article looks at the current guidelines for the management of vesico ureteric reflux in terms of antimicrobial prophylaxis and surgery.*

The suggested approach to antenatally diagnosed hydronephrosis is also discussed.

Keywords: *Vesico ureteric reflux, Antibiotic prophylaxis, Surgery, STING, voiding dysfunction.*

The current management of vesico ureteric reflux (VUR) has been based on the premise that prevention of urinary tract infections (UTI) or correction of reflux can lead to a reduction in the incidence of pyelonephritis and renal scarring. The potential for reflux to resolve spontaneously with time in many children has led to the recommendation that initial intervention be limited to medical management, with surgical treatments considered in those children who develop infections despite prophylaxis or are unable to comply with prophylaxis regimens.[1]

Randomized controlled trials (RCT) that compared anti-reflux surgery with antimicrobial prophylaxis showed no significant differences in the rates of recurrent urinary tract infection and renal scarring.[2-5] Further studies showed that antimicrobial prophylaxis was also not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.[6,7]

With these findings it became uncertain whether the identification of VUR itself confers any clinically important benefit in children.[8,9] However recent studies have shown that antibiotic prophylaxis could reduce febrile UTIs in children with VUR.[10,11]

The advent of endoscopic treatment, the sub- ureteric transurethral injection (STING), introduced a less invasive alternative but also raised the question about whether we are treating children who were previously observed without intervention. With so many controversial and conflicting reports, the management of VUR has undergone a paradigm shift, back and forth.

Antenatal hydronephrosis and VUR

Up to 30% of children with antenatal hydronephrosis (ANH) have been found to have VUR. There is no clear evidence to support or to avoid postnatal imaging for VUR. The degree of dilation does not correlate with the grade of VUR and a normal postnatal USG does not exclude reflux.[12,13] The revised guidelines by Indian pediatric nephrology group[14] recommended a voiding cystourethrogram (VCUG) in patients with unilateral or bilateral hydronephrosis with renal pelvic antero posterior diameter (APD)>10mm, grade 3-4 of Society for Urology (SFU) or ureteric dilatation.

They recommended that VCUG be performed early, within 24-72 hours of life, in patients with suspected lower urinary tract obstruction while in other cases, where it is aimed to rule out VUR, the procedure should be done at 4-6 weeks of age. With literature questioning the benefit of identifying VUR[8,9] and any intervention even if identified, we probably should reduce the number of invasive VCUGs in newborns and infants and probably restrict them to those where there is persistent hydroureteronephrosis on repeated ultra sonograms.

Evaluation for VUR following UTI

The most common cause of UTI in children is vesicoureteric reflux, and it accounts for about 40% of cases. However there is no consensus on when to evaluate children following an episode of UTI. The revised UTI guidelines by American Academy of Pediatrics (AAP 1999), state that febrile infants with UTI should undergo ultrasonography although VCUG should not be performed routinely after the first febrile UTI.[15] NICE guidelines

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recommended full evaluation with VCUG and Dimarcapto succinic acid scan (DMSA) only in the presence of atypical or recurrent UTI in infants less than 6 months of age. The revised guidelines by Indian Pediatric Nephrology Group[16] recommended a stepwise approach to evaluate children after the first UTI. They recommended full evaluation with USG, VCUG and DMSA in all infants, while a DMSA first approach (followed by VCUG if positive) in the 1-5 year age group. In India, VCUG first approach is still popular and this is probably due to non-availability of DMSA in some centres. Although evidence of pyelonephritis is found in 50% of early DMSA scans only 15% are eventually found to have scars (Fig. 1) on late DMSA scans following a febrile UTI.

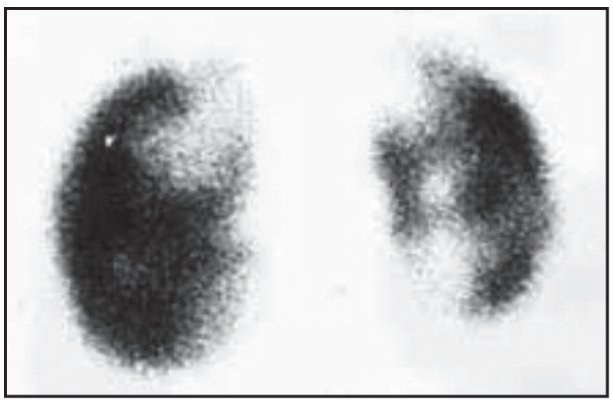

Fig. 1. DMSA scan showing renal scar.

The DMSA first 'top-down' approach pioneered by Hansson[17] helps a lot of children avoid VCUG, an invasive test with higher radiation exposure and should be the recommended approach.

Antibiotic prophylaxis in VUR

Although conventional medical management of VUR involved antibiotic prophylaxis, Williams felt the evidence on use of antibiotics to prevent recurrent symptomatic UTI was weak.[18] Conway concluded that antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.[7] However, the Swedish reflux trial showed that antibiotic prophylaxis was more effective than observation in preventing febrile UTIs, and that there was a strong correlation between febrile UTIs and the risk of new renal scarring.[10] More recently, the RIVUR trial showed that antimicrobial prophylaxis in children with vesicoureteral reflux was associated with a reduction in the risk for recurrent UTI.[11] The American Urological Association (AUA) guidelines[19] recommended antibiotic prophylaxis for children at high risk of UTI and further scarring (patients less than 1 year with history of febrile UTI or grade 3-5 VUR). Although a majority in India still favors starting antibiotic prophylaxis for all grades of VUR, using antibiotic prophylaxis for children with dilating reflux only (grade 3-5) is probably an evidence-based approach.

UTI, VUR and voiding dysfunction

Approximately 20%-30% of patients with vesicoureteric reflux have underlying dysfunctional voiding.[20,21] Upadhyay advised the use of dysfunctional voiding symptom score to predict resolution of VUR in children with voiding dysfunction.[21] Glazier felt urodynamics should be considered for children with UTI and voiding dysfunction,[22] while Soygür did not recommend routine urodynamics, as it did not generally change the management and treatment.[23] A detailed history with particular attention to symptoms of dysfunctional elimination syndrome is of paramount importance in successful medical management of these children. Urodynamics probably can be reserved for those with a history of voiding dysfunction or bladder wall thickening on USG.

Management of VUR

The International Reflux Society grading system (Fig. 2) is used as a general guide in decisions and grade 1-2 reflux is generally managed conservatively even without antibiotic prophylaxis. The AUA guidelines[19] recommended continuous antibiotic prophylaxis for grade 3-5 VUR as initial management, while ureteral reimplantation or STING in patients with a febrile breakthrough urinary tract infection. A curative intervention was favored in higher VUR grades and in

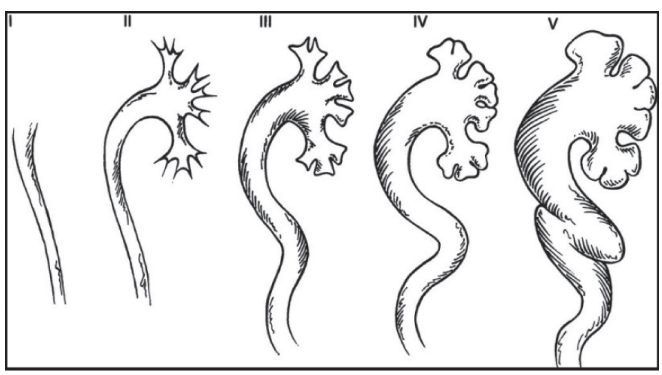

Fig. 2. International reflux society grading of VUR. Spontaneous resolution rate reduces from 80% (in grade 1-2) to 0% (in grade 5) as the VUR grade progresses.

the presence of scarring. The current indications for intervention favored by pediatric surgeons in India are as follows: breakthrough UTIs, worsening of scars, bilateral grade 4-5 VUR (Fig. 3), poor compliance with medical management and persistent reflux beyond 4 years of age. For those with unilateral VUR on VCUG, intervention for the contralateral side is preferable when: (a) there is scarring present on opposite side on DMSA, (b) cystoscopy shows dilated ureteral orifice (UO) on opposite side, (c) there is evidence of reflex on previous VCUG or (d) when USG shows dilatation on opposite side.

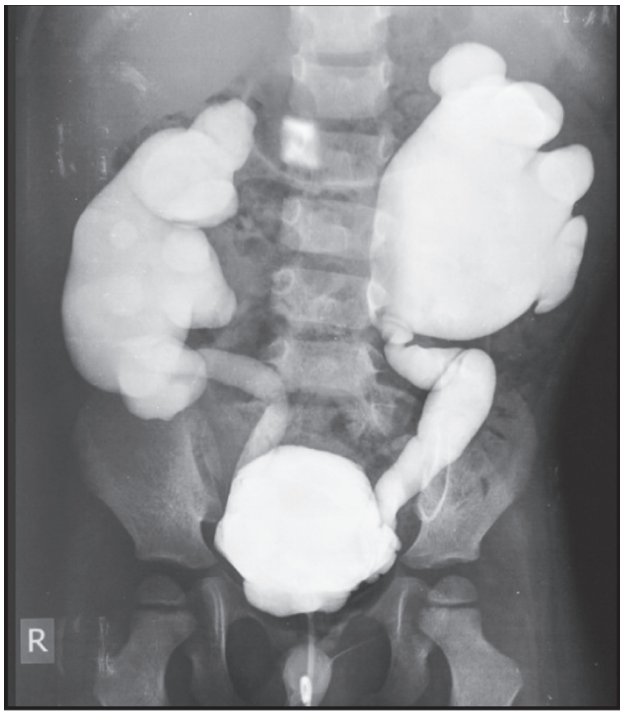

Fig. 3. Grade 5 VUR

Endoscopic injection (STING) is useful in grade 3 VUR (Fig. 4), with a success rate of above 70%. In infants with VUR and recurrent breakthrough UTI, a reimplantation is generally avoided as the bladder is not large enough for an adequate tunnel. Preferred temporizing options in this setting include continuous medical management (with rotation of prophylactic agents to reduce UTIs), circumcision (in male infants), STING procedure, or a ureterostomy / vesicostomy as a last resort.

Follow up evaluation after endoscopic or open intervention should include ultrasonogram plus a study to look for obstruction/reflux, 3-6 months following the procedure. A nuclear renogram with an indirect

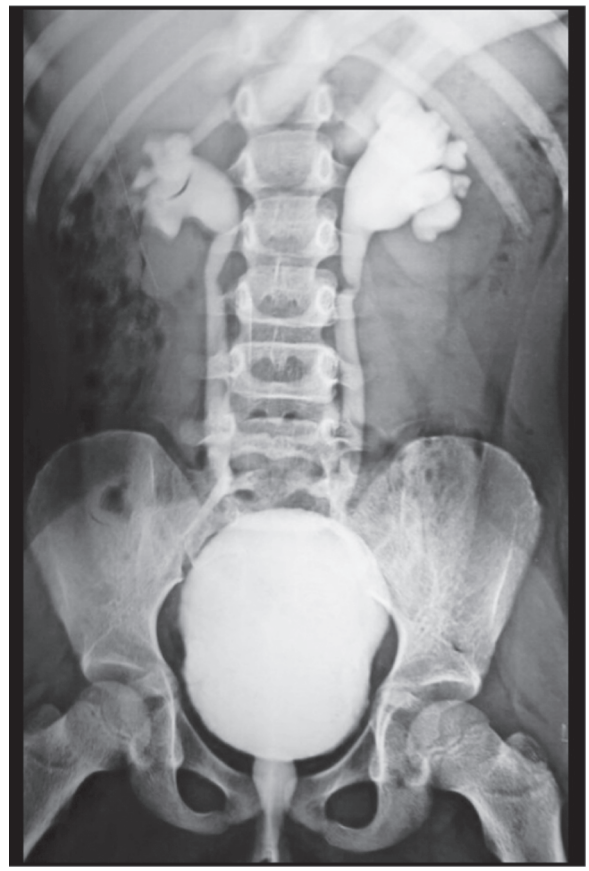

Fig. 4. Grade 3 VUR

cystogram (voiding phase to look for VUR) works as an ideal single study in this regard.

Summary

Although several earlier RCTs and meta analyses have questioned the usefulness of surgical or medical management in reducing the renal scars,[2-9] later studies have reported that the incidence of acute pyelonephritis could be reduced by treatment of VUR.[10,11] Since acute pyelonephritis is an established cause of renal scarring,[24] reducing its incidence by prompt treatment of VUR should be worthwhile.

With the introduction of a new, minimally invasive procedure for reflux therapy the number of such procedures for reflux has increased, while open surgery rates have remained stable reported a US data base study in 2006.[25] However a later study concluded that the endoscopic management is on the decline while open surgery rates for VUR were the same.[26]

There is no clear indication in the literature on the ideal imaging to screen for VUR. A survey of members

of AAP urology section indicated wide variation in this regard.[27] With increasing initiatives in minimizing radiation exposure[28] and use of radio nuclide cystogram (Fig. 5) instead of VCUG, it is essential to apply these concepts when evaluating children on medical management for VUR resolution, as well as for sibling screening.

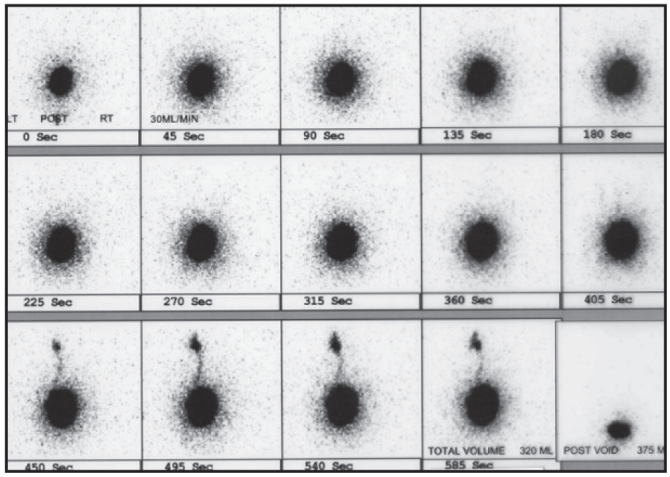

Fig. 5. Radionuclide cystogram

According to a study by Ogan, parents of children with vesicoureteric reflux preferred antibiotic prophylaxis as initial treatment.[29] However, when daily antibiotics and yearly VCUG was advised for 3 to 4 years, most parents chose definitive correction. Dave[30] felt that the physician should provide a balanced approach with pros and cons scenario for each intervention and try to modulate treatment based on the available literature and personal experience. Formulating institutional guidelines and revising them regularly based on current literature will help a lot in arriving at management decisions for a condition as controversial as VUR.

Points to Remember

- ***Primary goals in the diagnosis of UTI/VUR include prevention of recurrent UTI and acquired renal damage.***
- ***Approximately 15% of children develop renal scarring after first febrile UTI.***
- ***VUR is diagnosed in approximately 33% of children imaged after first febrile UTI.***
- ***The DMSA first 'top-down' approach helps a lot of children avoid VCUG, an invasive test with higher radiation.***
- ***Although the role of antibiotic prophylaxis is questionable in preventing renal scars, it is preferred for children with dilating reflux (grade 3-5).***
- ***Treatment of associated dysfunctional elimination syndrome is an essential part of successful medical management.***
- ***Endoscopic treatment (STING) is useful in grade 3 VUR.***
- ***Indications for surgical intervention include: breakthrough UTIs, worsening of scars, bilateral grade 4-5 VUR, and persistent reflux beyond 4 years of age.***
- ***Although endoscopic/surgical interventions have not been proven effective in reducing renal scarring, their benefit in reducing recurrent pyelonephritis has been established.***

References

1. Mathews R, Carpenter M, Chesney R, Hoberman A, Keren R, Mattoo T, et al. Controversies in the management of vesicoureteral reflux: the rationale for the RIVUR study. J Pediatr Urol 2009; 5(5):336-341.
2. International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. Pediatrics 1981; 67:392-400.
3. Birmingham Reflux Study Group. Pro¬spective trial of operative versus non-operative treatment of severe vesicoureteral reflux in children: five years' observation. Br Med J (Clin Res Ed) 1987; 295:237-241.
4. Smellie JM, Barratt TM, Chantler C, Gordon I, Prescod NP, Ransley PG, et al. Medical versus surgical treatment in children with severe bilateral vesico¬ureteric reflux and bilateral nephropathy: a randomised trial. Lancet 2001; 357:1329-1333.
5. Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). J Urol 1992;148: 1667-1673.
6. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128(3):595-610.
7. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections

in children: risk factors and association with prophylactic antimicrobials. JAMA. 2007;298(2):179-186.

8. Hodson EM, Wheeler DM, Vimalchandra D, Smith GH, Craig JC. Interventions for primary vesicoureteral reflux. Cochrane Database Syst Rev 2007; (3):CD001532.

9. Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesicoureteral reflux: a meta-analysis of randomised controlled trials. Arch Dis Child 2003; (8):688-694.

10. Holmdahl G, Brandström P, Läckgren G, Sillén U, Stokland E, Jodal U, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol 2010; 184(1): 280-285.

11. RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, Kropp BP, Skoog SJ, Nelson CP, Moxey-Mims M, Chesney RW, Carpenter MA Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014; 370(25):2367-2376.

12. Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010; 6(3): 212-231.

13. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics 2006; 118(2):586-593.

14. Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, et al. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol 2013; 23(2):83-97.

15. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imag-ing studies after a first febrile urinary tract infection in young children. N Engl J Med 2003; 348:195-202.

16. Indian Society of Pediatric Nephrology, Vijayakumar M, Kanitkar M, Nammalwar BR, Bagga A. Revised statement on management of urinary tract infections Indian Pediatr 2011; 48(9):709-717.

17. Hansson S, Dhamey M, Sigstrom O, Sixt R, Stokland E, Wennerström M, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol 2004; 172:1071.

18. Williams GJ, Wei L, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev 2006; (3):CD001534.

19. Peters CA, Skoog SJ, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol 2010; 184(3):1134-1144.

20. Homayoon K, Chen JJ, Cummings JM, Steinhardt GF. Voiding dysfunction: outcome in infants with congenital vesicoureteral reflux. Urology 2005; 66(5):1091-1094.

21. Upadhyay J, Bolduc S, Bagli DJ, McLorie GA, Khoury AE, Farhat W. Use of the dysfunctional voiding symptom score to predict resolution of vesicoureteral reflux in children with voiding dysfunction. J Urol 2003; 169(5):1842-1846.

22. Glazier DB, Murphy DP, Fleisher MH, Cummings KB, Barone JG. Evaluation of the utility of video-urodynamics in children with urinary tract infection and voiding dysfunction. Br J Urol 1997; 80(5):806-808.

23. Soygür T, Arikan N, Tokatli Z, Karaboga R. The role of video-urodynamic studies in managing non-neurogenic voiding dysfunction in children. BJU Int 2004; 93(6): 841-843.

24. Orellana P, Baquedano P, Rangarajan V, Zhao JH, Eng ND, Fettich J, et al. Relationship between acute pyelonephritis, renal scarring, and vesicoureteral reflux. Results of a coordinated research project. Pediatr Nephrol 2004 Oct; 19(10):1122-1126.

25. Lendvay TS, Sorensen M, Cowan CA, Joyner BD, Mitchell MM, Grady RW. The evolution of vesicoureteral reflux management in the era of dextranomer/ hyaluronic acid copolymer: a pediatric health information system database study. J Urol 2006; 176(4 Pt 2):1864-1867.

26. Herbst KW, Corbett ST, Lendvay TS, Caldamone AA. Recent trends in the surgical management of primary vesicoureteral reflux in the era of dextranomer/hyaluronic acid. J Urol 2014; 191(5 Suppl):1628-1633.

27. Herndon CD, Ferrer FA, McKenna PH. Survey results on medical and surgical followup of patients with vesicoureteral reflux from American Association of Pediatrics, Section on Urology members. J Urol 2001; 165(2):559-563.

28. Lee RS, Diamond DA, Chow JS. Applying the ALARA concept to the evaluation of vesicoureteral reflux. Pediatr Radiol 2006; 36 Suppl 2:185-191.

29. Ogan K, Pohl HG, Carlson D, Belman AB, Rushton HG. Parental preferences in the management of vesicoureteral reflux. J Urol 2001; 166(1):240-243.

30. Dave S, Khoury AE. The current evidence based medical management of vesicoureteral reflux: The Sickkids protocol. Indian J Urol 2007; 23(4): 403-413.

RADIOLOGY

DENSE BONES

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****Natarajan B**
****Jeya Rajiah**
****Kasivisalakshi KP**
*****Narendran N**

Increased density of bones is an X-ray finding that the eye easily appreciates. There are very few dysplasias characterized by generalized increase in density where bones appear chalky white. There is no differentiation between the whiter cortex and the less dense medullary part that is seen normally. Osteopetrosis and pyknodysostosis are the two congenital disorders of increased density where dense bones exist without much alteration in their shape. Another extremely rare condition is dysosteosclerosis.

Osteopetrosis is a common entity clinically characterized by anemia and hepatosplenomegaly. There are subgroups - autosomal recessive precocious type (early onset), dominantly inherited late onset type and the type associated with carbonic anhydrase deficiency. Fig.1 is the X-ray of a patient with osteopetrosis. The bones are dense. All bones of the axial and appendicular skeleton are involved.There is no differentiation between the cortex and medulla. This is because of defective osteoclasts or osteoclastic function that fail to resorb bone in the course of its development from the calcified cartilage stage to the tubular stage.

The incomplete resorption leaves an insufficient medullary cavity that is responsible for the anemia and leucopenia that these children eventually succumb to. However, resorption can be intermittent, though inadequate. This is the reason for the bone within bone appearance that you can see in the ilium in Fig.1 and in the hand x-ray in Fig.2.

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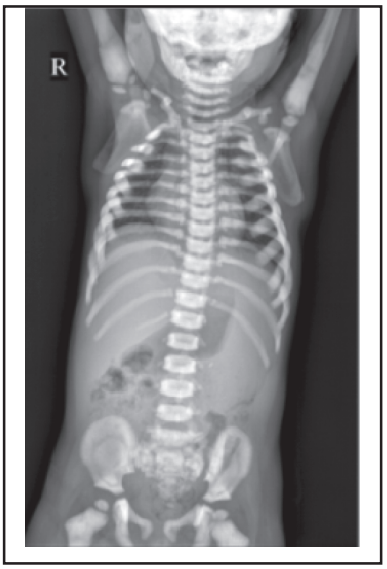

Fig.1.Osteopetrosis

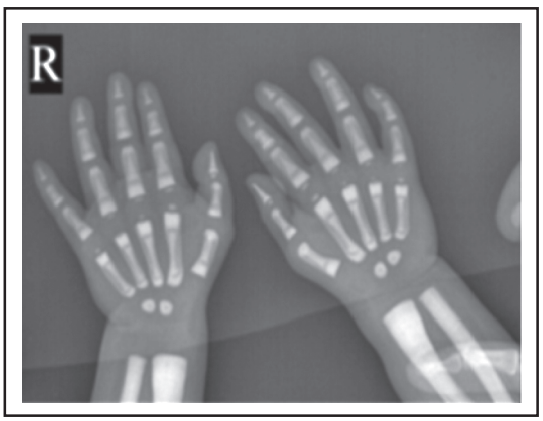

Fig.2. Osteopetrosis - bone within bone

Although dense, these bones are likely to fracture easily. The thickening also involves the base of the skull resulting in compressive neuropathies.Pyknodysostosis is also characterized by dense bones. Clinically it presents in infancy. Children are short and have stubby fingers due to acro-osteolysis which is evident in Fig.3.

Acro-osteolysis is a differentiating factor which is not seen in the other dense bones disorders. The acromial ends of the clavicles show some resorption. The skull is large and the fontanelles are open.

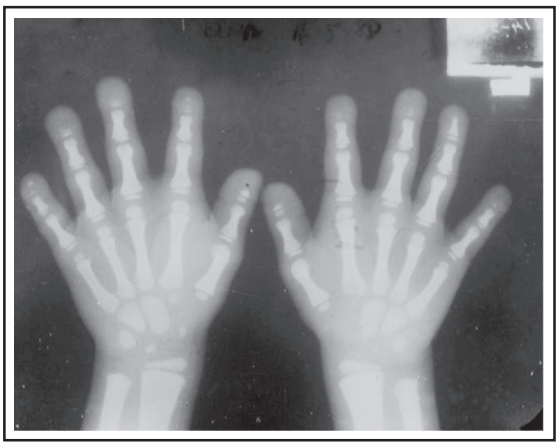

Fig.3. Pyknodysostosis acro-osteolysis

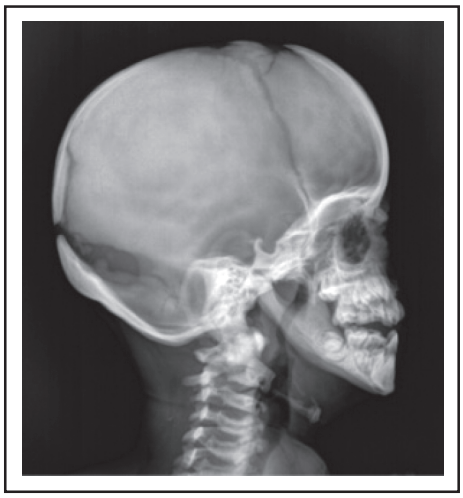

Fig.4. Pycnodysostosis - Obtuse mandibular angle

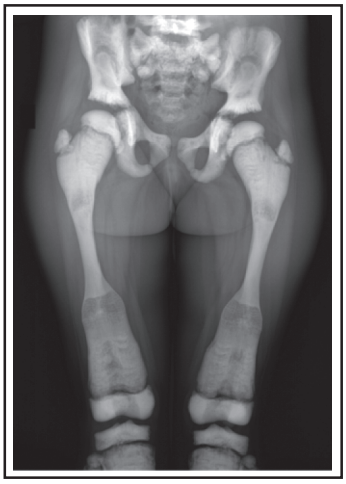

Fig.5.Dysosteosclerosis - dense bones with metaphyseal widening.

The other feature which differentiates this from osteopetrosis is the increase in angle of the mandible that becomes obtuse as in Fig.4. The medullary cavity of the bones are preserved so that they do not suffer from the hematopoietic effects of osteopetrosis.

Dysosteosclerosis is a rare, recessively inherited disorder with dense bones. The metaphyseal ends of bones are widened (Fig.5).

The skull is large and its base is sclerotic causing blindness and deafness. Teeth are hypoplastic and permanent teeth fail to erupt (Fig.6).

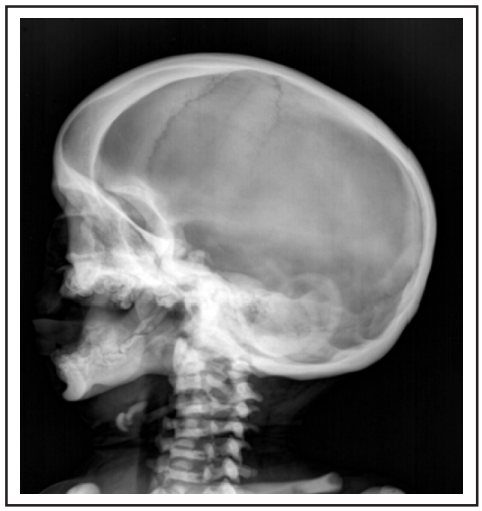

Fig.6. Dysosteosclerosis - Absent and hypoplastic teeth

Flattening of the vertebrae (Fig.7) is also peculiar to dysosteosclerosis. These features are not seen in the other disorders considered above.

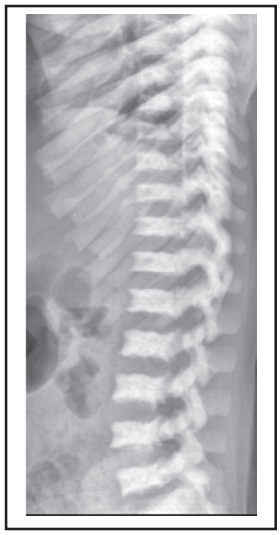

Fig.7. Dysosteosclerosis - Flattened vertebrae

CASE REPORT

GBS VARIANT: FACIAL DIPLEGIA WITH PRESERVED REFLEXES

*Ramakrishnan TCR
**Srinivasan C

Abstract : *Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy presenting in its classical form as a rapidly evolving symmetric and ascending motor paralysis with hypotonia and areflexia. Facial diplegia is an extremely rare condition which can occur with systemic conditions such as Lyme disease, sarcoid and Guillain-Barre Syndrome (GBS) to name a few. Here we present a child who presented to us with facial diplegia, a very rare presentation of GBS.*

Keywords: GBS, Areflexia, Facial diplegia.

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy presenting as a rapidly evolving symmetric and ascending motor paralysis with hypotonia and areflexia accompanied by albuminocytological dissociation. Facial diplegia is an extremely rare variant of GBS where the involvement of the opposite side occurs within 30 days of the onset.[1,2] It most often occurs as a special finding of a symptom complex in systemic disease. It occurs in about 0.3% to 2.0% of facial palsy cases.[3] A study of Adour, et al, found only three bilateral cases in a consecutive series of 1000 patients with Bell's palsy.[4] The relative lack of awareness of this condition often leads to dilemma and delay in diagnosis. Here we report a child who presented to us with only facial diplegia which is a rare variant of GBS.

Case Report

A 12-years-old girl presented to us with left-sided Bell's palsy. She had ear pain followed by deviated mouth, loss of taste and difficulty in closing left eye. She was diagnosed to have left-sided Bell's palsy and treated with steroids and supportive therapy. After 30 days she developed right-sided facial weakness with complete loss of taste. She had upper respiratory tract infection, one week before the onset of illness. She had bilateral facial weakness (right > left) and inability to close both eyes (right > left) (Fig.1). On examination, there was no sensory loss or motor weakness. All deep tendon reflexes were brisk with normal plantars. Her nerve conduction study (NCS) showed features suggestive of demyelinating form of GBS (Table I & II) and cerebrospinal fluid examination showed albuminocytological dissociation. Her urea, creatinine, electrolytes, calcium, phosphorous, magnesium, ANA, ESR, angiotension converting enzyme (ACE) level assay and vasculitic work up were all negative and stool culture for polio virus was negative. MRI brain was normal. As she was ambulant, she was treated with vitamin supplements and physiotherapy. Over a period of eight weeks, she improved well.

Discussion

GBS is a group of syndromes with several distinctive subtypes classified on a pathological basis into demyelinating and axonal forms.[5] The variants most commonly associated with hyperreflexia are acute motor axonal neuropathy [AMAN (33%-48% of cases)], acute motor conduction block neuropathy and acute facial diplegia with preserved reflexes.[6,7]

NCS shows features suggestive of predominantly demyelinating pathology involving motor nerves with root involvement and normal sensory nerve action potential of both upper and lower limb nerves.

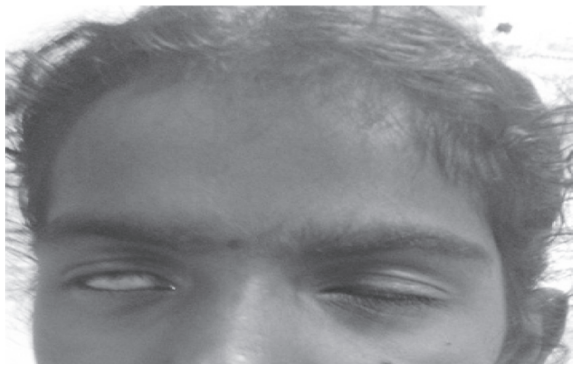

Fig.1. Inability to close both eyes (right > left)

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Table I. Motor nerve conduction study (MNCS)

Nerves Name	Latency	Amplitude	CB	NCV	Remarks
Rt.Median	Normal	Normal		Normal	
LT.Median	Normal	Normal	CB+	Normal	Demyelination
Rt.Ulnar	Normal	Normal	CB+	Normal	Demyelination
Lt.Ulnar	Normal	Normal		Normal	Normal
Rt.Peroneal	Normal	Normal	CB+	Normal	
Lt.Peroneal	Normal	Normal	CB+	Normal	
Rt.Tibial	Normal	Reduced < 80%		Normal	Axonal
Lt.Tibial	Normal	Normal		Normal	

Table II. Sensory nerve conduction study (SNCS).

Nerves Name	Latency	Amplitude (CMAP)	NCV	Remarks
Rt.Median	Normal	Normal	Normal	
LT.Median	Normal	Normal	Normal	
Rt.Ulnar	Normal	Normal	Normal	
Lt.Ulnar	Normal	Normal	Normal	
Rt.Radial	Normal	Normal	Normal	
LT.Radial	Normal	Normal	Normal	
Rt.Sup.Peroneal	Normal	Normal	Normal	
Lt.Sup.Peroneal	Normal	Normal	Normal	
Rt.Sural	Normal	Normal	Normal	
Lt.Sural	Normal	Normal	Normal	

CB: Conduction block, NCV: Nerve conduction velocity, CMAP: Compound muscle action potential

Facial diplegia can present either simultaneously or in alternating form. Simultaneous onset is defined as involvement of the opposite side within 30 days of involvement of the first side.[8] The possible systemic conditions that cause this kind of presentation are namely Bell's palsy, sarcoidosis, Lyme disease, poliomyelitis, Hansen's disease (leprosy), diabetes mellitus, brainstem encephalitis, brainstem stroke, Herpes zoster (Ramsay Hunt and Melkerson – Rosenthal syndrome), HIV and GBS.

Kaene, in a 23 year review found that out of 43 patients with bifacial palsy as the predominant sign, bilateral Bell's palsy (10/43) and GBS (5/43) were the most common underlying causes.[1] In our patient, the weakness remained localized to the face with no clinical evidence of progression.

In our case key points which were suggestive of the variant of GBS are the history of upper respiratory tract infection one week before facial palsy, NCS showing features of acute motor neuropathy with conduction block along with albuminocytologic dissociation in CSF.

A case report of Sethi, et al, demonstrates similar features of facial diplegia and hyperreflexia.[9] Hyperreflexia as a variant of GBS has also been described and is currently not thought to be inconsistent with the diagnosis.[9,10]

Conclusion

This case is presented to impress that a high index of suspicion should be maintained for GBS in any child who presents with facial diplegia.

References

1 Kaene JR. Bilateral Seventh nerve palsy: Analysis of 43 cases and review of the literature. Neurology 1994; 44: 1198–1202.

2 Chakrabarti D, Roy M, Bhattacharyya AK. Facial Diplegia: A Clinical Dilemma. J Indian Med Assoc 2013;111:410-411.

3 Stahl N, Ferit T. Recurrent bilateral peripheral facial palsy. J Laryngo Otol 1989; 103: 117-119.

4 Adour KK, Byl FM, Hilsinger RL, Kahn ZM, Sheldon MI. The true nature of Bell's palsy: analysis of 1,000 consecutive patients. Laryngoscope 1978; 88: 787-801.

5 Somarajan A. Guillain Barre Syndrome with brisk reflexes – Another variant. Neurol India 2006; 54: 215-216.

6 Gupta D, Nair M, Baheti NN, Sarma PS, Kuruvilla A. Electrodiagnostic and clinical aspects of Guillain-Barre syndrome: An analysis of 142 cases. J Clin neuromuscul Dis 2008; 10: 42-51.

7 Capaso M, Caporel CM, Pomilio F, Gandolfi P, Lugaresi A, Uncini A. Acute motor conduction block neuropathy. Another Guillain Barre Syndrome variant. Neurology 2003; 61: 617-622.

8 Narayanan RP, James N, Ramachandran K, Jaramilo MJ. Guillain Barre Syndrome presenting with bilateral facial nerve paralysis: a case report. Cases J 2008; 1:379.

9 Sethi KN, Torgovnic J, Arsura E, Johnston A, Buscher E. Facial diplegia with hyperreflexia – A Mild Guillain Barre Syndrome variant, to treat or not to treat? J Brachial Plex Peripher Nerve Inj 2007; 2:9.

10 Singhal V, Bhat KG. Guillain Barre Syndrome with hyperreflexia: A variant. J Peadiatr Neurosci 2011; 6: 144-145.

CLIPPINGS

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes.

Maternal nutrition during pregnancy is known to have an effect on fetal growth and development. It is recommended that women increase their calcium intake during pregnancy and lactation, although the recommended dosage varies among professionals. Currently, there is no consensus on the role of routine calcium supplementation for pregnant women other than for preventing or treating hypertension.

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension) as well as any possible side effects.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30th September 2014).

We considered all published, unpublished and ongoing randomised controlled trials (RCTs) comparing maternal, fetal and neonatal outcomes in pregnant women who received calcium supplementation versus placebo or no treatment. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Three outcomes were chosen for assessment with the GRADE software: preterm birth less than 37 weeks; preterm birth less than 34 weeks; and low birthweight less than 2500 g. Evidence for these outcomes was assessed as of moderate quality.

This review indicates that there are no clear additional benefits to calcium supplementation in prevention of preterm birth or low infant birthweight. While there was a statistically significant difference of 56 g identified in mean infant birthweight, there was significant heterogeneity identified, and the clinical significance of this difference is uncertain.

Pranom Buppasiri, Pisake Lumbiganon, Jadsada Thinkhamrop, Chetta Ngamjarus, Malinee Laopaiboon, Nancy Medley. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. First published: 25 February 2015Full publication history. Assessed as up-to-date: 30 September 2014. Editorial Group: Cochrane Pregnancy and Childbirth Group. DOI: 10.1002/14651858.CD007079.pub3.

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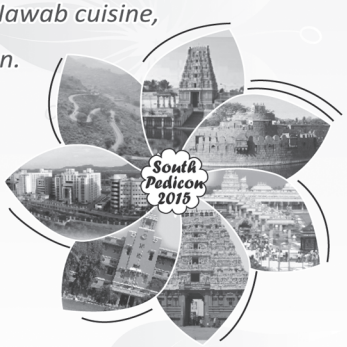

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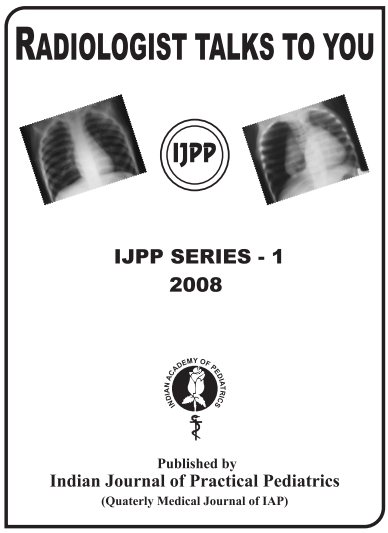

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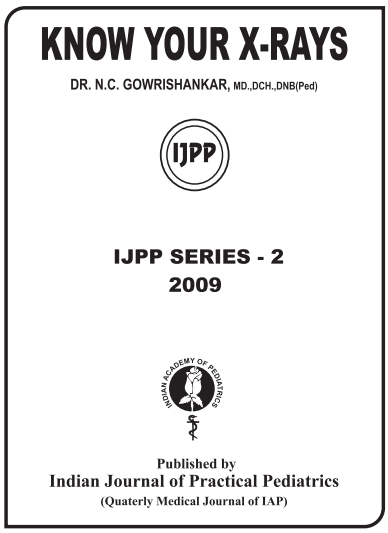

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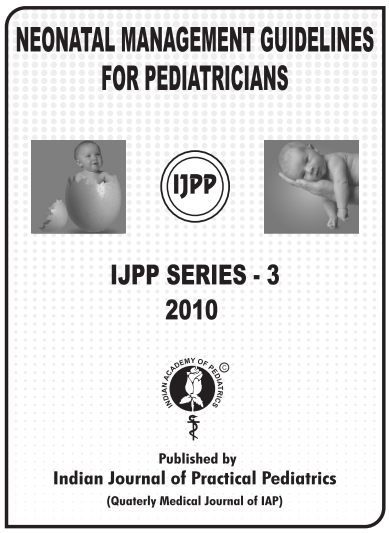

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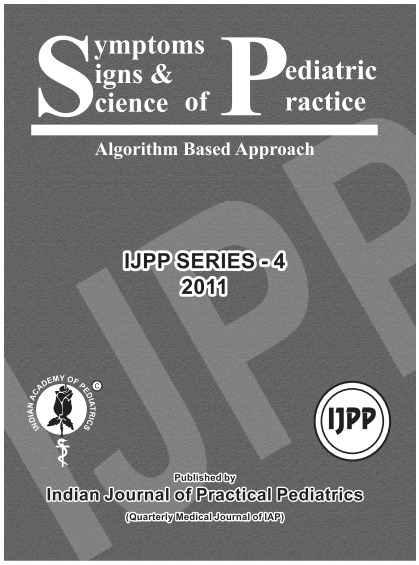

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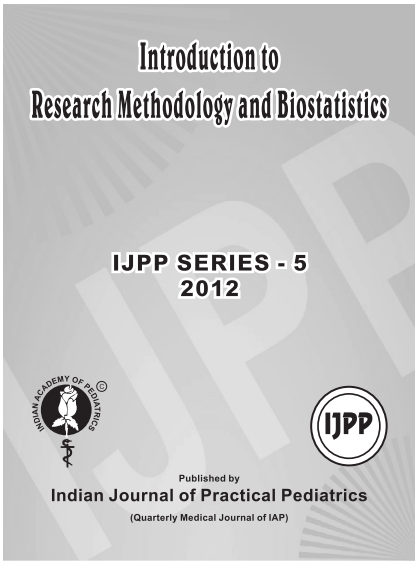

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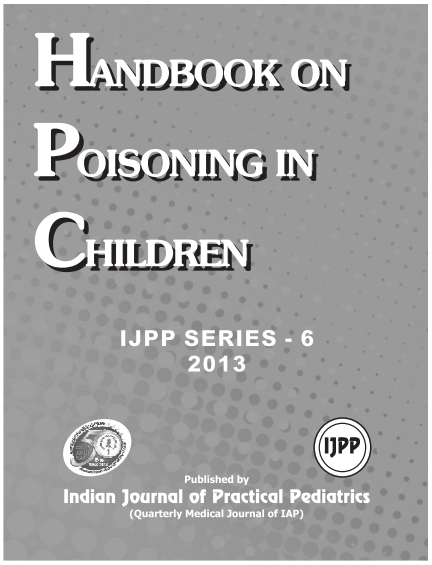

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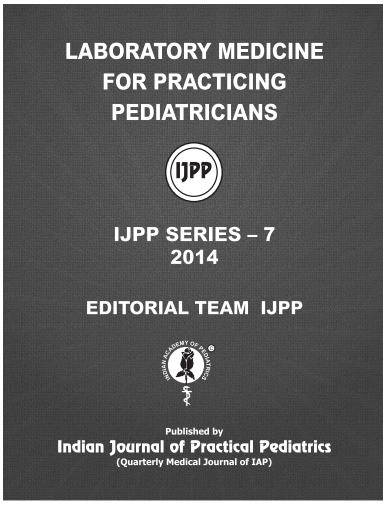

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