INDIAN JOURNAL OF PRACTICAL PEDIATRICS

CONTENTS

EDITOR'S DESK

Greetings from the Journal Committee of IJPP. This issue will bring out some more interesting articles on Neonatology. The topics will be useful for practicing pediatricians and postgraduates both at tertiary care centers and primary heath care level. The Journal Committee is taking utmost care in keeping the academic standards.

The article on 'Neonatal hyperbiliru-binemia' is discussed in detail by Dr.Diwakar. The respiratory distress is one of the most common causes of morbidity and mortality in neonatal period. The article on 'Ventilation strategies in neonates with respiratory distress' written by Dr.Karthik Nagesh will be an eye opener for younger colleagues in the NICU dealing neonates with respiratory distress. He has given a vivid picture about the various modalities of the management of neonates with respiratory distress. Feeding the low birth weight babies often pose problems among practitioners and is still a nutritional challenge.

Dr.Sheila Samanta Mathai has discussed the common problems encountered in the "Feeding low birth weight babies". She concluded that LBW babies need to be put on breast milk as soon as possible after birth and monitoring of the growth of these children during follow-up. The article on 'Fetal origins on adult disease – Implications for the 21st century' by Dr.Venkatesh Sampath, USA is quite interesting and will throw more light on this subject. The 'Neonatal sepsis' is the commonest cause of

morbidity and mortality in NICU. Dr.Ranjan Kumar Pejavar has given a detailed summary on the newer perspectives.

The practical value of plain x-ray in the evaluation of neonates' abdomen is well discussed by Dr.Muralinath. He has written the basic approach to the reading of an x-ray abdomen of a neonate with gastrointestinal disorders. We hope the postgraduates will appreciate the value of a plain x-ray abdomen at the bedside. The 'Follow-up of the high risk neonate' is an essential component in the tertiary neonatal care.

Dr.Shanmughasundharam, et al has highlighted the goals and the need for follow-up of high risk neonates. The recent advances in medical technology made the fetal diagnosis and therapy possible in this decade. Dr.Karthikeyan has reviewed the current status of the screening and diagnostic technologies that are available in fetal medicine as well as therapeutic interventions.

The Editorial Board of IJPP has discussed the FAQs in neonatal office practice. The article on 'Systemic lupus erythematosus in children' is well written by Dr.Uma Sankari Ali. She has discussed the clinical spectrum, management, outcome and follow-up with review of current literature.

Dr.Vijayalakshmi, et al has dealt about the important role of ultrasonogram while evaluating children with acute abdominal pain.

INSTRUCTIONS TO AUTHORS

General

Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript.

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2nd Page –

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Points to remember (not more than 5 points)

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With 1 or 2 images of clinically recognizable condition

(of which one could be in the form of clinical photograph / specimen photograph / investigation)

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NEONATOLOGY

NEONATAL HYPERBILIRUBINEMIA - A CONTINUING SAGA

* Diwakar KK

Abstract: Neonatal hyperbilirubinemia has always been a subject of significant clinical interest. Occurrence of bilirubin associated encephalopathy, lends an urgency to the diagnosis and management of neonatal jaundice. As therapy is primarily aimed at preventing bilirubin encephalopathy, it would be suitable to approach neonatal jaundice in a three-pronged manner. 1. Evaluation based on 'risk-for-encephalopathy', 2. Evaluation for etiology and 3. Management.

***Key words**: Hyperbilirubinemia, Neonatal jaundice, Phototherapy, Exchange transfusion*

Neonatal hyperbilirubinemia or jaundice in the newborn is still one of the most discussed topics in neonatology. The sheer prevalence of neonatal jaundice and periodic occurrence of bilirubin associated encephalopathy ensures sustained interest on this subject. While the etiology of hyperbilirubinemia may be varied, the principles of therapy have remained fairly constant over the decades. Better understanding of the genetic and biochemical variables contributing to bilirubin elevation has made 'the at-risk' approach and early intervention easier. Though a small percentage of neonatal jaundice

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belong to the 'direct hyperbilirubinemia' group, most of the discussion in neonatal jaundice is focused on the travails of 'indirect hyperbilirubinemia. The subject has been discussed under the following three headings;

1. Evaluation based on 'risk-for-encephalopathy'.

2. Evaluation for etiology.

3. Management.

Needless to say all the steps have to be done simultaneously.

At risk for encephalopathy

a. Level of unconjugated bilirubin

Quantifying the level of jaundice has been the foundation for satisfactory management of hyperbilirubinemia. The observer variability and the influence of the skin color in clinically evaluating hyperbilirubinemia by 'Kramer index' has been the Achilles' heel of this method (Table 1). On the other hand despite its reliability, the pain of repeated blood sampling makes evaluation of serum bilirubin a distasteful task for the baby and health care personnel. The advent of transcutaneous bilirubinometry has significantly simplified the task of monitoring the jaundice level in infants. The reliability of the instruments for bilirubin estimation [Minolta ® and Bilicheck ®] have shown reasonable dependability for both, with clinical assessment being considered least reliable[1].

The fear for the level of 20 mg/dL has given anxious moments to doctors and the relatives of the 'jaundiced' infant. Researchers have suggested that serum bilirubin level is preferably

Table 1. Criteria to estimate clinical jaundice (Kramer Index)

Area of body	Range of bilirubin (mg/100 ml)
Face	4–8
Upper trunk	5–12
Lower trunk and thighs	8–16
Arms and lower legs	11–18
Palms and soles	>15

maintained below 335 micromols/L (appr. 1 mg/dL = 18 micromol/L)[2]. However, what is often missed is that there is nothing sacrosanct about this level of bilirubin. At many an occasion levels lower than this value have also known to be associated with encephalopathy. No controversy exists about the mandatory requirement for monitoring the bilirubin levels of all infants, specially the at-risk neonates. The rise of bilirubin at a rate exceeding 1 mg/dL/hour is still considered an indicator for exchange transfusion in the 'at-risk' patient (0.25 mg/dL/hr for phototherapy as per American Academy of Pediatrics).

The gold standard for deciding therapy to prevent encephalopathy continues to be serum bilirubin levels for want of better parameters. After 48 hours of life, serum bilirubin is evaluated 8-12 hourly if levels are above 14 mg/dL, 6th hourly if above 16 mg/dL, 4th hourly if above 18 mg/dL and more frequently at higher values. It can never be over emphasized that at risk patients, and jaundice occurring before 48 hours of age must be monitored more frequently and more diligently.

It should be remembered that bilirubin rises by the 'hours' of life and hence the time of sampling must be as 'hours of life' and not 'day of life.' It must be recognized that 25 hours and 47 hours would both be 2nd day, but the risk for encephalopathy for *same* levels of serum bilirubin would be much higher for the earlier hours. This significance would be missed if the 'day of life' were to be the criterion.

b. Patient factors

The multifactorial etiology of bilirubin associated encepahalopathy is significantly influenced by the altered physiologic integrity of the blood brain barrier [3], sudden surge in free bilirubin levels, variable affinity of bilirubin to various neuronal sites and a multitude of hitherto known and unknown factors. This makes predicting encephalopathy a challenging task.

The concept of free bilirubin having a 'cytotoxic' effect on the neuronal cells has led to various theories interpreting the possible facilitators for bilirubin induced neuronal injury. The relative selectivity of injury being confined to areas like the basal ganglia implies an association of the higher metabolic rate, oxygen consumption and highly vascular characteristics of these areas and their vulnerability to bilirubin associated neuronal injury. MRI evaluation of bilirubin encephalopathy has shown a greater involvement of globus pallidus and putamen and the thalamus to be affected to a lesser extent[4].

The following host factors, play determining roles in promoting encephalopathy,

i. Gestation: A less developed hemopoetic and hepatic functions would result in the less mature infant having more prolonged and higher levels of serum bilirubin. As the gestational age increases, the permeability of the blood brain barrier to bilirubin and bilirubin – albumin complex decreases. Other systems like the gastro intestinal tract also become more functionally mature.

ii. Albumin levels: The albumin: bilirubin ratio seems to be a plausible predictor for encephalopathy. It seems logical that in

infants with lower albumin levels, the free bilirubin content would be more, thereby enhancing the risk of encephalopathy[5].

iii. Systemic compromise in the infant could result in various alterations – each being an additional deleterious contributor to bilirubin encephalopathy. Factors reducing the albumin levels would contribute to reduced albumin binding and a larger load of free bilirubin in the serum. The integrity of the blood brain barrier is affected by acidosis and hypoxic ischemic damages, facilitating greater permeability to the bilirubin complexes. A large surge of bilirubin or enhanced contact time of the bilirubin to the neurons is found to be essential to precipitate an encephalopathy. The factors increasing the circulation time would ensure greater period of contact of the bilirubin moieties to the neurons – facilitating neuronal damage, thus explaining the higher risk of encephalopathy in asphyxiated or septic neonates in shock. The compounding factors of metabolic acidosis would damage the blood brain barrier.

iv. Increasing post natal age, tends to decrease the risk of hyperbilirubinemia and the associated encephalopathy. While maturation of the blood brain barrier and greater vasomotor stability would be the explanation for preventing encephalopathy, multiple factors of gastro intestinal maturity are useful protectors. Increasing gut motility, passage of meconium with its additional bilirubin load, maturation of the GIT hormones, resulting in the antegrade flow of bile, bacterial colonization of the gut with the resultant reduction in the efficacy of intestinal glucoronidase all result in reducing enterohepatic circulation and total body bilirubin load. Structural anomalies of the GIT would influence the gut motility and reduce propagation of the intestinal contents, resulting in an increased amount of enterohepatic circulation.

Evaluation for etiology

Recognizing the etiology is essential for the comprehensive management of any disease. While therapy of neonatal jaundice with the ubiquitous phototherapy and exchange transfusion has effectively reduced its morbidity, identifying the exact cause for the hyperbilirubinemia could often be daunting.

As in all aspects of clinical medicine, history provides many clues. The hour of occurrence of jaundice, and the rapidity of rise must always be sought for.

Clinical jaundice noticed beyond 36 hours of life, increasing by 72 to 96 hours, with a tendency to reduce, and disappear by the 7th - 10th day has become the accepted pattern of the so called physiologic jaundice in a term infant. In preterm infant, the jaundice tends to peak by the 7th day and disappear by the 14th day. It has been the custom to state that serum bilirubin in term infants having 'physiologic jaundice' rarely rises above 12 mg/dL. There is a significant regional and ethnic variation in this levels. Levels as high as 14-15 mg/dL are not uncommonly seen in many term infants with physiologic jaundice. However, it must be reiterated that all causes for elevation in serum bilirubin must be ruled out before labeling an infant as having 'exaggerated physiologic' jaundice. Similarly persistence of jaundice beyond the accepted periods viz. 7 days in term infants and 14 days in preterm infants, in the absence of any other discernable cause is often termed as 'prolonged physiologic jaundice'.

It must be appreciated that the onset of jaundice within 24 hours should always be considered 'unphysiologic' and must be evaluated in detail. Hemolytic disease of the

newborn – Rh isoimmunization or ABO incompatibility could present as early onset jaundice. It must be recognized that other causes of hemolysis like congenital spherocytosis, G6PD deficiency etc. could also present as neonatal hyperbilirubinemia. The history of jaundice in the previous sibling should always be sought for, as this could provide an insight to the etiology and possible cause of the jaundice. Beware of an elder sibling with bilirubin encephalopathy. The approach to management in such cases must be with utmost caution and aggressive strategies for reducing bilirubin levels must be initiated at the earliest. An often forgotten event, is asking for the color of urine and stools of neonates presenting with jaundice. Obtaining the history of high colored urine or pale stools would highlight the chances of conjugated hyperbilirubinemia or cholestatic jaundice.

The approach based on serum bilirubin is often helpful (Table 2). The presence of unconjugated hyperbilirubinemia must always be complemented with the examination of the peripheral blood smear. The evidence of hemolysis in the peripheral smear has sinister implications to the course of jaundice and the neonate requires more aggressive management like exchange transfusion. The absence of hemolysis would direct us to the other less common causes (Table 2) for neonatal hyperbilirubinemia or could finally result in the nonspecific diagnosis of 'exaggerated physiologic jaundice'. Hypothyroidism must always be ruled out, in all cases of unexplained jaundice. This becomes even more important as regular neonatal screening for hypothyroidism is not undertaken in our country. This incidental jaundice could therefore be the first clue to alleviate a treatable cause of mental retardation. Glucoronyl transferase hypofunction has been attributed to many an unexplained neonatal hyperbilirubinemia. Specific enzyme assays could confirm these abnormalities.

Prolonged jaundice has many times been a presentation of neonatal hepatitis and other causes of conjugated hyperbilirubinemia. It must therefore be realized that evaluation of jaundice is always incomplete, without assessing the direct bilirubin.

Of late, significant interest has been generated on the role of bilirubin as an antioxidant. The association of free radicals with elevated unconjugated bilirubin levels have been assessed by many workers. The diminished

Table 2. Etiology of hyperbilirubinemia

Serum Bilirubin			
Unconjugated		Conjugated	
Increased Bilirubin production:	Others:	Cholestasis	Infection
Hemolytic disease, Rh, ABO, minor blood group incompatibility etc.	Exaggerated physiologic jaundice	Non surgical (eg drugs)	Congenital / Acquired
Extravasated blood, eg. Cephalhematoma Subgaleal bleeds, cutaneous bruising, hematoma	Conjugation disorders; Hypothyroidism; Breast milk jaundice	Surgical	
Polycythemia			

antioxidant associated oxidative stress of the premature infants has also been considered as a cause for hyperbilirubinemia.[6]

Management

The functional maturity of the liver would be the final determinant of the levels of unconjugated bilirubin in the blood. Therapy is therefore aimed at tiding over the interim period of rising bilirubin load until the hepatic system is functionally effective in reducing the unconjugated bilirubin. Therapy is aimed at ensuring that serum bilirubin remain well below the 'encephalopathic levels'. It is perhaps for this reason that radical therapy like exchange transfusion is rarely encountered in infants beyond the first week of life as presumably the liver would have 'matured' by that time. In the presence of additional risk factors for encephalopathy, therapy is initiated at lower serum bilirubin levels. Eg. Treatment would be initiated at lower levels of serum bilirubin in an infant who is premature, while the same level of serum bilirubin in a term infant would not warrant any therapy. Investigations and treatment continue to be the twin pillars of management.

Investigations

All investigations are for ascertaining the etiology and the risk for encephalopathy in the infant (Table 3). Serial evaluation of bilirubin must be done in all infants considered to have jaundice level higher than normal for the age and gestation. This could be by transcutaneous bilirubinometry or by serum bilirubin estimation. The frequency of assessment increases as the bilirubin values approach 'encephalopathic' levels. It is our practice to evaluate serum bilirubin every 8 hours if the bilirubin levels are about 14 mg/dL beyond 48 hours of life in term infants. Bilirubin is assessed every sixth hourly if values are above 16 mg/dL and fourth hourly for values over 18 mg/dL. Any value above 18 mg/dL is considered as 'high risk for encephalopathy' and two hourly monitoring to be done along with the assessment of serum albumin level.

Relevant investigations have to be undertaken depending on the presence or absence of hemolysis. Congenital hemolytic anemias must be considered if peripheral smear examination is suggestive of hemolysis, in the absence of fetomaternal blood group incompatibility. Similarly unconjugated hyperbilirubinemia in the absence of hemolysis would warrant evaluation for sepsis, hypothyroidism and hypo functioning hepatic enzyme system. A missed cephalhematoma or borderline prematurity have been responsible for many an unexpected hyperbilirubinemia. Conjugated bilirubin values

Table 3. Investigations

Tests	Implication
Biochemical	
a) Serum Bilirubin, Direct and Total	Type of hyperbilirubinemia Unconjugated / Conjugated
b) Serum albumin	Bilirubin: Albumin Ratio – Risk for encephalopathy if ratio high
Hematologic	
a) Blood group and Rh typing of infant and mother	Isoimmunization
b) Peripheral smear	For evidence of hemolysis

greater than 1.5-2.0 mg/dL must also be taken seriously and evaluated for infections and cholestasis[7].

Some interest has been generated in considering end-tidal carbon monoxide levels as a predictor for significant hyperbilirubinemia in infants with hemolysis[8].

Treatment

The mechanisms and nuances of each form of therapy is beyond the purview of this article. It should suffice to say that the aim of treatment should be to reduce, if possible the bilirubin production, reduce serum bilirubin by direct removal or making it water soluble, increase enterohepatic circulation and reduce factors facilitating encephalopathy.

Photherapy

The recognition that phototherapy with light of 425-475 nm wave length can convert unconjugated biliubin of the skin to water soluble isomers-geometric and structural (Lumirubin) has radically changed the prognosis of hyperbilirubinemia in the newborn. A spectral irradiance of 6-15 micro watts/nm/cm^2, is found to be effective, with higher irradiance resulting in a greater degree of isomerization.

Phototherapy is usually started in term infants when the serum bilirubin levels are over 12mg /dL at 25-48 hrs of life or over 15mg/dL at 48-72 hrs[9] (Table 4). It is prudent to commence phototherapy as soon as serum bilirubin value reaches 5-6 mg/dL below the indicated value for exchange transfusion for that infant. It would therefore be obvious why phototherapy is initiated in premature and at- risk infants, at lower levels of serum bilirubin as compared to normal term infants.

Intensive phototherapy is commenced as the requirement for exchange transfusion becomes more plausible – the aim being to reduce the serum bilirubin by 1-2 mg/dL every 6 hours.

Exchange transfusion

The indications and timing for exchange transfusion has always been a matter of debate. Serum bilirubin values above 20 mg /dl has been traditionally accepted as a strong enough indication for exchange transfusion. However, the increasing awareness of transfusion related diseases and normal outcome observed in term infants with bilirubin values well above 20 mg/dL has resulted in a rethink about the sanctity of the number '20'. In the absence of risk factors, exchange transfusion has been

Table 4. Phototherapy: Birth weight is plotted against infant's age in days. If the serum indirect bilurubin (mg/dL) is greater than the plotted number, consider phototherapy[14].

Days	1	2	3	4	5	6	7
Birth wt. (gms)							
<1000	3	3	3	5	5	7	7
1000-1249	5	5	5	7-8	8	10	12
1250-1499	8	8	8	10	12	12	12
1500-1749	10	10	10	12	12	13	13
1750-1999	10	10	12	13	13	13	13
2000-2499	10	12	12	15	15	15	15
>2500	10	12	13	15	17	17	17

Table 5.Total bilirubin (mg/dL) and bilirubin/albumin ratio (mg/g) as criteria for exchange transfusion[11]

	Birth weight (gram)				
	<1250	1250-1499	1500-1999	2000-2499	>2500
Standard risk	13.0	15.0	17.0	18.0	25-29
Or bilirubin/albumin ratio*	5.2	6.0	6.8	7.2	8.0
High risk#	10.0	13.0	15.0	17.0	18.0
Or bilirubin/albumin ratio*	4.0	5.2	6.0	6.8	7.2

* Exchange transfusion at whichever criterion comes first

Risk factors: Apgar <3 at 5 minutes, PaO_2 <40 mm at > 2 hour, pH< 7.15 at >1 hour, body weight <1000 g, Hemolysis, clinical CNS deterioration, total protein <4 g/dL or albumin <2.5 g/dL

delayed to values as high as 25-29 mg/dL[10]. Recommendations for exchange are often subjective and could at times be even termed as vague. We have in our center utilized the observation of Ahflors and modified it, thus using the product of albumin and bilirubin levels as guideline to decide the timing for exchange transfusion (Table 5) [11].

Exchange transfusion continues to be the ultimate weapon in the armamentarium against hyperbilirubinemia and prevention of bilirubin associated encephalopathy. Well conducted double volume exchange transfusion using the appropriate group and Rh typed blood reduces the serum bilirubin by 50-60 % in most instances. 'O positive' blood would be required for exchange transfusion in cases of ABO incompatibility. Infants with Rh isoimmunization will ideally require Rh negative blood of the baby's group, in the absence of which 'O negative' blood should suffice. The importance of a good blood bank with all protocols for safe blood banking can never be over emphasized under these circumstances. 'Rh negative' donors must also be evaluated for 'Du' antigen, and should be accepted for donation only if they are 'Du' negative in addition to being 'Rh-negative' by standard reagents.

While the 'pull –push method' through the umbilical vein continues to be the most common method for exchange transfusion, dual portal routes for exchange transfusion are becoming equally popular. Peripheral or umbilical artery have been used by many workers to withdraw blood with the peripheral or umbilical vein being used for transfusing the blood. It has been our practice to use the umbilical vein to withdraw the 'jaundiced blood' and use the peripheral vein to infuse the compatible blood by syringe infusion pump at a synchronized predetermined rate.

While 'fresh blood' has for long been the choice, it has become increasingly difficult to obtain, especially since the mandatory screening requirements of standard blood banks. The sheer non-availability of a compatible donor could also make obtaining 'fresh blood' difficult.

In the present days of component blood banking saline washed compatible packed cells could be reconstituted with the compatible plasma to the acceptable packed cell volume (PCV), and used for exchange transfusion. The saline washing reduces the risk of hyperkalemia of the stored packed cell, and the plasma reconstitution to appropriate PCV reduces the chances of post-exchange transfusion hyperkalemia.

Newer therapies

Intravenous gama globulin in immune hemolytic jaundice, Tin-mesoporphyrin and Bilirubin-oxidase are some of the modalities used in experimental or limited clinical trials by various workers. Antenatal phenobarbitone given to the mother in doses of 30 mg three times a day have been shown to reduce exchange transfusion in neonates with hemolytic disease [12].

Supportive care

The treatment of neonatal hyperbilirubinemia would never be complete without mentioning the concomitant supportive care. Satisfactory oral feeds ensures adequate hydration and nutrition. The ensuing bowel movements are very useful in reducing the enterohepatic circulation. Trans-epidermal loss of water in low birth weight infants undergoing phototherapy can be reduced by coating the skin with clear ointment [13].

Breast feeding, in addition to the nutritional benefits, would serve as a good indicator to monitor encephalopathy. Any reduction in the jaundiced infant's interest to suck at the breast should be considered sinister and an indicator for immediate exchange transfusion.

Follow-up

All infants with significant jaundice — hyperbilirubinemia to an extent where exchange transfusion was undertaken or seriously contemplated — must be meticulously followed up for auditory assessment and developmental evaluation.

In the absence of an identifiable cause for the jaundice, the search for an etiology should be continued at follow up. In addition to providing an insight to the current problem, the information obtained could be invaluable for subsequent pregnancies.

Management of hyperbilirubinemia should follow the basic tenets of

1. At Risk Approach: Greater caution for infants with higher risk for encephalopathy.

2. Low threshold for initiating phototherapy in these patients.

3. A regular hospital policy for evaluation of bilirubin levels in all infants and management of hyperbilrubinemia.

4. Exchange transfusion when indicated.

5. Specific recommendations for follow-up bilirubin assessment in infants discharged before 72 hours of age.

Neonatal hyperbilirubinemia will continue to be a much debated topic. Research has contributed to a better understanding about the etiopathogenesis of bilirubin encephalopathy. It is however interesting to realize that despite the large amount of scientific evaluation, the basic tenets of managing hyperbilirubinemia during the early neonatal period have remained relatively unchanged.

Points to remember

1. *Neonatal hyperbilirubinemia could result in bilirubin associated encephalopathy.*

2. *Serum bilirubin levels have to be regularly monitored in the newborns especially the at risk infants.*

3. *Prematurity, low serum albumin levels, asphyxia, sepsis and other factors that could interrupt the integrity of the blood brain barrier, increase the risk of encephalopathy even at lower levels of serum bilirubin.*

4. *Phototherapy must be initiated appropriately in infants with hyperbilirubinemia.*

*5. **Exchange transfusion would have to be undertaken if bilirubin levels and associated risk factors predict a high risk for encephalopathy.***

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NEONATOLOGY

VENTILATION STRATEGIES IN NEONATES WITH RESPIRATORY DISTRESS

Karthik Nagesh N

Abstract: Mechanical ventilation continues to be one of the most common therapies in neonates with respiratory failure. The aim in ventilating these babies with respiratory failure is to achieve adequate gas exchange without injuring the lungs. We now have the opportunity to apply a number of advanced ventilatory modes which were not previously available for treating newborns.These offer multiple mode selection and improved pneumatics.Ventilatory strategy should take into account the pathophysiology, nature and course of the disease.Newer ventilation strategies are more 'kinder and gentler' on the newborn lungs in order to reduce ventilator induced lung damage.

Key words: Neonatal ventilation,Strategies

Respiratory distress constitutes the largest cause of morbidity and mortality in the neonatal period due to minimal respiratory reserve and transition from intrauterine to extrauterine life. It is estimated that 10-15 percent of babies with respiratory problems die in the neonatal period.

Assisted ventilation can be defined as the movement of gas in and out of the lungs by an external source connected directly to the patient[1]. In the neonate, it is usually a temporary measure to support pulmonary function till the baby can breathe adequately without help. Ventilatory support may be required in neonates with impaired ventilation and gas exchange. The goal is to optimise gas exchange, improve pulmonary mechanics and to reverse the underlying cause of respiratory failure. Recent advances in neonatal ventilatory care have led to an increased survival of smaller and critically ill babies.

Respiratory distress - Evaluation

To evaluate the respiratory distress, at least three aspects should be considered: (1) clinical signs of respiratory distress, (2) blood chemistry and (3) chest radiography. Table 1 provides a list of clinical entities that can lead to respiratory distress in neonates.

Infants who have some respiratory difficulty in the delivery room may have elevation of respiratory rate and retractions for a few hours. This may subside in many neonates while some of them continue to manifest these symptoms. Careful recording of respiratory rate and retractions are to be kept from birth. Various clinical scores have been developed to evaluate respiratory distress. The consistent features of these scores were respiratory rate, retractions, grunting, cyanosis and auscultatory findings of breath sounds.

Clinically one should look for the following signs:

- Increase in respiratory rate

- Increasing retractions / effort

- Prolonged apnea with cyanosis / bradycardia or both.

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Table 1. Clinical entities leading to respiratory distress syndrome

I. Obstructive airway disease

Congenital anomalies:
1. Choanal atresia
2. Laryngeal webs
3. Laryngomalacia
4. Tracheal aplasia / stenosis
5. Tracheoesophageal fistula and esophageal atresia

External compression of the upper airway:
1. Vascular ring
2. Tumors and cysts

Trauma:
1. Post extubation laryngeal edema and subglottic stenosis
2. Vocal cord paralysis
3. Laryngeal fracture
4. Tracheal perforation

II. Lung parenchymal diseases

Congenital anomalies:
1. Lung cysts
2. Congenital cystic adenomatoid malformation
3. Congenital lobar emphysema
4. Hypoplasia and agenesis of the lungs
5. Chylothorax
6. Congenital pulmonary lymphangiectasis
7. Congenital stridor

Acquired disorders:
1. Transient tachypnea of newborn
2. Hyaline membrance disease
3. Meconium aspiration
4. Pneumonia
5. Bronchopulmonary dysplasia
6. Pulmonary hemorrhage
7. Wilson Mikity syndrome
8. Pneumothorax and pneumomediastinum

III. Non-pulmonary causes
1. Heart failure
2. Intracranial causes
3. Metabolic acidosis
4. Shock
5. Severe asphyxia
6. Diaphragmatic hernia (congenital)
7. Phrenic nerve paralysis
8. Muscular disorders and weakness
9. Chest wall deformity

- Cyanosis unrelieved by oxygen

- Hypotension / pallor or decreased peripheral perfusion.

- Periodic breathing with prolonged pauses

- Gasping with the use of accessory respiratory muscles.

Downes' and Vidyasagar's score describes a clinical scoring system which was simultaneously compared with sequential arterial pH and blood gas measurements. The scoring system (Table 2) consisted of 0-2 numericals given to 5 major clinical features, to provide the pediatricians who lack access to blood gas analysis. It is a simple clinical scoring system that also provides a guide to treatment as well as prognosis. The score can also be used to predict the inspired O_2 concentration requirements.

A point to remember is that such clinical scoring systems only provide an objective method of assessment of respiratory distress and not a final diagnosis.

Laboratory studies

Blood gases usually are obtained from either an indwelling arterial (umbilical) catheter or an arterial puncture. Blood gases can exhibit respiratory and metabolic acidosis along with hypoxia.

- Respiratory acidosis occurs because of alveolar atelectasis and / or overdistension of terminal airways.

- Metabolic acidosis is primarily lactic acidosis, which results from poor tissue perfusion and anerobic metabolism.

- Hypoxia occurs from right-to-left shunting of blood through the pulmonary vessels, PDA and / or foramen ovale. 'Pulse oximetry' is used as a noninvasive tool to monitor oxygen saturation, which should be maintained at 90-95%.

X-ray Chest

Radiology plays an important role in the evaluation of a sick neonate. The use of immobilisation techniques and fast exposure time, has enabled efficient roentgenographic examinations of the newborn.

Respiratory distress in a newborn can be due to a variety of causes. 'Hyaline membrane disease' (HMD) is characterized by hypoventilated lungs. The lungs may appear homogeneously dense to granular with air bronchograms, or almost normal. 'Pulmonary air leaks' may present as pulmonary interstitial emphysema, pneumothorax, pneumomedia-stinum and pneumoperitoneum. The "spinnaker sail" sign of elevated thymus along with air in the subcutaneous tissues of the neck is a classic radiologic feature of pneumomediastinum. Meconium aspiration causes typical changes in the chest, i.e., hyperventilated lungs with coarse patchy densities from meconium plugs or distal atelectasis. Air trapping by the lungs is the predominant feature of 'meconium aspiration'. Pneumonia may vary and lungs may show lobar consolidation, small diffuse nodularity, coarse patchy infiltrates, diffuse haziness or perihilar streaks. Complications of pneumonia, such as abscess, empyema and pneumatoceles are a manifestation of staphylococcal, streptococcal or Escherichia coli pneumonias. Multiple cystic lesions in the chest may be seen with congenital lung anomalies such as cystic adenomatoid malformation and diaphragmatic hernia. A mediastinal shift may be seen in these conditions. Congenital lobar emphysema is often associated with adjacent lobar atelectasis and can be diagnosed by chest X-ray.

Indications for ventilatory support in the neonate

The most common cause for beginning assisted ventilation in newborn is 'respiratory failure'. This could take two forms; one is apnea when ventilation is mandatory, as the patient is not breathing. The other is when the mechanism of pulmonary gas exchange is impaired.

Types of respiratory support currently available for respiratory distress in neonates include a) Continuous positive airway pressure and b) Mechanical ventilation

A. Continuous positive airway pressure (CPAP)

When infants continue to exhibit respiratory difficulty with increasing respiratory rate, retractions and grunting and require inspired oxygen concentrations greater than 40%, the infant should be supported with constant positive airway pressure (CPAP) – Table 3.

Table 2. Clinical respiratory distress scoring system* (Downe's and Vidyasagar's)

Score	0	1	2
Respirations (rate/min)	<60	60-80	>80 or apnea
Cyanosis	None in room air	In 40% O_2	More than 40%O_2
Retractions	None	Mild	Moderate to severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry	(N)	Delayed or decreased	Barely audible

*Score in normal infant=0. Score in infants with severe respiratory distress=10

Indications for CPAP

- $FiO_2 > 0.4$ to 0.5 (by O_2 hood)*

- Frequent apnea with documented hypoxemia**

- Clinically significant chest retractions after recent extubation from mechanical ventilation for RDS.

    *Especially, in a preterm with Respiratory Distress Syndrome (RDS)

    ** In practice, any baby with distress scoring more than 3/10 on the Downe's or Silverman Respiratory distress score or requiring more than 2-3 litres per minute of oxygen flow to maintain SaO_2 qualifies for CPAP therapy[2,3].

    CPAP aims to maintain a continuous distending pressure to the alveoli during expiration to prevent them from collapsing.This is especially useful in treating babies with RDS, who have low functional residual capacity (FRC) and lung compliance(c).This helps in better ventilation perfusion matching (V/Q), and decreases the frequency of apneic spells[2]. It also produces a more regular breathing pattern in preterms,helps splint the airway and diaphragm , reduces obstructive apnea and enhances surfactant release in RDS.

Technique:CPAP through a ventilator or other device e.g a CPAP driver is administered through a continuous flow of heated, humidified gas (air/oxygen mixture) at a set pressure of 3-8 cm H_2O while the baby breathes spontaneously. It can be delivered through nasal prongs, nasopharyngeal tube or the endotracheal tube. The equipment is simple to use, is less invasive, causes less barotrauma than mechanical ventilation, has a greater cost benefit, and has a more universal application. Essentially, any CPAP delivery system consists of three components: A). Circuit

for continuous flow of inspired gases,which are oxygen and compressed air.B).Oxygen-air blender enables to deliver the appropriate FiO_2. The rate of the continuous flow of inspired gas is controlled by a flow meter. The minimal flow rate required should be sufficient to prevent rebreathing of carbon dioxide, i.e. atleast two and half times the infant's minute ventilation, and should also compensate for leaks around connectors and CPAP prongs. Usually flow rates of 5-10 (LPM) is sufficient in neonates.The gases are warmed and humidified by an incorporated heated humidifier prior to delivery to the infant. C).CPAP –Patient airway interface device: Nasal masks, nasal cannula, single and binasal tubes/ prongs of varying lengths ending at either nasal or nasopharyngeal level have been used as interfaces.

The procedure is initiated by positioning the infant in supine position with the head elevated to about 30 degrees. Appropriate size nasal/ nasopharyngeal cannula are chosen and are moistened with sterile water or saline prior to insertion and fixation.Nasal CPAP is preferred[4,5]. Endotracheal CPAP (ETCPAP) may increase dead space airway resistance thereby increasing the work of breathing in small babies and hence is less preferred. Initial desired CPAP pressure is usually kept at 4- 5 cm H_2O. The inspired gas temperature is kept at 36°C. After the CPAP is properly applied, the infant should breathe more easily and the respiratory rate and retractions should decrease. The FiO_2 should be adjusted to keep the PaO_2 between 50 and 70 mm Hg or SaO_2 at low 90's. As the infant's respiratory distress improves, the FiO_2 should be lowered gradually in decrements of 2 to 5% while maintaining the PaO_2 of 50 to 70 mm Hg. The CPAP pressure is kept at 5 cm H_2O until the tachypnea and retractions become minimal or disappear. At this time, the requirement of FiO_2 should be in the range of 25% or even at the level of room air.

The CPAP may then be discontinued. The CPAP circuit should be changed at least once in 3 days. If the infant becomes tachypneic or is having retractions, desaturations or frequent episodes of apnea / bradycardia while off CPAP, the CPAP should be reintroduced even though the infant may be breathing room air and the signs of respiratory disease are minimal or no longer present. If CPAP of 6-7 cm H_2O with FiO_2 of 0.5-0.6 is not sufficient to maintain SaO_2, the infant probably needs to be ventilated mechanically.

Underwater "Bubble CPAP" has provided an alternative to pressure derived from conventional ventilators. It is in use since first devised in the 1970's[4]. The bubble CPAP uses a column of water, in a bottle, to provide the positive airway pressure rather than a variable resistor valve. The lightweight corrugated expiratory limb tube, preferably with a heating wire inside, is inserted into a bottle of 0.25% acetic acid solution or sterile saline with an antiseptic like povidone iodine filled up to a height of 7 cm. The tube must be immersed to a depth of 5 cm to create + 5 cm H_2O CPAP. In addition to providing positive airway pressure, bubble CPAP results in small vibrations in the infant's chest at the frequency of 15-30 Hz. Data in preterms ready for extubation suggest that in comparison with standard CPAP, bubble CPAP reduces respiratory rate and minute ventilation significantly without increasing $PaCO_2$[3]. Comparing underwater bubble ETCPAP with conventional ventilator derived ETCPAP in preterms suggested that the bubbling also contributed to gas exchange[3].

Prophylactic CPAP in absence of RDS: There is currently insufficient information to make recommendations for the clinical practice of prophylactic CPAP as in preterm infants it does not lead to a decreased incidence or severity of RDS and does not reduce rate of complications or mortality[6].

Early treatment of RDS with CPAP: Early randomized trials evaluating the effect of CPAP versus no CPAP in the treatment of RDS[7] showed that it improved oxygenation, reduced the need for subsequent mechanical ventilation and reduced the death rate. No effects on chronic lung disease (CLD) was however demonstrated and CPAP was found to increase the incidence of pulmonary air leak. Decreased cardiac output and shock can occur with prolonged CPAP due to increased intrathoracic/intrapleural pressure causing reduced systemic venous return[3].

A recent multicenter controlled trial has demonstrated that early nasal CPAP in combination with early treatment with surfactant (Curosurf) significantly improved oxygenation and reduced the subsequent need for mechanical ventilation. Recent meta-analyses conclude that CPAP is most beneficial early in established RDS and decreases the need for mechanical ventilation and may reduce mortality[3,8].

CPAP following extubation: A recent meta-analysis of controlled trials[9], concluded that CPAP was effective in preventing failure of extubation in preterms.

B. Mechanical ventilation

Absolute indications for mechanical ventilation

- Prolonged apnea
- PaO_2 < 50 mm Hg on an FiO_2 > 0.8 (except in cyanotic congenital heart disease)
- $PaCO_2$ >60mm Hg with persistent acidosis
- Failure of CPAP at FiO_2 > 0.6 to 0.7

Relative indications for mechanical ventilation

- Frequent, intermittent apnea (unresponsive to drugs)

- To prevent deteriorating gas exchange with anticipatory early mechanical ventilation.

- To relieve the "work of breathing" in a newborn with signs of respiratory distress.

Ventilation modalities available - Intermittent Positive-Pressure Ventilation (IPPV)/Intermittent Mandatory Ventilation (IMV)

Positive pressure inflation of the lung during a positive-pressure breath causes gas to flow into the lung because airway pressure is greater than alveolar pressure. The volume of gas entering the lung over timeperiod is a function of the Peak inspiratory pressure (PIP), inspiratory time (Ti), and respiratory system compliance and resistance. Most ventilators that are currently in use in neonatal intensive care units are-time cycled and pressure limited in which PIP, Positive End-Expiratory Pressure (PEEP), inspiratory time (Ti) and expiratory time (Te) are adjusted independently. The rate [breaths per minute, (BPM)] is altered by changing Ti or Te or both. Continuous flow of fresh air-oxygen mixture enables babies to breath spontaneously between ventilator derived breaths (Intermittent Mandatory Ventilation, IMV).

Mean airway pressure (MAP) is 'the average' pressure at the proximal airway over time,if the inspiratory pressure waveform resembles a square wave. An understanding of the basic pathophysiology of the underlying respiratory disorder is essential to optimize the ventilatory strategy. For example, Respiratory Distress Syndrome is characterized by low compliance and low FRC. The 'time constant' of the respiratory system is proportional to the compliance and the resistance and is a measure of the time necessary for the alveolar pressure to reach 63% of the change in airway pressure. Lungs with decreased compliance (eg, in RDS) have a shorter time constant and hence complete

inflation and deflation occurs faster than normal lungs. Increasing the MAP increases PaO_2 in infants with lung disease. MAP is a function of PIP, PEEP, and Ti. Hence, increasing MAP by increasing PIP increases the driving pressure for gas flow into poorly ventilated lung units. Increasing MAP by increasing Ti allows more time for gas to distribute to these units and increasing MAP by increasing PEEP splints the small airways open, decreases airway resistance, decreases the time constant for inspiration, and allows more gas to enter the lung unit for any given PIP or Ti. All three techniques improve ventilation to the poorly ventilated lung units and increase their PaO_2. However for a given increase in MAP, increasing PEEP or PIP results in a greater increase in PaO_2 than increasing Ti.

Changes in PIP affect both PaO_2 (by altering MAP) and $PaCO_2$ (by its effects on tidal volume and alveolar ventilation). Therefore, an increase in PIP improves oxygenation and decreases $PaCO_2$. A high PIP may however increase the risk of barotrauma with resultant air leaks and chronic lung disease (CLD). A useful clinical indicator of adequate PIP is a gentle chest rise with every breath, though presence of breath sounds is not very helpful in determining optimal PIP. Absent breath sounds however, indicate inadequate PIP (or a blocked and/or displaced ETT or even ventilator malfunction). The minimum possible effective PIP should be used and frequent changes in PIP in the presence of change in pulmonary mechanics are often necessary.

Adequate PEEP helps to prevent alveolar collapse, maintains lung volume at end-expiration, and improves V/Q matching. Increases in PEEP usually increase oxygenation associated with increase in MAP. However, in neonates, a very elevated PEEP (>5-6 cm H_2O) may not improve oxygenation any further and, in fact, may decrease venous return, cardiac

output, and oxygen transport. High level of PEEP also may decrease pulmonary perfusion by increasing pulmonary vascular resistance. While both PIP and PEEP increase MAP and may improve oxygenation, they have opposite effects on $PaCO_2$. With RDS, an improvement in compliance occurs with low levels of PEEP, followed by a worsening of compliance at higher level PEEP (>5-6 cm H_2O). A minimum PEEP of 2-3 cm H_2O atleast is recommended during IMV, since endotracheal intubation eliminates the attempt to maintain FRC by vocal cord adduction and closure of the glottis (grunting) in neonates with RDS.

Changes in frequency (BPM) alter alveolar minute ventilation and, thus, $PaCO_2$. Increases in rate and, therefore in alveolar minute ventilation decrease $PaCO_2$ proportionally, and decreases in rate increase $PaCO_2$. Frequency changes alone usually do not alter MAP nor substantially alter PaO_2. Changes in inspiratory time however that accompany frequency adjustments may change the airway pressure waveform and thus alter MAP and oxygenation. Generally, a high-rate, low-tidal volume strategy is preferred in RDS. A long inspiratory time increases the risk of pneumothorax as it results in alveolar overdistension. There is a higher incidence of pneumothorax in infants ventilated with a long Ti than in those ventilated with a short Ti. As the ventilator rate increases, the absolute time allotted for expiration decreases. If Te decreases to less than three time constants for expiration, gas trapping and alveolar overdistension may occur[1,7,10,11].

The major effect of an increase in the inspiratory-to-expiratory (I/E) ratio is to increase MAP and thus improve oxygenation. However, when corrected for MAP, changes in the I/E ratio are not as effective in increasing oxygenation as are changes in PIP or PEEP. A reversed I/E ratio as high as 4: 1 has been demonstrated to be effective in increasing PaO_2 which however may cause adverse effects of airleaks.

Changes in fraction of inspired oxygen (FiO_2) alter alveolar oxygen pressure and thus

Table 3. Suggested Guidelines for Management of neonates with Respiratory Distress

S.No.	Condition of Infant	Score(Downe's)	Management
1	Severe retractions	>6	Initiate
	Apnea		Mechanical
	Requires O_2>60%		Ventilation with
	Chest X-ray (Extensive lesion)		IMV
2	Spontaneous breathing	>3-6	Initiate CPAP
	Mild-moderate retractions		
	Requires 40%-60% O_2		
	Chest X-ray mild to moderate changes		
3	No retractions	0-3	Initiate O_2 by hood
	Pink in 40% O_2		
	R 40-60 / min		
	X-ray normal to mild abnormality		

oxygenation. Because FiO_2 and MAP determine oxygenation they can be adjusted alternatingly. During increasing support, FiO_2 can be increased till about 0.6-0.7, when further additional increases in MAP are required. During weaning however, FiO_2 needs to be decreased to about 0.4 before reducing MAP. Oxygen-air flow rates of 5-12 L/min are sufficient in most newborns, depending on the mechanical ventilator and ET-tube being used.

Hypercapnia usually is caused by hypoventilation or severe V/Q mismatch. Adequate ventilation is indicated by $PaCO_2$ which is equal to the rate of CO_2 production divided by the alveolar ventilation (VA).The latter is represented by the equation VA = (VT - VD) X RR, (VT- tidal volume, VD- dead space volume, and RR- respiratory rate). Elimination of carbon dioxide from the alveoli is directly proportional to alveolar minute ventilation which is affected by tidal volume. $PaCO_2$ decreases if either RR or VT is increased and $PaCO_2$ increases if RR or VT is decreased. On a pressure-limited ventilator at a constant Ti, the VT is determined by the lung compliance and by PIP and PEEP. $PaCO_2$ can be decreased by increasing RR, by increasing PIP, or by decreasing PEEP.

Ventilation strategy in various newborn disease states

Respiratory failure can result from numerous illness due to varied patho-physiological mechanism. Hence the ventilatory strategy should take into account the pathophysiology and nature/course of the disease.

1. Respiratory Distress Syndrome (Hyaline Membrane Disease) (RDS):

   In RDS there is severe decrease in compliance and stiff lungs. This causes diffuse alveolar collapse and serious V/Q mismatching. Ventilation is needed in severe RDS unresponsive to CPAP requiring high FiO_2 and in babies who tire from the increased work of breathing. The current approach is to use rapid ventilator rates (60-80 breaths/min) while reducing peak pressure (PIP) to a minimum with low inspiratory times (Ti 0.3 to 0.4 secs). The PEEP is kept about 4 to 5cm H_2O. Initial PIP settings are based on auscultation of good breath sounds and observation of good chest wall movements and are increased if required. Usually, weaning is initiated after atleast 48-72 hours by decreasing the pressure first and then rate and then FiO_2. Extubation to head box O_2 or CPAP is done when there is evidence of improvement in lung compliance and decrease in work of breathing with good blood gases achieved through spontaneous breathing. High frequency ventilation is resorted to in case conventional ventilation fails to maintain gas exchange.

2. Meconium Aspiration syndrome: Aspirated meconium causes acute airway obstruction, increased airway resistance, patchy atelectasis with V/Q mismatching and hyperexpansion due to partial airway obstruction with 'ball valve effect'. Ventilatory strategy aims to keep pressures moderate, rates slow and PEEP low (4-5 cm H_2O) so as to prevent pneumothorax and to keep open the partially obstructed airways. Rapid rates can be used if a secondary inflammatory penumonitis develops later. A "hyperventilation" strategy is adopted for babies developing Persistent Pulmonary Hypertension (PPHN) associated with severe MAS. This entails using high rates upto 120 breaths/min with low inspiratory times (0.25 to 0.3 secs) to keep the $PaCO_2$ in the range of 25 to 30mm Hg in order to promote pulmonary vasodilation. Big babies with severe meconium aspiration may require

sedation and paralysis to prevent them "fighting" the ventilator and thereby causing pneumothorax or other air-leaks.

3. Airleaks, Pneumothorax and Pulmonary Interstitial emphysema (PIE): These disorders seriously reduce lung compliance. Hence the ventilatory goal is to reduce airway pressure by reducing peak inspiratory pressure, inspiratory time or PEEP and to give a high FiO_2 to improve oxygenation. This prevents air from being driven into the interstitium with each cycle. Very rapid rates. 80-120 breaths/min may be tried. High frequency ventilation (HFV) is a good alternative to deal with this problem.

4. Apnea due to any cause: Apnea may require ventilatory support if recurrent or prolonged. The aim here is to provide a near physiologic respiration using 30-40 breaths/min, low PEEP (4-5 cm H_2O) and PIP (12-18 cm H_2O). This strategy reduces risk of barotrauma.

5. Severe asphyxia, severe sepsis and shock: The aim in these conditions is to stabilize the respiratory parameters of the neonate through appropriate ventilatory techniques and to prevent hypoxia and acidosis. Rates of 40-60 breaths/min with the least possible pressures (PIP-18-20) are used to maintain adequacy of gas exchange till the neonate's primary problem stabilizes. Increase in pressures, PIP alongwith higher PEEP in the range of 7-9 cm H_2O may be warranted sometimes when the baby's lungs become poorly compliant with features of ARDS.

6. Pulmonary hemorrhage: In acute pulmonary hemorrhage the strategy would be to keep the PEEP as high as possible to the tune of 8-10 cm Hg initially till the active bleeding stops and then gradually bring it down to 6-7 cm H_2O after a few hours. Endotracheal suctioning is to be avoided.

7. Pneumonia: In severe respiratory infections, the decision to ventilate babies is based on the same principles as outlined above. Ventilation strategy is to use the minimal possible pressures to achieve adequate oxygenation as well as ventilation. Short Ti is preferred.

In many conditions other than RDS,e.g. Pneumonias, Meconium Aspiration, Pulmonary hemorrhage etc.,exogenous surfactant replacement can be tried with good results.

Respiratory care strategy in Neonates with Respiratory Distress

A plan, as is followed in our unit, for intervention using routinely available conventional respiratory supports in neonates with respiratory failure is outlined below. Once intubated,initial settings for IMV could be aimed at keeping the ventilator rates about 60 BPM,PIP of about 18-20 cm H_2O,PEEP of 4-5 cm H_2O and Ti of 0.3-0.5 with FiO_2 about the same as what was required during CPAP or oxygen given through hood.It is desirable to hand-ventilate the baby initially to determine the minimal PIP necessary to achieve good chest wall excursion , good bilateral breath sounds and good SaO_2. After recovery from the initial stress of intubation if the infant still requires FiO_2> 0.4 or A/a **ratio < 0.22** and the chest x-ray is compatible with RDS (HMD), exogenous surfactant should be given. We would prefer to give exogenous surfactant even in congenital pneumonias, pulmonary hemorrhage and bad meconium aspirations. Because tiny preterm babies with weight <1250 g., have structurally immature lungs and weak chest walls with poor respiratory drive, it is preferred to routinely provide some form of respiratory support i.e., nasal CPAP or maybe even IMV electively from birth in them. For babies who weigh between 1250 and 1500 g and have RDS, mechanical ventilatory assistance

may also be needed. An optimal conventional ventilation strategy suggested for any condition is by using the lowest PIP possible ,modest PEEP (3-5 cm H_2O), mild permissive hypercapnia (paCO$_2$ 45-60 mm Hg), judicious use of sedation/paralysis, and aggressive weaning. Blended air/oxygen mixture should be delivered warmed and humidified to prevent excessive water loss from the respiratory tract and injury to the lung. The target range for oxygen is SaO_2 of approximately 88% to 96%. Assuming modest permissive hypercapnia is not harmful, the $PaCO_2$ should be approximately 40 to 55 mm Hg in most patients without pulmonary interstitial emphysema, gross air leak, hyperinflation, or chronic changes on chest radiograph. Higher $PaCO_2$ values may be tolerated in patients with these complications. In most patients, arterial pH should be at least 7.25, although pH in the range of 7.20 to 7.25 may be acceptable.At lower pH, the PaO_2 has to be higher to maintain adequate oxygen saturation. Tracheal suctioning and chest physiotherapy should be minimized in infants with RDS in the first few days after birth because secretions are scant, and there is little evidence that suctioning and chest physiotherapy are of benefit as these interventions also might increase the risk of IVH[1]. Suctioning is often associated with acute side effects of hypoxia, hypertension, and bradycardia[1,7]. Using optimal conventional ventilation strategy for neonates with varied problems, and applying similar principles of respiratory care has shown good outcomes, as frequently reported in the Indian literature as well.

Adjuncts to ventilation: During ventilation, sedation can be used to reduce agitation or distress or a tendency to "fight" the ventilator. This may help in better oxygenation[9,10]. Morphine, Lorazepam, Fentanyl and short acting benzodiazepines like Midazolam in a continuous IV infusion have been tried. Muscular paralysis with pancuronium bromide may be indicated in some babies who tend to breathe out of phase with the ventilator and thus "fight" the ventilator. Gas exchange probably is facilitated with the use of muscle relaxation. But this may result in decreased dynamic lung compliance and increased airway resistance and removes any contribution of the infant's own respiratory effort from tidal breathing, often necessitating increase in ventilator pressures.Venous return is also impaired by lack of movement and decreased muscle tone therefore causing generalized edema. Pancuronium seems to have a favourable effect on IVH and airleaks in ventilated preterms with evidence of asynchronous respiratory efforts[12].

Monitoring and supportive care during ventilation: Needless to say, proper ventilatory care demands continuous monitoring of all vital parameters-BP (intra-arterial preferred), arterial blood gases through indwelling arterial catheters, pulse oximetry (to determine SaO_2 continuously), transcutaneous pO_2/pCO_2 and capnography in addition to various biochemical, hematological and microbiological parameters. Supportive therapy is required to minimize the work of breathing,heat losses,and to provide adequate fluids and calories.Good neonatal respiratory and nursing care are the essential tools for improved survival[7,10,11]. Supportive therapy includes the following:

- Temperature regulation: Hypothermia increases oxygen consumption, thereby further compromising infants with respiratory distress,especially who are born prematurely. Therefore prevent hypothermia in infants during delivery, resuscitation, and transport. Care for these infants in a thermo-neutral environment with the use of incubators or radiant warmers.

- Fluids, electrolytes and nutrition: In infants with respiratory distress, initially administer 5% or 10% dextrose intravenously at 60-80 ml/kg/day. Closely monitor blood glucose, electrolytes, calcium, phosphorous,

renal function and hydration (determined by body weight and urine output to prevent any imbalance). Add calcium at birth to the initial intravenous fluid. Start electrolytes as soon as the infant voids and as indicated by electrolytes. Gradually increase the intake of fluid to 120-140 mL/kg/day. Extremely premature infants occasionally may require fluid intake of as much as 180 ml/kg/day. Once the infant is stable, add intravenous nutrition with amino acids and lipid. After the respiratory status is stable, initiate a small volume of gastric feeds (breast milk) via a nasogastric tube to initially stimulate gut development and thereafter to provide nutrition as intravenous nutritional support is being decreased.

- Circulation and anemia: Assess the baby's circulatory status by monitoring heart rate, peripheral perfusion, and blood pressure. Administer blood or volume expanders and use vasopressors (eg. Dopamine) to support circulation. Monitor blood withdrawn for laboratory tests closely in tiny infants and replace the blood by packed cell transfusion when it has reached 10% of the infant's estimated blood volume or if the hematocrit level is less than 40 - 45%.

- Antibiotic administration: Start antibiotics in all infants who present with respiratory distress at birth after obtaining blood cultures and discontinue antibiotics after 3-5 days if blood cultures are negative.

- Support of parents and family: Often parents undergo much emotional and / or financial stress with the birth of a critically ill infant and its associated complications. The parents may feel guilty, be unable to relate to the infant in the intensive care setting, and be anxious about the prognosis for the infant. In addition, the infant may provide inadequate cues to arouse mothering. These factors interact to prevent maternal-infant bonding. Hence, provide adequate support for these parents and other family members to prevent or minimize these problems.

Weaning from ventilation

Weaning newborn infants from mechanical ventilation is an involved process which takes into account a number of physiological, mechanical and pharmacological factors. Infants must exhibit a reliable respiratory drive, display neuromuscular competence and be able to overcome the respiratory system load while maintaining oxygenation and minute ventilation. Close attention to spontaneous tidal volumes and respiratory frequency helps.It is important to ensure proper nutrition status and observe for conditions or complications like infection, neurologic dysfunction, neuromuscular disease,metabolic alkalosis, congestive heart failure and anemia that might impede successful weaning and extubation and may depress spontaneous breathing.

For larger infants, weaning down on rates to 5-10 BPM or short period of ETCPAP may begin when PIP has been stable at less than 16-18 cm H_2O and FiO_2 is less than 0.30 for at least 24 hours and a good respiratory drive has been demonstrated.Later, extubating/depronging to an oxygen hood when the infants require less than 4 cm H_2O of CPAP is done. For infants weighing less than 1750 g, when PIP requirement is less than 13-15 cm H_2O and FiO_2 is less than 0.30, it is possible to decrease the respiratory rate to 15-20 BPM gradually and then to wean directly to nasal CPAP .For this group of infants, the resistance of the endotracheal tube is such that the periods of ETCPAP or ventilatory rates less than 15 BPM cannot be tolerated for long. It would seem likely that nasal CPAP would be most useful for extubation of infants <1750 g[3]. Randomized study has shown that there is no advantage of either method in infants with acute

or chronic respiratory distress. Approximately one-third of its patients required re-intubation within 48 hours of extubation regardless of which extubation method was used[3]. Physiotherapy prior to extubation has been shown in a retrospective and prospective controlled study[3] to reduce postextubation atelectasis.There is no evidence either supporting or refuting the use of inhaled nebulized racemic epinephrine in extubation[13].

Complications of ventilatory therapy

Prolonged orotracheal intubation may cause palatal grooving which may interfere with dentition whereas nasotracheal. intubation may result in cosmetic deformities of the nose and even nasal obstruction. Subglottic stenosis, although rare, can be a disastrous complication of intubation. A too snugly fitting endotracheal tube, duration of intubation, and number of reintubations all correlate with subsequent subglottic stenosis. Necrotizing tracheo-bronchitis, a necrotic inflammatory process involving the trachea and mainstem bronchi has been described in newborns requiring mechanical ventilation. Atelectasis occasionally occurs after extubation from mechanical ventilation, with the right upper lobe most commonly affected[1,7]. Gas trapping during mechanical ventilation may manifest as decreased tidal volume, carbon dioxide retention, and/or lung hyperexpansion. A short expiratory time, a prolonged time constant, or an elevated tidal volume can result in gas trapping. Although PaO_2 may be adequate during gas trapping, venous return to the heart and cardiac output may be impaired; thus, oxygen delivery can be decreased. Acute airleaks of course may cause catastrophic deterioration, intraventricular hemorrhage (IVH) and even risk to life.

Ventilators used in newborn practice

Ventilation is achieved usually by the use of intermittent positive pressure. Several parameters are used to define and classify "positive pressure ventilators". Most classifications are based on the mechanism by which the machine enters its inspiratory phase. 'Negative pressure ventilators' on the other hand provide assisted ventilation without endotracheal intubation, thus avoiding airway trauma and reducing the risk of infection, atelectasis and airleaks. However, the device entails enclosing the baby from the neck down, in a close fitting air tight compartment which makes the patient inaccessible for routine procedures, x-rays, etc. and disallows proper observation.Hence this modality is not in favour currently.

The positive pressure ventilators currently available include

1. Pressure limited time cycled continuous flow ventilators: These are used most frequently in neonatal practice. Examples are Sechrist IV-I 00, Health Dyne 100, Infant Star, Bournes BP 200, Bear Cub, VIP Bird, and Baby bird ventilators. A continuous flow of heated and humidified gas is circulated past the infant's airway. The rate and duration of inspiration(Ti) and expiration(Te) are preselected. Maximum Peak Inspiratory pressure (PIP) and Positive End-Expiratory Pressure (PEEP) can be set according to the babies need. The system is simple to operate and can maintain good control over respiratory pressures. Continuous flow enables successful spontaneous respiratory efforts between ventilator breaths (Intermittent Mandatory Ventilation,IMV). However, there is very poor control over the tidal volume delivered. Recent ventilators have an optional 'patient triggering device' in order to give Synchronised IMV(SIMV) to the baby in phase with the baby's own respiratory effort.

2. Volume Cycled Ventilators: Less frequently used in newborns, as the tidal volumes in infants are small and most of the selected tidal volume is lost in the ventilator circuit or from airleaks around the uncuffed endotracheal tubes. Also, high pressures generated can cause airleaks as there is no control .

3. High Frequency Ventilators: These are of three types: a). High Frequency Oscillators (HFO) b). High Frequency Jet Ventilators (HFJ). C). High Frequency Flow Interrupters (HFFI). These machines deliver extremely rapid rates (300 to 1500 breaths/min, 50 to 250 Hz) with the tidal volume often smaller than 'dead space'. The exact physiology of gas exchange mechanism with these is not well characterized though these machines can achieve adequate ventilation at lower pressure. They are more expensive and complex in their use.

Dozens of neonatal ventilators/modes are available today, each proclaiming to be better. But no one ventilator is really perfect for every type of respiratory pathology.

New ways to ventilate neonates

High Frequency Ventilation(HFV): Three types of HFV are under current use ie. high frequency oscillation (HFO), high frequency jet ventilation (HFJ) and high frequency flow interrupted ventilation (HFFI). High-frequency ventilation (HFV) has evolved to be an established method of treating neonates with respiratory failure. Controversy however remains about when and how HFV should be used. Some use it as a primary mode of ventilation for infants who require ventilatory support, whereas at the other extreme are those who view it strictly as a rescue technique. Others use HFV in an early rescue manner in babies at high risk for complications , or those who have developed air leak, even if they are maintaining adequate gas exchange on conventional ventilation.

The High Frequency Jet Ventilator (HFJV) delivers short pulses of heated and humidified gas at high velocity to the upper airway through a narrow injector lumen in a special 15-mm endotracheal tube adaptor that eliminates the previous need for reintubation with a triple lumen endotracheal tube. Pulses of high-velocity gas stream down the center of the airway, penetrating through the dead-space gas, which simultaneously moves outward along the periphery of the airway. Enhanced molecular diffusion probably plays an important role in the gas exchange occurring in the distal airways and alveoli. The measured airway pressure is used to servocontrol the driving gas pressure and maintain the desired peak inspiratory pressure. When desired, a conventional ventilator used in tandem also provides 'intermittent sigh breaths' in the form of background IMV breaths, typically at a rate of 2 to 10 BPM. The amplitude of the HFJV breaths is determined by the difference between the jet peak inspiratory pressure and the conventional ventilator PEEP.

The High Frequency Oscillatory Ventilator (HFOV) generates a quasi-sinusoidal pressure wave with a diaphragm driven by an electromagnet. By varying the power applied to the magnet, both the excursion of the diaphragm and the frequency at which it moves can be adjusted. The sinusoidal pressure wave that is generated by the diaphragm is transmitted through the airways to the alveoli. The HFOV breaths are characterized primarily by their frequency, amplitude and the MAP. All three of these parameters can be independently adjusted. In addition, the bias flow and I/E ratio can be adjusted.

The High Frequency flow Interrupter (HFFI) is designed around microprocessor controlled

solenoids that open and close at high frequencies. The opening and closing of these solenoids generates a pulse of high velocity gas, which is transmitted down the airways. The pulse of gas also leads to a small recoil in the ventilator circuit that leads to an active expiratory phase.

Physiology of high frequency ventilation: In all three modes of HFV,the volume of individual breaths delivered are near, or even less than the dead-space volume. Additionally, gas exchange partly occurs by 'enhanced molecular diffusion' resulting from increased mixing of gases in the airways. The exact mechanisms by which this high-frequency mixing occurs has been most thoroughly studied with HFOV. The mechanisms which are named, bulk flow, Pendelluft, Taylor-type dispersion, and radial diffusion, are well described. In simple terms, one can think of these small rapid breaths as shaking the gas in the airways and the alveoli, causing extremely efficient mixing between the fresh gas delivered to the upper airway and the gas at the alveolar surface.

High-frequency ventilators, help improve both oxygenation and ventilation. Increasing MAP with any HFV results in improved oxygenation. The relationship between ventilation (CO_2 removal) and ventilator settings is more complex for HFV than it is for conventional ventilation. With conventional ventilation, CO_2 removal is proportional to alveolar minute ventilation . With HFV however, CO_2 is removed largely by the extremely efficient mixing of gas in the airways, also referred to as enhanced diffusion. An important difference between HFV devices and conventional ventilators is the relationship between the pressure amplitude measured at the hub of the endotracheal tube and the pressure amplitude that is delivered to the alveoli. With conventional ventilation, pressure applied at the airway opening is fully transmitted from the upper airway to the alveoli. As rates increase with a proportional decrease in inspiratory and expiratory time, there is insufficient time within the respiratory cycle for the pressure to equilibrate fully, leading to gas trapping or 'inadvertent PEEP'. With HFV, gas exchange occurs predominantly by enhanced diffusion and the pressure amplitude or volume delivered to the alveoli is significantly less than the amplitude measured at the airway opening. The optimal range of frequencies selected for HFV is dependent on both the size of the patient and the patient's intrinsic lung mechanics. In general, the smaller the baby, the higher the optimal frequency, and vice versa. Short time constant situations with poor compliance like in RDS can be ventilated effectively at higher frequencies than those with longer time constants.There is no simple way to calculate ideal HFV frequency for each individual patient,and is based on clinical experience .

Ventilatory strategies of high frequency ventilation

The greatest advantage HFV offers is the ability to achieve uniform lung expansion and to support a patient at higher mean airway pressures without excessive tissue stretching and overexpansion.

Initial settings on the HFOV could have mean airway pressure at least 2 cm H_2O greater than the MAP the patient was receiving on conventional ventilation, frequency of 8 to 10 Hz,and amplitude (AP) adjusted based on adequacy of chest wall movement or improvement in transcutaneous PCO_2 monitored. The PEEP is increased to the range of 6 to 8 cm H_2O, depending on the degree of atelectasis and oxygen requirement.Inadequate PEEP has affected effectiveness of HFV in RDS. HFV allows use of higher mean and end-expiratory pressure safely, because of the lower AP. Background IMV at a rate of two to ten breaths

per minute is initiated with an inspiratory time of 0.4 to 0.5 seconds. The PIP is initially maintained at the original value on both the HFV and conventional ventilation to achieve alveolar recruitment. Within a few minutes on HFV, however, the improved lung expansion commonly results in better lung compliance. If this occurs, the PIP should be lowered promptly by 10% to 20% to avoid overventilation. Further weaning of PIP should be guided by adequacy of chest wall movement or transcutaneous PCO_2 monitoring.

Because optimizing lung inflation is a key part of the strategy of HFV, patients on HFV usually need fairly frequent chest radiographs. The magnitude of mean airway pressure adjustment should be proportional to the degree of underinflation or overinflation. At a given frequency, $PaCO_2$ is primarily determined by HFV amplitude. Once a frequency appropriate for the infant's size and clinical condition is chosen, changes in frequency should only be done if there is reason to believe that the time constants/compliance have changed. Adjustment of amplitude are helped through seeing adequacy of chest wall movement or transcutaneous PCO_2 monitoring, in addition to blood gases. Once stable, weaning should be attempted on a regular basis though it is important to avoid causing sudden atelectasis by dropping MAP below the critical closing pressure of the lungs. The FiO_2 should be weaned first in response to good oxygenation. In most cases, MAP should not be weaned until the FiO_2 is less than 0.4. Inadvertent drop in MAP can be avoided by simultaneously increasing the PEEP as needed .

After consideration of all initial trials, it seems reasonable to conclude that HFV should not be used for the initial treatment of neonates with any respiratory failure.Meta-analysis data does confirm this as well[14]. In preterms managed with exogenous surfactant; there is no conclusive evidence that HFV reduces the incidence of CLD, and there is certainly no evidence that it affects the mortality of infants with RDS. Should conventional ventilation and surfactant fail, however, HFV is a reasonable form of rescue therapy.

Patient-Triggered Ventilation (PTV)

It is well documented that neonates do frequently make spontaneous breathing movements while being mechanically ventilated. Those who actively expire against positive pressure inflations develop pneumothoraces, Such asynchrony may reduce the effectiveness of the ventilator, increase the work of breathing, and enhance the risk of barovolutrauma to the lung. It can also accentuate the negative cardiovascular effects of positive pressure ventilation[15]. In contrast,blood gases improved in those who breathed synchronously with their ventilator (i.e., the beginning of inspiration coincided with the onset of each positive pressure inflation [synchronized ventilation). Synchronization could be achieved by increasing the ventilator rate to match the baby's respiration pattern or by reducing the inspiration time though this is not always successful. An alternative method to achieve synchronization is to use the infant's own respiratory efforts to trigger the delivery of positive pressure inflations such that they arrive at a defined point in the infant's respiratory cycle (Patient-Triggered Ventilation, [PTV]).

Triggering devices used for PTV: The triggering device senses the infant's respiratory efforts and the signal from the triggering device is then fed to the ventilator such that it triggers a positive pressure inflation. The signal from a 'Graseby respiration monitor', which detected the neonate's respiratory efforts by changes in abdominal movement triggering a neonatal pressure capsule,was first used as a trigger device. The signal from the pneumatic capsule has also been used to trigger ventilator breaths delivered

by nasopharyngeal prongs. Other triggering devices are now used ; most of these sense changes in airflow or airway pressure during inspiration. This technology achieves a greater degree of synchrony between the infant's breathing and the ventilator, and this may improve oxygenation if the infant's breathing was previously asynchronous.

Patient- triggered ventilation (PTV) is used in two modes: (1) In Synchronized Intermittent Mandatory Ventilation (SIMV), a single triggered breath is given in equal windows of time, with the other patient breaths in each window not assisted; this means that the rate can be slowly reduced during weaning with all assisted breaths well synchronized. (2) In Assist/Control Mode (A/C), all breaths are triggered, so that the baby controls the ventilator rate, and weaning is accomplished by reducing the PIP gradually. A number of different advantages to these systems have been suggested, but perhaps the most promising is a reduction in cerebral blood flow variability.The major benefit of PTV is that weaning from the ventilator is facilitated.).

Nasal Ventilation

The evidence for the use of IPPV, SIMV, or HFOV delivered by 'nasal prongs' is yet inconclusive and it is not possible to conclude that these modes are useful. Randomised trials comparing nasal IPPV and nasal CPAP for apnoea of prematurity have yielded conflicting results. Data from meta-analysis showed no difference in carbon dioxide levels after four to six hours of support, and trials did not report on gastrointestinal complications[15], although an association between the use of ventilation through nasal prongs and increased risk of gastro-intestinal perforation had been previously noted.

Conclusion

The rationale to use any form of assisted ventilation should be to optimise patient-

ventilator synchronisation, improve patient comfort, facilitate or reduce the duration of ventilation, and avoid undesirable respiratory/cardiovascular consequences. Newer ventilation modes should only be introduced into routine practice when proved efficacious in appropriately designed studies and no adverse outcomes have been identified by long term follow up. It is important to realise that improper and unwarranted use of ventilators can be detrimental to sick babies and ventilators if used promiscuously can be worse than the disease. It is essential to hence entrust ventilatory care to the experienced and knowledgeable.

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NEWS AND NOTES

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Date: 25th and 26th February 2006

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$$\boxed{\textbf{NEONATOLOGY}}$$

FEEDING THE LOW BIRTH WEIGHT BABY

Sheila Samanta Mathai

Abstract: Feeding the Low Birth Weight (LBW) baby is a nutritional challenge. Breast milk feeds should be started as soon as possible after birth. In babies more than 1500 grams full feeds should be achieved in 5 days. In smaller, stable babies trophic feeds with expressed breast milk (EBM) should be started from day 1 along with IVF for 3-4 days, followed by advancing feeds.Full feeds should be reached in 2 weeks. Feeds are given by paladai, cup or feeding tube 2-3 hourly. Babies less than 1200 grams, unstable babies and sick babies need early total or partial parenteral nutrition but even in these babies trophic feeds with EBM are recommended. LBW babies need human milk with supplementation of proteins, minerals and vitamins till they attain 3 Kg in preterms and 2 Kg in severely growth retarded babies. Iron should be added at 2-4 weeks in preterms. Supplementation is done either by Human Milk Fortifiers (HMF) or individual supplements when feeds reach 100 ml/Kg. Close monitoring of growth is essential to prevent long term malnutrition.

Key words: Low Birth Weight (LBW), Expressed Breast milk (EBM), trophic feeds, Human Milk Fortifiers (HMF), supplementation

Low birth weight (LBW) babies, or those weighing less than 2500grams at birth, constitute approximately 30-33 % of all live births in India.

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11% of all babies weigh less than 2000 grams and 3.7% weigh less than 1500 grams at birth[1]. More than half of these newborns are born full term. Out of an estimated 18 million low birth weight babies born worldwide annually, India accounts for about 7-8 million. This large group of high-risk babies constitutes a major drain on the national resources due to both immediate neonatal problems and long-term implications like chronic malnutrition, recurrent infections and neurodevelopmental delay. Although low birth weight babies constitute only about 14% of all babies born worldwide, they account for 60-80% of all neonatal deaths[2].

The goal of nutritional management of the low birth weight baby is to provide optimal nutrients for continued, adequate ex–utero growth without stressing the metabolic or excretory function of the infant. This apparently simple aim is notoriously difficult to achieve. Varied causes of low birth weight place these neonates in distinct categories, each with its own inherent risks for nutritional inadequacies. The preterm baby is vulnerable due to poor suck-swallow coordination, small gastric capacity, incompetent gastro-esophageal sphincter, decreased activity of lactases, lipases and other enzymes and immaturity of various metabolic and excretory pathways[3]. The growth-retarded baby, on the other hand, is particularly prone to feed intolerance, necrotizing enterocolitis and micronutrient deficiencies[4]. In addition, a high incidence of early neonatal illnesses in all categories of low birth weight babies with difficulty in reaching full feeds quickly make them particularly prone to nutritional problems.

Table 1. Nutrient requirements and need for supplementation in preterm babies fed human milk[5,6,10]

Nutrient	Breastmilk	Recommended	Supplement
Protein	1.1 g/dL	2.7-3.7 g/kg/day	Only if BM<180ml/kg
Fat	4.5 g/dL	4.5 g/kg/day	No
Carbohydrate	7.1 g/dL	8-19gm/kg /day	No
Calcium	33 mg/dL	120 mg/kg/day	66 mg/kg/day
Phosphorus	15 mg/dL	90 mg/kg/day	30 mg/kg/day
Iron	0.3 mg/dL	2 mg/kg/day	2.5 mg/kg/day
Zinc	0.18-0.5 mg/dL	1 mg/kg/day	0.5 mg/kg/day
Sodium	0.8 mEq/dL	2-3 mEq/kg/day	1-2mEq/kg/day
Potassium	1.4 mEq/dL	2-3 mEq/kg/day	No
Chloride	1.1 mEq/dL	2-3 mEq/kg/day	No
Vitamin A	50 IU/dL	600 IU/kg/day	500 IU/kg/day
Vitamin D	8 IU/dL	400 IU/kg/day	400 IU/kg/day
Vitamin E	5 IU/dL	6 IU/kg/day	No
Folate	5 µg/dL	25 µg/day	20 µg/day
Calories	67 cal/100 ml	Max 165cal/kg/day	If BM<180 ml/kg/day
Fluid		Max 200 ml/kg/day	No

What are the dietary requirements of the LBW baby?

Sources of recommendations for the nutritional requirements of preterm babies include the American Academy of Pediatrics (AAP) and European Society for Pediatric Gastroenterology and Nutrition (ESPGAN)[4,5,6]. The requirements shown in the table (Table 1) are for preterm babies but can be used for any baby less than 2 kg. Thereafter term LBW babies would need the same nutrition as normal, term neonates.

What is the ideal milk for the low birth weight baby?

It is unanimously agreed upon that human milk is the ideal nutrition for the first six months of life for normal growth and development of the healthy, term infant[4,7]. Besides the nutritional advantages, there are numerous non-nutritional benefits like protection from infections, improved gastrointestinal function and better long-term neurodevelopment[8]. However the optimum nutrition for premature infants is less well defined. The AAP has acknowledged that human milk is beneficial to the premature infant. Breast-feeding is associated with a lower mortality than artificial feeds even in LBW babies[9,10]. But whether or not unsupplemented human milk can maintain accretion and growth rates comparable to those seen in–utero in the preterm, is debatable.

Preterm milk maintains a composition similar to that of colostrum (higher in protein, nitrogen, sodium and calories as compared to term milk) especially during the first month after parturition. The transition from colostrum to

mature milk proceeds much more slowly after premature delivery. Preterm milk also has a higher concentration of magnesium, iron, copper, zinc, vitamin A and secretory IgA[4]. The higher IgA content protects against intestinal infections. Preterms fed human milk manifest a lesser imbalance in plasma concentrations of aminoacids like phenylalanine, tyrosine and methionine compared to infants fed casein-dominant milk. Very long chain fatty acids found in human and not in bovine milk have been functionally associated with better cognition, growth and visual function. Preterms have better absorption of fat from human milk because of the large number of lipases present, which makes up for their immature pancreatic functions. The Vitamin E to Poly Unsaturated Fatty Acid (PUFA) ratio in preterm human milk is 0.9mg/g, which is adequate for Vitamin E absorbtion, and hence Vitamin E supplementation may not be required in those preterms fed human milk. Preterms absorb more than 90% of the lactose in human milk and the excess lactose in the gut results in a unique bacterial flora, softer stool consistency and improved absorption of minerals[11].

Even at maximum levels of feeding (200ml/kg/day) the calcium and phosphorus in human milk represent only 25% of the amount thought to be required for normal bone mineralisation[5,6]. The recognition that growth and nutrient deficits of preterms can be improved with the use of nutrient supplements has led to enthusiasm in the use of human milk fortifiers for these infants[12]. Fortification, or adding of extra nutrients, (either as single or multi-nutrient fortifier) to breast milk is different from supplementation where these extra nutrients are given in addition to and in-between feeds. Single or multi-nutrient supplementation of human milk has been associated with improvement in short-term growth and nutritional status. Balanced study data demonstrate that the use of fortified

human milk results in net nutrient retention that approaches or is greater than intrauterine rates of accretion[13]. Fat absorption, however, has been lower than expected. A greater fat absorption is reported with human milk fortifiers containing lower quantities of minerals. No fortifier to date has adequate iron and hence iron supplementation is required. Considering the advantages of breast milk most advisory bodies (AAP, CPS, ESPGAN) have opined that fortified breast milk is the recommended food for the preterm babies. It has been shown that the preterms fed fortified human milk have a shorter hospitalization as a result of better health than infants fed preterm formula[12]. As it stands today, the general recommendation is that fortification be started when the milk intake in a preterm baby of less than 1800 grams reaches 100ml/Kg and be continued till a weight of at least 1800 grams is attained. However, it is essential that the infant receives at least 180-200ml/kg/day of human milk. There after individual supplements are added till 3-4 kgs weight is attained.

Fortification may seem the ideal solution to preterm nutrition but it is not without its shortcomings. A major concern with Human milk fortifier (HMF) is whether the added nutrients affect human milk's complex system of host defense and immune functions. However, analysis of large, prospective multi-center studies have shown no significant increase in confirmed infections and necrotizing enterocolitis (NEC) in the group fed fortified human milk as compared to that fed partially supplemented human milk[13]. Also, fortification has not been found to affect the concentration of secretory IgA content of human milk. When fortified human milk was evaluated under simulated nursery conditions, bacterial colony counts were not significantly different after 20 hours of storage at refrigerator temperature but did increase from 20 to 24 hours when maintained at incubator temperature[13]. The process of adding multi-component HMF (bovine

derived) to the physiologically stable breast milk has shown to result in poorer absorption of fat. Human milk fat digestion and absorption are facilitated by the structure of the fat globules, the presence of lipases and the pattern of fatty acids. The addition of large quantities of minerals to human milk may create an unfavorable milieu for human milk lipid absorption. Fortification of human milk has not been found to significantly influence gastric emptying time[14].

How is fortification of human milk done?

Human Milk Fortifier, available in sachets in a powdered form, is added to EBM (2 grams in 50 ml), which can be kept for upto 4 hours at room temperature. Alternately the sachet is divided into smaller aliquots and added to the quantity of milk expressed for a particular feed.

When should feeds be started in the low birth weight baby?

Early enteral feeding with breast milk has been found to be protective against necrotizing enterocolitis and gastrointestinal infections[15,16]. Stable LBW babies weighing more than 1500 grams should be fed as soon as possible after birth, preferably within 30 minutes at which time extrauterine adaptation should be complete. However, they should be given special care to ensure feed acceptance. Since LBW babies have very little energy stores, even short durations of starvation should be avoided. These babies may not demand feeds like term neonates and hence need to be given scheduled feeds every 2 hours. Very low birth weight babies (VLBW) babies less than 1500 grams have to be managed differently. If they are between 1200-1500 grams and stable, they may be started on trophic feeds from day 1 along with IV fluids. If less than 1200 grams it is advisable to start on IV fluids for the first 48 to 72 hours and thereafter commence total parenteral nutrition or trophic feeds depending on the condition of the baby (Fig. 1).

What are trophic feeds?

Small EBM feeds at 10-20 ml/kg/day given every 2-6 hours to stimulate gastric maturity and function are known as trophic feeds or Minimal Enteral Nutrition (MEN). These have been found to improve feed tolerance and shorten the time to attain full feeds and decrease incidence of necrotizing enterocolitis and hospital stay[17]. This has also been shown to improve lactase activity[18]. It is not advisable to give formula as trophic feeds.

How should the LBW baby be fed?

Feeding can be divided into the transitional phase (less than 1 week), growing phase and post discharge phase. Most LBW babies regain their birth weight by 14-21 days. Thereafter, a weight gain of 10-15gms/kg/day is expected. LBW babies generally need 150-175 ml/Kg/day by the end of the first week. During the transition phase this can be given by tube feeds for babies   less than 1500 grams and by cup or paladai for bigger babies. Thereafter feeds are given either directly from the breast for bigger babies (more than 1500 grams) or by cup and spoon or "paladai" for smaller, more fragile preterms (1200-1500 grams). For this latter group, during the growing phase few tube feeds daily are preferable so as to ensure a definite amount of feed. Check for gastric residues and feed intolerance and decrease energy expenditure. Cup feeding has not been shown to have adverse effects on physiological parameters and may be used in place of a paladai if the mother is more comfortable with it. However one should ensure that the rim of the cup is thick, rounded and smooth and the size is appropriate to the size of the baby's face[19]. Babies less than 1200 grams who are well enough to be started on feeds, usually tolerate tube feeds only and should not be compelled to accept feeds in
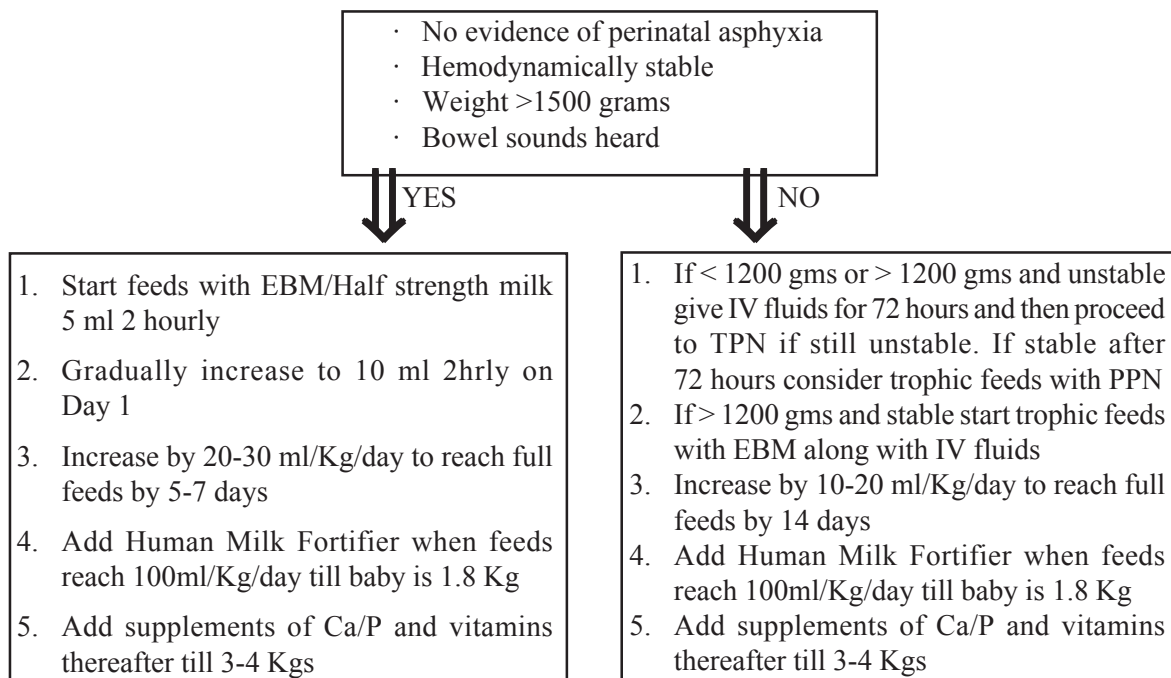
> - No evidence of perinatal asphyxia
> - Hemodynamically stable
> - Weight >1500 grams
> - Bowel sounds heard

YES ⬇

1. Start feeds with EBM/Half strength milk 5 ml 2 hourly
2. Gradually increase to 10 ml 2hrly on Day 1
3. Increase by 20-30 ml/Kg/day to reach full feeds by 5-7 days
4. Add Human Milk Fortifier when feeds reach 100ml/Kg/day till baby is 1.8 Kg
5. Add supplements of Ca/P and vitamins thereafter till 3-4 Kgs

NO ⬇

1. If < 1200 gms or > 1200 gms and unstable give IV fluids for 72 hours and then proceed to TPN if still unstable. If stable after 72 hours consider trophic feeds with PPN
2. If > 1200 gms and stable start trophic feeds with EBM along with IV fluids
3. Increase by 10-20 ml/Kg/day to reach full feeds by 14 days
4. Add Human Milk Fortifier when feeds reach 100ml/Kg/day till baby is 1.8 Kg
5. Add supplements of Ca/P and vitamins thereafter till 3-4 Kgs

Fig 1. Algorithm for starting feeds in low birth weight babies

any other form. However, non-nutritive sucking is recommended even for these babies so that the orofacial and gastric reflex maturity is enhanced[4].

What are the problems associated with feeding?

Feed intolerance, increased gastric residues, gastroesophageal reflux, hypoglycaemia and failure to gain weight are some of the common problems encountered during enteral feeding of the well, LBW baby. A weight gain of < 10 g/day is a cause for concern and one should look for inadequate intake, easy fatigability during feeding, cold stress, anemia or infection as a cause. Initially some well LBW babies may exhibit unexplainable feed intolerance and may need reduction of the feeds and supplementation with IV fluids for a short time. Low-dose (6-12mg/kg/day) oral rrythromycin, which has a promotility action and decreased gastric emptying time has been shown to improve feed tolerance in such babies[20].

How should adequacy of nutrition be monitored?

Daily weight gain, weekly length, hematocrit estimation and biochemical tests for early diagnosis of osteopenia of prematurity are a must. Even after discharge LBW babies should be called weekly for follow-up for at least three visits to ensure that adequate weight gain is continuing at home. Human milk fortifiers if used should be stopped when the baby reaches 1800 grams of weight and calcium and phosphorous supplementation should be continued till 3 months or till the baby reaches a weight of 3 kgs. Prophylactic iron supplements at 4 mg/Kg/day of elemental iron should be started at 4 weeks of age in all stable preterms who do not have evidence of infection.

Key Messages

1. *LBW babies need to be put on breast milk as soon as possible after birth.*

2. *Those requiring IVF or PPN should also be given trophic feeds.*

3. *Supplementation in the form of HMF or individual supplements of protein, minerals and vitamins is recommended for preterms and severely growth retarded babies.*

4. *Monitoring of growth is essential on follow-up.*

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NEONATOLOGY

FETAL ORIGINS OF ADULT DISEASE – IMPLICATIONS FOR THE 21ST CENTURY

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Abstract: The incidence of metabolic syndrome, type II diabetes and cardiovascular disease is increasing both in the developed and developing countries. This has imposed an economical burden on society and led to intensive efforts in detection and treatment of these diseases. While the cause of this phenomenon is likely to be multi-factorial, evidence is accumulating that adaptive responses made by the fetus in-utero to malnutrition can result in increased susceptibility to adult onset diseases, - the fetal origins hypothesis. A better understanding of fetal programming is essential to initiate efforts aimed at prevention of fetal growth restriction and subsequent adult onset cardiovascular disease.

Key words: *Fetal programming, metabolic syndrome, malnutrition*

The incidence of the metabolic syndrome is reaching epidemic proportions in Europe and United States and has the potential to rise alarmingly in developing nations in the coming decades. Defined as a combination of three of the following five disorders: rising blood pressure, central adiposity, raised serum triglycerides, lowered serum HDL cholesterol and fasting hyperglycemia[1], this syndrome may progress to type 2 diabetes mellitus and cardiovascular disease. While this phenomenon is multi-factorial, Dr. Barker and his associates at the Medical Research Council's Epidemiology Unit at Southampton, England have proposed the concept of fetal and early developmental programming as being important in the development of cardiovascular diseases in the adult. In this article we shall outline the Barker's hypothesis[2], present evidence for fetal programming from epidemiological and animal studies, discuss mechanisms which underlie fetal programming and explore its clinical implications for neonatologists and pediatricians.

The fetal origins hypothesis: Barker and colleagues proposed that fetal undernutrition in middle to late gestation leading to disproportionate fetal growth is associated with hypertension, insulin resistance and dyslipidemia in later life[2]. While it is easy to conceive that injury to fetus can cause long-term harm (eg. teratogens), the fact that fetal adaptive responses to malnutrition can result in increased susceptibility to adult-onset disease suggests that modulation of the genetic milieu in-utero is important in evolution of human disease. Fetuses exposed to malnutrition in-utero, make adaptive responses to maximize fuel uptake and conserve available nutrients. Such mechanisms established in utero while giving the fetus a survival advantage in the womb might program susceptibility to adult onset diseases. "Programming" encompasses any stimulus or insult in the developing organism which results in permanent long-term adaptive responses.

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Epidemiological evidence for fetal origin hypothesis: Most investigators have focused on the relationship between birth-weight and adult disease by studying large cohorts of people in geographically localized areas. Leon et al[3] studied a cohort of 14611 babies born in Uppsala Academic Hospital, Sweden between 1915 and 1929 and followed up till the year 1995. Cardiovascular disease showed a significant inverse relationship with low-birthweight both in men and women. In comparison to men with the lowest birth-weight quartile for gestational age, mortality from cardiovascular disease in the second, third and fourth quartile was 0.81 (0.66-0.98), 0.63 (0.50-0.78) and 0.67 (0.54-0.82), clearly demonstrating the association with fetal growth and adult cardiovascular disease. Barker et al[4] studied the relationship between adult hypertension and low birth-weight in 449 men and women from Lancashire. They could demonstrate a 11mm decrease in systolic blood pressure as birth-weight increased from less than 5.5 pounds to greater than 7.5 pounds. The highest blood pressure occurred in small babies with large placentas. They postulated that the discordance in the placental and fetal size resulted in circulatory adaptation in the fetus which programmed hypertension in adults. Hales and Barker[5,6] studied a cohort of around 400 men born in Herfordshire between 1920-1930 into late adulthood and established clear associations between metabolic syndrome, type II diabetes and a low birth-weight (Figs 1a and 1b). Other investigators have linked birth weight to development of dyslipidemia and obesity.

The impact of poor maternal nutrition leading to low birth-weight and subsequent adulthood disease have been established by studying large cohorts of women who were exposed to famine and starvation during pregnancy. During the Dutch famine (1944-1945) malnutrition was rampant and pregnant women had an average daily caloric intake of only 500-800 calories. Exposure to starvation in late gestation was associated with adult obesity and glucose intolerance in infants and exposure in early gestation was associated with hypertension[7,8]. Smaller babies from this cohort (especially females) faced a higher risk of adult onset diabetes. Similar studies undertaken in other disadvantaged populations in the USA, Caribbean, India and Australia have identified similar association between maternal malnutrition and adult disease in their infants. Hales and Barker et al[5] have proposed the "thrifty phenotype hypothesis" to explain the association between low birth-weight and adult type II diabetes. They postulated that fetal malnutrition resulted in a decrease of the insulin secreting B-cell mass and function in the pancreas and also insulin resistance. When such individuals with a small phenotype are exposed to abundance of calories, their decreased B-cell function and insulin resistance would result in type II diabetes and the metabolic syndrome. During the Leningrad siege (World War II), conditions similar to the Dutch famine existed but birth-weight was not correlated with impaired adult glucose homeostasis[9]. The important difference between the two populations was that in Leningrad, nutritional status did not improve even after the war so that children continued to be malnourished. This suggests that catch-up growth in childhood against a background of fetal malnutrition is essential for development for adult onset diseases. While data from epidemiological studies clearly show that components of the metabolic syndrome can be programmed in-utero, use of animal models are essential for understanding the nature, duration and timing of insults to the fetus which programs adult diseases.

Animal studies: As animals typically have a shorter life span and can be used in experiments
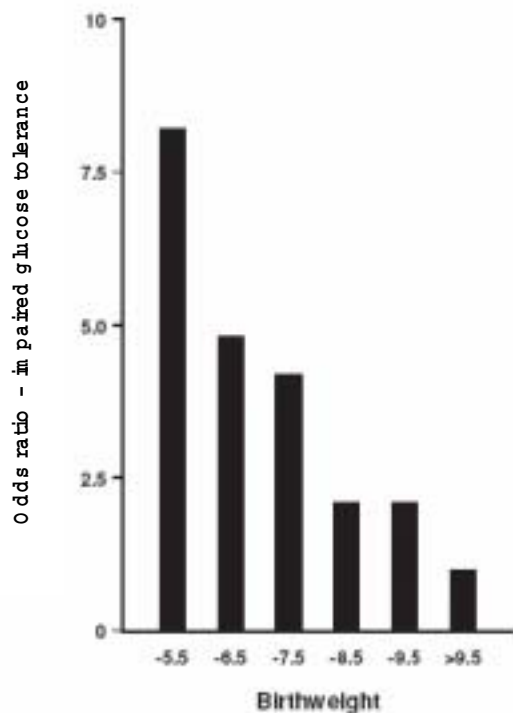
Odds ratio for impaired glucose tolerance or type 2 diabetes according to birth weight (lbs) among 370 men aged 64 years born in Hertfordshire (adjusted for adult body mass index).(5)
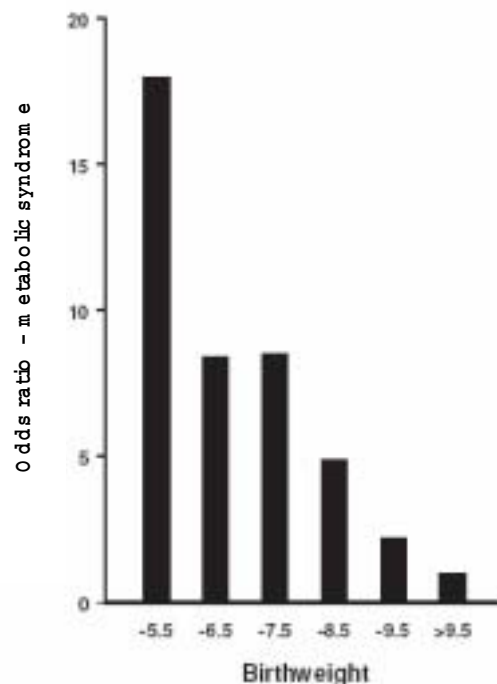
Odds ratio for the metabolic syndrome according to birth weight (lbs) among 407 men born in Hertfordshire (adjusted for adult body mass index). (6)

Fig 1. Association between birth-weight and (a) impaired glucose tolerance, (b) metabolic syndrome.

where their genetic and environmental influences can be manipulated, animal models have emerged as powerful tools to study various components of the metabolic syndrome. While studies in animals may not reproduce accurately the patterns of disease observed in humans, it is remarkable how phenotypes observed in animals closely mimic the human metabolic syndrome. Caloric or protein restriction in animals mimics conditions existing in many developing countries and underprivileged members of western societies and can help in studying the effects of fetal programming. In this review, data from restriction models and also models using high fat or cholesterol diets in pregnant rodents will be presented.

Maternal dietary challenge and insulin resistance: Garofano et al[10] used restricted calorie intake in pregnant rats to 50% ad lib and measured beta-cell mass and glucose tolerance in offspring. They also studied the effect of postnatal malnutrition by comparing control animals with animals that had been malnourished during fetal life only and with animals who had been malnourished during fetal life and early postnatal life. When compared to controls, rats who had

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┌─────────────────────────────┐
│     Maternal malnutrition    │
└─────────────────────────────┘
              │
              ▼
   ┌──────────────────────┐
   │   Fetal malnutrition  │
   └──────────────────────┘
              │
              ▼
┌──────────────────────────────────────────────────────────────┐
│ Diversion of fuels away from liver, pancreas, kidneys,         │
│ skeletal tissue to brain                                       │
└──────────────────────────────────────────────────────────────┘
              │
              ▼
      ┌──────────────────────┐
      │ Fetal growth restriction │
      └──────────────────────┘
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| ↓ Renal mass & ↑ RAS | ↓ Islet cell mass & function | ↓Skeletal & liver tissue |

Nutritional divergence after fetal life

| Hypertension | ↓Insulin secretion | ↑ Insulin resistance and dyslipidaemia |

Metabolic syndrome
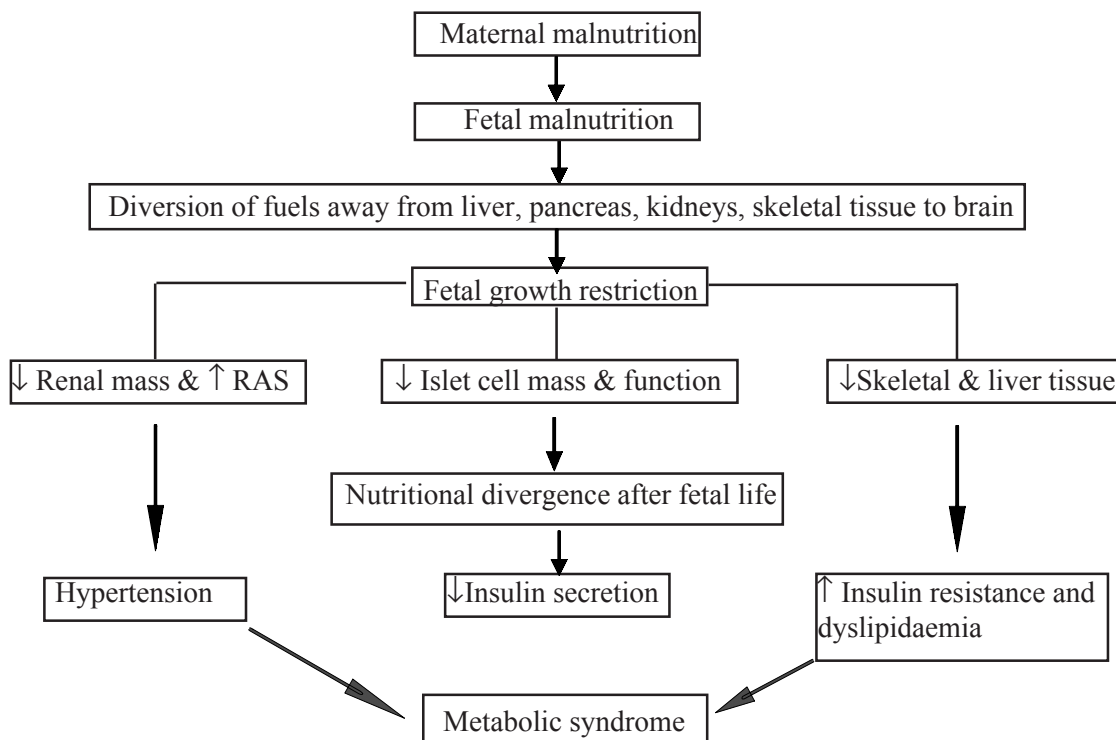
Fig 2. Biological mechanisms underlying fetal programming of adult onset diseases.

been malnourished in fetal life had borderline glucose tolerance and slightly decreased beta cell mass. Rats exposed to both fetal malnutrition and early postnatal malnutrition had a 50% reduction in beta cell mass and profound insulinopenia and abnormal glucose tolerance. These experiments and others clearly demonstrate that protein and or caloric restriction during pregnancy can predispose offspring to impaired glucose tolerance, insulin resistance and decreased beta cell mass. During periods of maternal malnutrition the fetus diverts nutrients to critical organs like the brain at the expense of the liver and pancreas leading to possible permanent structural and enzymatic changes. A reduction in beta cell mass, decreased mitochondria copy number in the islet cells, decreased glucokinase expression and increased insulin resistance have

been demonstrated in rats as a result of fetal programming caused by dietary imbalances. These changes can persist to adulthood and lead to development of type II diabetes in adults.

Maternal malnutrition and blood pressure in infants: Increased blood pressure is an important component of the metabolic syndrome and studies in rats clearly demonstrate the effect of maternal malnutrition and blood pressure in offspring. Vehaskari et al[11] restricted pregnant rats to a 6% protein diet and measured blood pressure in the offspring. By 8 weeks of age, both male and female offspring had a 20-25 mm increase in systolic blood pressure and by 18 months of age survival was significantly decreased compared to controls. They could also demonstrate a 30% decrease in glomeruli in the

kidney by 8 weeks of age which could possibly contribute to the hypertension. Ozaki et al[12] used a calorie restriction model and could demonstrate increases in mean blood pressure in both male and female offspring though the effect was seen earlier in males.

Maternal malnutrition, central obesity and dyslipidaemia: In rat models of maternal dietary imbalance, offspring obesity is not a consistent feature suggesting that maternal malnutrition alone is not enough to induce central adiposity if postnatal nutrition is normal. However Ozanne et al[13] have demonstrated increased body weight in offspring of protein restricted mice fed a high carbohydrate diet. Similar studies have shown that increased adiposity in offspring is inducible only with a calorie rich or high fat diet. Dyslipidemia, characterized by increased triglyceride and low-density lipoprotein level and decreased high-density lipoprotein levels is central to the diagnosis of metabolic syndrome. Studies of maternal nutritional restriction in rats and guinea-pigs have not demonstrated increased triglyceride or cholesterol levels in offspring. Ghosh et al[14] observed lowered HDL cholesterol and increased triglyceride concentrations in 160-day-old offspring of dams fed a lard rich diet during pregnancy and suckling. This suggests that fetal or postnatal nutritional excess and not fetal malnutrition programs dyslipidemia.

In summary, data from animal models show that abnormal insulin/glucose homeostasis is programmed by in-utero dietary restriction. With regards to hypertension most studies suggest that this can be programmed in-utero too, though not always. The data with regards to dyslipidemia and central obesity is not conclusive, though rats may not be the best model and vigorous studies have not been done using other animal models.

Biological mechanisms underlying fetal programming: The effects of fetal programming

can best be understood by understanding the phenomena of "phenotypic plasticity",[15] "metabolic imprinting"[16] and "nutritional divergence" after birth. Metabolic imprinting encompasses adaptive responses made by an organism during critical ontogenic window early in life in response to specific nutritional conditions which can result in persistent effects lasting through adulthood. Phenotypic plasticity refers to the phenomenon whereby one genotype gives rise to a range of physiological and morphological states in response to different environmental conditions during development. During critical periods of development it appears that genotypic expression can be influenced permanently by adaptive metabolic responses resulting in a specific phenotype. Nutritional divergence occurs when there is disparity between the nutrition of the fetus and nutrition of the more mature organism. When nutritional divergence is outside the predictive adaptive response of the organism, disease results as the more mature organism loses the ability to alter genotypic expression to adapt to newer conditions.

Thus in the fetus, malnutrition results in decreased B-cell mass or islet function in the pancreas. This results in decreased fetal growth, smaller skeletal mass, smaller liver and kidneys. After birth, if such fetuses are exposed to prolonged periods of excessive nutrition insulin resistance, decreased insulin secretion, hypertension and dyslipidemia result. (Fig 2).

Neonatal perspectives: The fetal origins hypothesis has raised many questions and poses many challenges for neonatologists and pediatricians. Nutritional strategies adopted in the NICU are often inadequate, as many of premature infants are discharged home as SGA infants. Evidence is emerging that these infants develop components of the metabolic syndrome early in life. Hofman et al[17] studied premature infants with

gestational age less than 32 weeks between the ages 4-10 years and showed that insulin sensitivity was decreased when compared with term controls. Arends et al[18] demonstrated an almost 60% reduction in insulin sensitivity and increased systolic blood pressure in short prepubertal children born small for gestational age when compared to age-matched AGA controls. If fetal programming occurs in premature infants, what are the nutritional strategies which will prevent malnutrition and subsequent programming? Does catch-up growth predisposes to the metabolic syndrome and what is the optimal nutrition for premature and SGA infants during childhood? These issues need to be addressed as they are of great importance to the future health of coming generations.

Challenges in the developing world: In the developing world, up to a third of infants can be born with growth restriction primarily due to maternal malnutrition. With improvements in neonatal care, the proportion of premature and SGA infants who survive to adulthood is likely to increase and could potentially contribute to the burden imposed on the society from diabetes and cardiovascular disease. This is a cause of concern as the World Health Organization estimates that the number of adults with diabetes in developing countries will increase by 170% from 84 million in 1995 to 228 million in 2025[19]. A concerted effort to improve nutrition of adolescent girls and women of child bearing age by protein, vitamin and iron supplementation is essential to prevent fetal malnutrition. Such an approach will decrease infant mortality and possibly morbidity from adult onset diseases.

Points to remember:

1. *Maternal malnutrition results in fetal growth restriction and fetal programming.*

2. *Adaptive responses made by the fetus to malnutrition can result in persistent long term effects.*

3. *Nutritional excess or deprivation during fetal life and early childhood can program adult onset diseases.*

4. *Fetal growth restriction puts infants at risk of adult onset type 2 diabetes, dyslipidemia and cardiovascular disease.*

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NEWS AND NOTES

| NEONATOLOGY |

NEONATAL SEPSIS - NEWER PERSPECTIVES

*** Ranjan Kumar Pejaver***

Abstract: Sepsis is the main cause of morbidity and mortality in newborns. As the clinical features are nonspecific, diagnosis is not easy. The diagnostic tests available have low predictive value and decreased sensitivity and specificity. Antibiotic abuse has resulted in further confusion in diagnosis and emergence of resistance to antimicrobials. It is now understood that sepsis is a complex syndrome caused by an uncontrolled systemic inflammatory response (SIR), of infectious origin, characterized by multiple manifestations and which can result in dysfunction or failure of one or more organs and even death. The sepsis cascade has stimulated search for interventions at various levels of this process. The article summarises the triumphs and agonies of this ongoing research in diagnosis and treatment of neonatal sepsis.

Key Words:Neonatal sepsis, diagnosis, management, septic shock.

Magnitude of the problem

Sepsis is the commonest primary cause of mortality and morbidity among neonates. In our country, current Neonatal Mortality Rate (NMR) is around 45/1000 live births. Among these, 40% occur on day 1, 56.3% within three days and 73.3% occur in the first week of life. Sepsis

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accounts for almost half the deaths that occur during neonatal period. Globally, WHO estimates 5 million neonatal deaths a year. 98% of these occur in developing countries. The commonest etiology is sepsis which constitutes more than one third of the causes. Estimated incidence is7.1 to 38/1000 live births in Asia; 6.5 to 23/1000 live births in Africa; 3.5-8.9 / 1000 live births in South America and Carribeans; 6/1000 live births in USA and Australia.

Neonatal sepsis could be of different variety, which would prompt different approaches in prevention, diagnosis and treatment. **Early onset sepsis**(EOS) is that which occurs within 72 hours after birth and is due to microbes acquired before or during delivery. **Late onset sepsis** is that which occurs due to microbes acquired after delivery. **Nosocomial sepsis** is hospital acquired infection. **Colonisation** refers to bacterial colonization which is inevitable in all human beings and has its own advantage and usually occurs in respiratory tract, gastrointestinal tract and skin.

What is the scene generally in most places?

Clinical features of sepsis are highly nonspecific. This has led to both under diagnosis and over diagnosis. A high index of suspicion is required for early diagnosis of sepsis. For the last two decades, the following set of investigations are relied upon to diagnose sepsis:-

Total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil count (I/T Ratio), C-reactive protein (CRP), micro ESR, buffy coat smear, acridine orange staining.

These laboratory tests are not of high specificity or sensitivity. Eg: Sensitivity and specificity of elevated CRP was found to be 75% and 86% and for white cell count disturbance 67% and 90%.

Predictive value of these tests are low and these tests are not available every where nor standardized. Lab tests are bypassed due to lack of availability or affordability in many places.

Culture of blood and various other body fluids is considered as the gold standard. It is to be noted that even in the best of centres, yield of blood culture has been less than 30%.

Regarding treatment in most centres especially the peripheries, antibiotics has been the only modality. Antibiotic therapy could be empiric due to various reasons and at times, specific. There are several factors which make antibiotic therapy ineffective or at times hazardous. To mention some:

a. Mothers would have received antibiotics.

b. Infants before transfer are already given antibiotics.

c. Lack of antibiotic policy. (which is supposed to state the following) is lacking in most centers.

- when to give/stop

- what to give.

- how much to give.

- how long to give.

As a result there is this mammoth problem of antibiotic resistance. Lack of monitoring of a suspected or proven case of sepsis, makes the further management difficult. Supportive therapy though available to some extent, is not given due to, lack of knowledge, difficulties in availability or affordability.

Evolution of newer perspectives in sepsis

Over the last several years we have come to understand that **Sepsis** is a complex syndrome caused by an uncontrolled systemic inflammatory response (SIR), of infectious origin, characterized by multiple manifestations, which can result in dysfunction or failure of one or more organs and even death.

It is just not a given microbe invading the body and causing disease but a complexity of pathogen-host relationship. Features of the host that influence this are portals of entry, host immunity, antibiotic exposure and prematurity. Features of microbe that have bearing are pathogenicity, dose and competition. There has been a coordinated effort among the researchers to investigate the pathophysiology and the various dynamic changes that happen in different systems of the body as a response to sepsis. The sepsis cascade (Fig 1) explains these changes. There are several ways in which the microbe injures the cell and there are equally diverse ways in which the host responds. Microbes injure hosts through toxins directly or by an inflammatory reaction, as a result of host's own immune response. Cytokines, a family of cell signaling peptides are liberated, which can be proinflammatory or anti inflammatory in nature. Ultimately it is the end organ effect of this inflammation that determines the seriousness.

It is now understood that the situation could be a spectrum from mild sepsis to hemodynamic alteration-to multi organ failure and septic shock.

Hypovolemia, peripheral vasodilatation, myocardial depression, increased endothelial permeability and hypermetabolism occur.

The more the complexity and interdependence of the pathophysiological mechanism of sepsis are understood, more
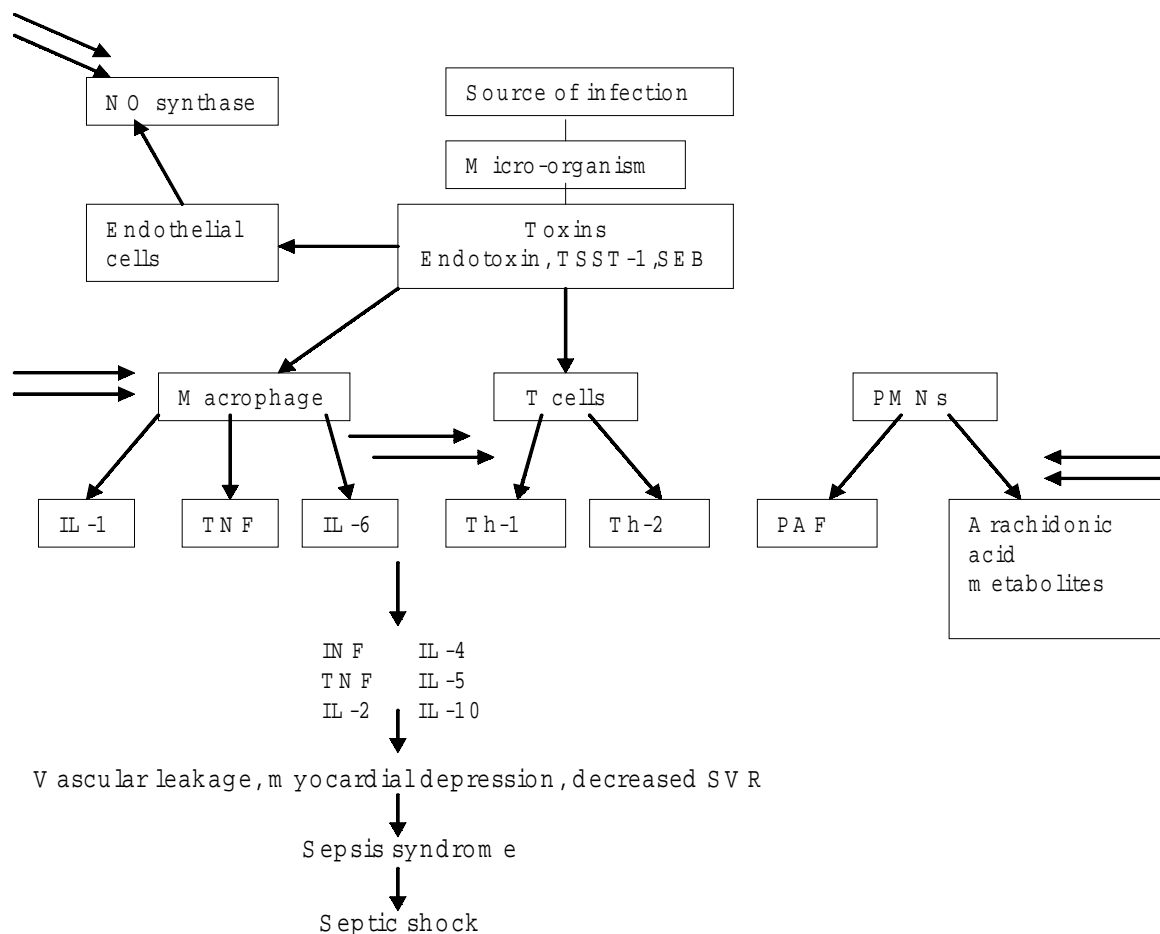
NO=Nitric Oxide, TSST=Toxic shock syndrome toxin, IL=Interleukin, TNF=Tumour necorsis factor, Th=T-helper cells, PMNs=Polymorphonuclear leukocytes, PAF=Platelet activating factor, SVR=Systemic vascular resistance

Fig 1. Sepsis cascade: Open tail arrow = area of potential intervention

diagnostic and therapeutic strategies based on substances, which modulate or interrupt the effects of endogenous and exogenous sepsis mediators can be sought.

Newer developments in diagnosis of neonatal sepsis

Laboratory or complimentary, evaluation is capable of revealing two distinct aspects of sepsis. The first is related to the search for the aggressive agent, the second relates to the identification of alterations in metabolism or homeostasis, indicative of systemic compromise or of specific organ involvement.

Blood Culture is the definitive test, as the vast majority of neonatal infections are associated with bacteremia. Conventional culture and sensitivity tests take anywhere between 24-72 hours for results. Newer rapid methods like **'Bactec', 'VersaTREK'** give us early clues

regarding presence of bacteria. They measure the head space pressure in the bottle relating to oxygen consumption or gas production. (carbon monoxide, nitrogen, hydrogen) by the micro organism. They are designed to perform aerobic, anaerobic, and mycobacterial culture and sensitivity on the same system. However, method of blood collection, contamination and interpretation of the result have a bearing. Collection from multiple sites and repetition of the test may be more useful. Despite the great efforts made, on average, blood cultures are positive in 34% of 'patients with sepsis' varying from 9 to 64%. In patients who have long duration ICU stay, an investigation for systemic infection by fungus is mandatory. Currently, fungi are responsible for around 5% of sepsis.

Immunological studies: Antigen detection studies by counterimmunoelectrophoresis and others have been used to detect the presence of bacterial antigens in blood, urine or CSF. The application in neonatal sepsis is still not widely practiced. Rapid screening for Group β streptococci (GBS) by latex particle agglutination is one area where it is more used. This has been found to have 90% sensitivity, 70% specificity, positive predictive value of 12% and negative predictive value of 99%.

Antibody detection tests: More valuable in viral infections. Organism specific IgMs are available. Especially significant increase in titres on repeat samples is diagnostic.

Genetic techniques: It is now possible to amplify highly conserved DNA sequences from a variety of Gram-positive and Gram –negative organisms, as well as many viruses using PCR, while avoiding the simultaneous amplification of associated human DNA. In a recent study, portions of DNA encoding the 16-S ribosomal RNA has been used to define an organism as bacteria. These are amplified using PCR by automated methods allowing rapid diagnosis.

Sensitivity was 100%, and specificity 95.6%. This method has the potential to be automated and to provide rapid diagnosis of bacteremia. Other DNA amplification techniques are also becoming available.

Detection of acute phase reactants Orosomucoid (alpha1-acid glycoprotein), haptoglobin, alpha1 antichymotrypsin have all been used in assessing neonatal infections, but add little to what is learnt from studying CRP. Fibronectin assay has been found to be useful in diagnosing sepsis. Many septic preterm infants develop significantly low plasma fibronectin concentrations which may impair their ability to combat infection.

Increase in serum lactate, plasma nitric oxide (by means of nitrite/nitrate plasma levels): can be early indicators of SIRS. But means to measure these are not available freely.

Serum granulocyte stimulating factor (G-CSF) concentration with a cutoff value of 120pg/ml has been shown to have a sensitivity of 95% , a specificity of 73% and a negative predictive value of 99% in the diagnosis of culture proven neonatal sepsis.

Granulocyte elastase concentration elevation in amniotic fluid has recently been shown to have a useful predictive value for neonatal sepsis. It merits further evaluation as an early screening test.

Serum assay of certain cytokines: Interleukin1 (IL -1), IL -6, IL-8,IL-10 and tumour necrosis factor (TNF) are some of the substances measured in diagnosing sepsis. As IL-6 plays a critical role in inducing CRP synthesis it should provide an earlier indication to sepsis. It has been found to be more sensitive than CRP. In addition to elevated plasma concentrations, TNF alpha concentrations have been found in lung lavage fluid of babies with pneumonia.

Procalcitonin is a 14-kDa protein encoded by the Calc-1 gene along with calcitonin and katacalcin. The function and regulation of this protein are quite different from those of the other gene products. Blood concentration of procalcitonin is increased in systemic inflammation, especially when this is caused by bacterial infection. Studies of its behaviour in patients with bacterial sepsis have led to the proposal that it may be a useful marker of systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein. Several studies are in progress to establish serum levels in various age groups and also to refine the assay techniques.

Newer developments in the treatment of neonatal sepsis

Early intervention to prevent hemodynamic disturbances, appropriate use of antimicrobials, toxin removing, increasing innate immunity and use of inflammatory response blockers are the various modalities to be discussed.

Antimicrobials form the mainstay of treatment of sepsis. During the last decade several newer antibiotics have been introduced, namely, Carbapenem group, (imipenem, meropenem); 3rd and 4th generation cephalosporines; wide spectrum penicillins (ticarcillin, piperacillin); monobactams (astreonams) and quinolones. Many antiviral agents are now available. For fungemia amphoterecin and flucanazole are now regularly used in intensive care units.

Supportive therapy: This is still very essential for a good outcome. Constant monitoring of vital signs, central venous pressure (CVP) and urinary output is mandatory. Definitive resuscitatory strategies with therapy oriented by goals include, correction of preload (CVP), post-load (mean arterial pressure), cardiac contractility and oxygen saturation. Maintainance of adequate cellular perfusion and prevention of organ dysfunction should be the aim.

Vigorous volumetric resuscitation and continous use of inotropes should be practiced. In childhood septic shock there is always considerable volume deficit, which warrants infusion of large volumes of crystalloid solutions. It should be noted that even with a volumetric deficit of 25% to 30%, the MAP remains stable at the cost of increased systemic resistance.

Adjunctive therapy: It is now evident that though antimicrobials form the mainstay, in immunocompromised, premature and low birth weight babies, additional modalities will help in combating sepsis. It is based on the intervention and support at various points of the sepsis cascade.

Immunoglobulin therapy: Both prophylactic and therapeutic use of immunoglobulins have been tried in neonatal sepsis. There is evidence of improved humoral immunity and enhanced opsonophagocytosis with immunoglobulin therapy. Hyperimmunoglobulins and refined preparations are now available. Meta-analysis has still not revealed distinct and statistically significant benefits. It is recommended to use immunoglobulins in selected cases. However, specific immunoglobulins have a definite role. Eg: Hepatitis immunoglobulin, varicella immunoglobulin etc.

Fresh frozen plasma (FFP) has been used to enhance humoral immunity. In vitro a lot of evidence about its usefulness is available. There are also concerns about the safety as it is a blood product. It is quite useful when DIC is associated with the sepsis.

Granulocyte colony stimulating factor (G-CSF); granulocyte macrophage colony stimulating factor (GMCSF) are important in inducing granulocyte production and activation

in the newborn during sepsis. The granulo-cytopenia that accompanies severe sepsis in a newborn is due to its lack. Several trials have shown an increase in neutrophil counts and enhanced functional activity as judged by the C3bi expression. But there is still no concrete evidence that the ultimate outcome is improved by these modalities.

Exchange transfusion(ET): provides humoral factors, removes noxious products, such as bacterial toxins, fibrin degradation products, and cytokines. There have been reports of dramatic improvements following ET, but well designed ,prospective randomized controlled trials to confirm this is absent.

Granulocyte transfusion: Obtained from donor blood or plasmapheresis, given to babies with sepsis, in particular when their illness has been complicated by neutropenia and granulocyte storage pool depletion as judged by bone marrow aspiration, has shown benefit. But overall, the literature is not convincing.

Agents which bond with or neutralize components in the bacterial cell wall: Use of Anti-endotoxin antibodies, lipopolysaccharide binding protein antagonist, CD14 receptor inhibitor and permeability increasing protein antagonist have not yet proven to be practical and useful in treating neonatal sepsis. Monoclonal antibodies in common or specific like E5 have shown some success.

The process of polymorphonuclear neutrophil activation and degranulation caused by inflammatory mediators results in large scale free radical production. **Antioxidants** like vitamin C and E, beta carotene, catalase and superoxide dismutase ,to neutralize free radicals and scavange them are being used. Other antioxidant agents, alpha tocopherol, dimethyl sulphoxide, Q10 coenzyme, N- actylcystiene, glutathione and allopurinol are being evaluated.

It is believed that products of metabolism of arachidonic acid, by both cyclooxygenase and lipoxygenase routes and also prostaglandins and thromboxane appear to have role in target organ dysfunction. Their inhibitors like indomethacin, ibuprofen appear to have beneficial effects at specific points in the inflammatory cascade and on the survival.

Heparin has also been studied for its immune modulatory properties and in vitro it inhibits the bond between L and P selectin leading to protection against lethal endotoxemia. But large studies have failed to substantiate this and haemorrhages and its antithrombin activity may be detrimental.

In experimental studies, use of **antithrombin** prevented to a significant extent, endothelium-leukocyte interaction and capillary damage. But in observational studies it was not found to be of great use.

One treatment that has shown promise for sepsis appears to be **recombinant human active C protein, or drotrecogin-að**. Active C protein is an endogenous protein which promotes fibrinolysis and inhibits thrombosis and inflammation. In sepsis, because of the effects of inflammatory cytokines, there is a reduction in the conversion of inactive C protein into active C protein. The anti inflammatory effect of drotrecogin can come directly from the inhibition of neutrophil activation, from the production of cytokines induced by lipopolysaccharides, and from activated cell adhesion to the endothelium. The effect can also be indirect, by means of inhibiting thrombin generation, which leads to reduced platelet activation, neutrophil recruitment and leucocyte degranulation. In a randomized, multicenter, double-blind, placebo-controlled trial of continuous drotrecogin-að for 96 hours or placebo, in 1,690 patients with severe sepsis, overall mortality was lower at 28 days among the treated group, representing a reduction

of 6.1% in the absolute risk of death. The drug was cleared for use on the basis of this single trial. Due to its potential to cause severe hemorrhages and its high cost, it has been recommended that patients be extremely carefully selected before receiving this treatment.

More than 30 randomised blind trials involving 12000 patients showed that the use of **antibody blockers** such as platelet activation factor antagonists, antibradykinin, anti-prostaglandin, monoclonal anti-TNF antibody, IL-1 receptor antagonist, soluble TNF receptor, nitric oxide synthesis inhibitor did not change the clinical course or mortality, and sometimes even compromised the patients.

Pentoxifylline is an anti-inflammatory drug . It is a xanthine derivative and a phosphodiesterase inhibitor possessing a broad spectrum of activity modulating inflammation. Several trials conducted , have shown a reduction in 'all cause mortality during hospital stay'. Current evidence suggests that use of pentoxifylline as an adjunct to antibiotics in neonatal sepsis reduces mortality without any adverse effects.

It has been observed that many critical patients, even those who are not diabetic, have hyperglycemia and a reduced response to endogenous insulin, possibly because of increase in the level of insulin-like growth factor binding protein. The use of exogenous insulin to maintain glycemia within normal parameters has proved to be of benefit, in terms of outcome. In sepsis, normoglycemia restores neutrophil phagocytic capacity, antiapoptosis activity.

Another strategy which has been suggested and has already won a place among sepsis treatment is the use of **extracorporeal substitution, such as continuous arterio-venous hemofiltration and plasmapheresis,** especially in cases of severe sepsis . They may be used at any phase of the inflammatory process with the objective of reducing concentrations of inflammatory mediators (exogenous and endogenous), and consequentially their potential to cause damage to target organs

Steroids in sepsis: Corticosteroids have always been considered to have some sort of cytokine synthesis blocking action and being intermittently used in treatment of sepsis. Perhaps, its use very late in the process and the side effects caused the disrepute for its usage. The observation that severe sepsis may be associated with relative adrenal insufficiency and resistance to glucocorticoid receptors induced by systemic inflammation has awakened interest again.

A randomized double blind placebo controlled study by Annane D, et al showed benefit with physiological doses of corticosteroids for 7 days with reduction in duration of vasopressor usage and lower mortality when compared with controls. Keh D, et al showed that continuous ,low dose hydrocortisone in septic shock restored haemodynamic stability as compared with controls.

In conclusion, research continues looking for diagnostic and therapeutic avenues .Many a trials are small in size and encounter many variables. No single test for diagnosis, and no single therapeutic agent which is successful constantly and consistently has been found or probably will be discovered.

Several combinations will have to be tried out. However,certain strategies are certainly of benefit, such as early recognition of sepsis, aggressive initial intervention against hemodynamic disturbances and rational handling of antimicrobials. Any advance in the understanding of these three strategies will undoubtedly increase the chances of a good prognosis, although it is not expected that the increase would be of any great magnitude. The combination of immunomodulatory therapies

appears to be the future for research in this area. Corticoid use, for patients with or without adrenal insufficiency is resurfacing as a promising strategy. Similarly, drotrecogin-að appears to be the only substance which has demonstrated an impact on mortality, although in an unexceptional manner. Because of the peculiarities of children, the scarcity of studies and the complexity of sepsis in this age group, pediatricians should be alert to new discoveries in this area.

Prevention of sepsis has to be given its due importance..Prevention of prematurity and LBW infants, hand washing, aseptic techniques in delivery room, transport and wards is crucial. Rational antibiotic policy and proper protocols in utilization of antimicrobials will reduce development of resistance which is emerging as a global threat.

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NEWS AND NOTES

AIIMS GOLDEN JUBILEE SYMPOSIUM ON "PEDIATRIC MALIGNANCIES"

Date: 29th to 31st December 2005

Venue: New Delhi

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<div align="center">**NEONATOLOGY**</div>

X-RAY ABDOMEN IN THE NEONATE

* Muralinath S

Abstract: This article is about the practical value of plain x-ray in the evaluation of a neonate's abdomen. A basic approach to the reading of an x-ray of the abdomen along with the essential views to be done at the bedside are considered. The focus is on the evaluation of the neonatal gastrointestinal tract.

Keywords:*Neonate, X-ray abdomen, Bowel gas.*

The plain x-ray of the abdomen is an important study in the evaluation of problems of the abdomen in the neonate. Its major advantage lies in the fact that it is a relatively simple study, practically available anywhere and can be done at the bedside. With the present day focus on advanced imaging techniques, it is not surprising that less attention is now paid to the plain x-ray evaluation of the abdomen than in the past. Nevertheless, plain films remain a valuable tool in the assessment of abdominal abnormalities. Intestinal obstruction, free intraperitoneal air and intra abdominal calcifications are readily seen on plain films. More often than not plain films are an excellent guide to determining the proper imaging study to perform for a particular problem.

The abdominal radiograph is not as rewarding as the chest radiograph, yet it is an important study. In the chest radiograph, the bilateral symmetry of structures and densities is of immense value and offer an excellent ground for comparison. In the abdomen symmetry is of minor consideration. In the abdomen, it is a matter of becoming familiar with the appearance of relatively fixed organs seen through the ever changing intestinal gas patterns. " No one normal configuration looks exactly like another and the overall "normal" picture comes only through examining many roentgenograms over many years". - Swischuk.

In the evaluation of the x-ray of the abdomen, one will do well to focus initially on the relatively fixed areas of the gastrointestinal tract and then move on to the others. Relatively fixed hollow viscus like the stomach (nasogastric tube placement helps in its localization in difficult cases) in the upper abdomen and rectum in the lower pelvis are assessed; the solid abdominal viscera like the liver and spleen are then evaluated. A general survey of the bowel gas pattern is then done. This is usually an ever changing pattern, with no obvious focal area of prominence. Evaluation of the bowel gas pattern and the anatomic localization of the intraabdominal gas is the key to the diagnosis in the evaluation of diseases of the G.I. tract. The diaphragmatic leaflets, the bony structures and the soft tissues are then evaluated for normality. The overall visceral situs can be assessed and intra abdominal calcification is specifically looked for and evaluated.

The essential and basic view to be done at the bedside is the supine view of the abdomen. In the evaluation of abnormal intra abdominal

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gas patterns (and fluid levels), alternative decubitus views, prone and supine translateral views may be taken. Erect view is seldom utilized in neonatal practice at the bedside. A sick neonate is unnecessarily subjected to stress and the alternative views mentioned can provide all the information, if one is tuned to interpret these views. It is imperative that unnecessary and unwarranted stress should never be placed on the sick neonate, and views that require minimal handling of the neonate are resorted to instead.

The focus of this article is on the role of plain x-ray of the abdomen in the evaluation of GI tract disorders in the neonate.

In the evaluation of the hollow viscus in the neonate, the assessment of bowel gas pattern is the key. The bowel gas in the neonate is essentially swallowed air. In the term infant, the swallowed air at birth reaches the stomach and

Fig 1. Gasless abdomen in Oesophageal Atresia

duodenum by 30-60 minutes, the jejunum by 2-4 hours, the ileum by 4-6 hours, the colon by 12-18 hours and the rectum by 24 hours; by which time most of the newborns would have passed meconium. From the above statement it is evident that knowledge of the time at which the study was done is essential in the interpretation of bowel gas pattern/distribution. Diminished bowel gas is seen in conditions that impair swallowing (eg. CNS depression, prematurity) and absent bowel gas when there is anatomic discontinuity (eg. oesophageal atresia without fistula) (Fig.1). Thus observation of bowel gas pattern can be a clue to the diagnosis.

Analysis of the gas pattern can be broadly grouped in to : Abnormal intraluminal and abnormal extraluminal gas. Extraluminal gas may be intramural or extraintestinal.

Abnormal intraluminal gas patterns

Airless, opaque non-distended abdomen is seen in oesophageal atresia without fistula, as the air does not reach the intra abdominal bowel (Fig1). Diminished bowel gas is seen in conditions that impair the act of deglutition. Repeated vomiting and prolonged nasogastric aspiration can result in diminished bowel gas. In all these conditions there is no abdominal distention. When the abdomen is opaque, airless and distended it is usually due to dilated fluid filled bowel loops and/or ascites.

Excessive bowel gas with abdominal distension is seen when there is an impediment to the onward transit of gas distally; this impediment may either be functional or organic. The more distal the impediment/obstruction, more pronounced is the abdominal distension. When there is intraluminal gaseous distension of the abdomen, the crucial distinction that one has to make is between paralytic ileus and mechanical ileus; for one is a medical condition and the other a surgical entity. The plain x-ray plays a vital

Fig 2a. Paralytic Ileus

role in the decision making process. In paralytic ileus there is generalized distension/dilatation of the entire hollow viscera of the abdomen (Fig.2a), i.e. there is no differential distension of the GI tract. In other words, all portions of the GI tract dilate in proportion to each other, and in the classic case the colon remains larger than the small bowel. The dilated bowel loops are less orderly (appear chaotic) and look disorganized. In mechanical ileus the picture is different. The gut proximal to the obstruction dilates and the distal bowel collapses. There is no proportional
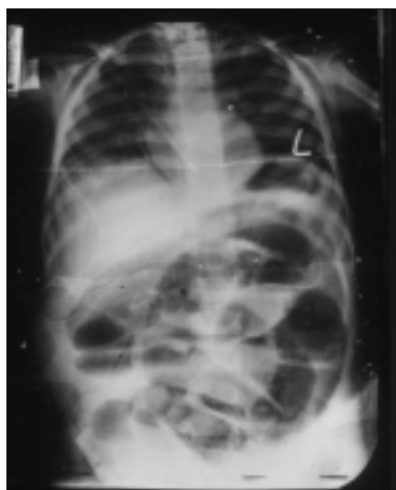
Fig 3a. Mechanical Ileus

Fig 2b. Prone translateral - Air in rectum

dilatation of the entire gut. The number of dilated loops will depend on the site of obstruction; proximal obstruction will show a few loops while distal obstruction shows many. Hence, in duodenal atresia it is the "double bubble" and in ileal atresia it is multiple loops. The gas distal to the obstruction will depend on the degree of obstruction. In complete obstruction the distal bowel will be devoid of gas and in incomplete obstruction, the distal bowel gas will be present but diminished. In duodenal atresia, there will be no gas distal to the site of duodenal obstruction – "Double bubble"; where as in duodenal stenosis or septum with a hole diminished gas will be seen in the distal gut. In mechanical ileus the dilated loops (number of loops will depend on the level of obstruction) are visualized discretely and are rather orderly in appearance. In the supine view the loops are often seen stacked one over the other – the stepladder pattern. This is characteristic of mechanical ileus (Fig.3a). When there is confusion regarding distal bowel obstruction (ileal atresia, meconium plug etc.,) and paralytic ileus; a simple prone-translateral view (which disturbs the infant the least) will settle the issue.
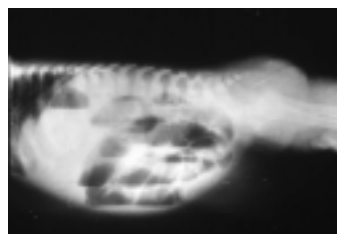
Fig 3b. Prone translateral - No rectal gas

In paralytic ileus one will see gas in the rectum (Fig.2b) whereas in mechanical ileus the rectum will be devoid of gas (Fig.3b). This study should be done before any rectal procedures or examination, as that would introduce air in the rectum and mar the inference.

Abnormal, extraluminal gas pattern

Extraluminal gas may be in the intestinal wall itself (intramural). Intramural air usually is associated with a loss of intestinal mucosal integrity secondary to intestinal ischemia or severe inflammation with resulting necrotizing enterocolitis. The classic radiographic appearance of intramural air consists of linear or curvilinear collection of gas within the bowel wall. Unfortunately this is not so in all cases, in some the collection of intramural gas appears so bubbly that it is difficult to differentiate it from intraluminal meconium admixed with gas. In these situations, clinical correlation is mandatory.

Extraintestinal gas – pneumoperitoneum – usually indicates a hollow viscus perforation, but occasionally can also be seen secondary to thoracic airleak (Pneumomediastinum). In the supine position, pneumoperitoneum manifests as increased transradiancy of the abdominal cavity, that diminishes the hepatic density and outlines the falciform ligament; giving rise to the "foot ball sign" (Fig.4a). The diagnosis rests essentially on the fact of distinguishing gas that appears not to fit in with intraluminal gas patterns. It is surprising to see how large collections of free air may remain undetected in the supine view for the uninitiated. When in doubt a supine translateral (Fig.4b) or a left lateral decubitus view may be taken to identify the free air lying below the anterior abdominal wall or between the liver and the right lateral wall of the abdomen. To state again, an erect view is seldom required.

It is the clinical presentation that necessitates and directs the imaging strategy. It is the clinical correlation that often draws the right conclusion while analyzing images from the point of view of diagnosis. GI tract disorders may present as excessive drooling, choking with feeds, respiratory distress, vomiting, abdominal distension, non-passage/delayed passage of meconium, bleeding per rectum or as sepsis. It is the presentation that determines the need for imaging. When the presentation is excessive drooling, choking with feeds and respiratory distress, the suspicion is oesophageal atresia with or without fistula. A plain film of the chest and abdomen with an NG tube placed will settle the diagnostic issue. In oesophageal atresia, the NG tube will be coiled in the upper pouch with an airless abdomen; when there is associated fistula, NG tube will be seen coiled in the upper pouch but the abdomen will be quite gaseous (Fig.5).

Fig 4a. Pneumoperitoneum - Supine

Fig 4b. Pneumoperitoneum - Supine translateral

Fig 5. Oesophageal atresia with fistula (→ denotes coiling of tube)

'H' type fistulas are difficult to diagnose and require a more specialized imaging approach.

In the case of vomiting, the nature of vomitus whether bilious or non-bilious provides a clue to the site of obstruction. Bilious vomiting denotes obstruction distal to the ampulla of Vater. Hypertrophic pyloric stenosis and duodenal obstruction (intrinsic or extrinsic) will present radiographically as distended stomach, but the nature of the vomitus will reveal the site of obstruction. In hypertrophic pyloric stenosis there will be distended stomach (Fig.6a) along with some distal gas as the obstruction is incomplete. The diagnosis is confirmed by US imaging (Fig.6b). In duodenal atresia, the classic 'double bubble' is often seen with no distal gas (Fig.7a), as the obstruction is a complete one. Duodenal stenosis, web / membrane with a hole and annular pancreas, all may have a similar appearance, but usually there will be some distal

Fig 6b. US - IHPS

Fig 6c. US - Normal

Fig 6d. US - Malrotation

Fig 6a. Distended Stomach

air. Down's syndrome is commonly associated with duodenal atresia and a survey of the pelvis will reveal that association (Fig.7b). The most important duodenal obstruction (which is an extrinsic one) that has to be diagnosed as early as possible is malrotation with volvulus. This is a surgical emergency. An early diagnosis is a must, as a delayed diagnosis of volvulus may severely compromise the bowel because of ischemia. In the neonate, upper abdominal fullness or scaphoid abdomen with haematochezia is taken as malrotation with volvulus unless proved otherwise. Plain film will show a distended stomach with paucity of distal gas when there is associated volvulus. The vomitus / aspirate is bilious. An ultrasound may be done to evaluate the orientation of the superior mesenteric vessels; normally the vein is seen to the right of the artery and this orientation is reversed in malrotation (Fig.6 c and d). The definitive diagnosis is made by an upper GI contrast study (Fig 8). In jejunal atresia, a few loops beyond the duodenum will be seen distended with no distal gas; distal the atresia, more are the number of dilated loops.

In the evaluation of abdominal distension, it will do well to remember that not all obstructions produce distension (proximal obstructions do not manifest as abdominal distension and vomiting reduces that further) and not all distensions are due to obstruction – paralytic ileus is the classic example. Hence the first step is to determine whether the distension is due to organic/obstructive cause or functional/paralytic one. This distinction is mandatory as the former may warrant a surgical intervention while the latter a conservative medical approach. The differentiating features between the two have already been dealt with. In general, distal the obstruction greater the abdominal distension. Distal obstruction may present as delayed passage or non-passage of meconium. In distal bowel obstruction due to ileal atresia and meconium ileus or meconium plug syndrome, the radiographic distinction may not be clear-cut. Generally air and fluid will be seen in ileal atresia, while it is mostly air in meconium related disorders. The so called classic "soap bubble" appearance of meconium and air admixture may be seen in cases of meconium ileus. Further imaging and contrast studies are required to

Fig 7a. Duodenal atresia

Fig 7b. Duodenal atresia/Down's syndrome
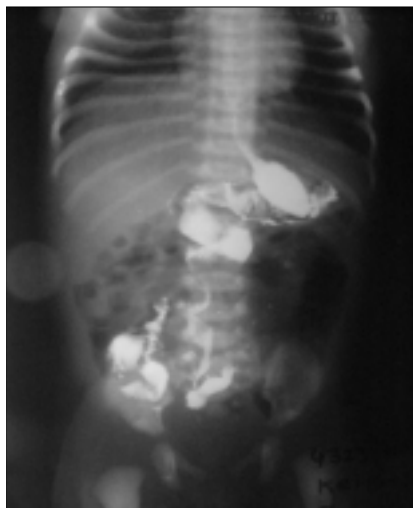
Fig 8. Malrotation - Barium

elucidate these cases. Intraabdominal (linear or amorphic) calcification may be seen in meconium peritonitis with or without pseudocyst.

Abdominal distension with delayed passage of meconium raises the suspicion of Hirschprung's disease. Barium enema is the imaging study of choice in the evaluation of Hirschprung's disease. An important differential diagnosis in abdominal distension with delayed passage of meconium is hypothyroidism. The presentation practically mimics Hirschprung's disease. A high index of clinical suspicion is required for detecting this entity. Radiographically, the clue lies in the evaluation of the knees; in hypothyroidism there is delay in the appearance and in the maturation of the epiphysis of the lower end of femur and upper end of tibia (Fig.9a & b). This is an excellent clue. The final assessment is provided by the hormonal study.

Non-passage of meconium will be seen in colonic atresia and anorectal malformations. Once an anorectal malformation is identified; imaging must be performed to assess the local anatomy as well as the known associations (VACTERL). It is worthwhile to remember that in anorectal malformation, a good clinical examination of the perineum is far more rewarding than radiographic evaluation. For radiographic documentation a prone translateral view with a marker at the anal site will suffice. "Invertograms" are hazardous. They do not provide any additional or worthwhile information and have no place in modern practice to assess whether the anomaly is high or low (supralevator or infralevator). Many lines and measurements

Fig 9a. Normal – Femoral and Tibial epiphysis

Fig 9b. Hypothyroid – Small Femoral and absent tibial epiphysis

have been advocated to assess where the airfilled rectum terminates so as to determine whether it is a high or low anomaly. These are not safe guidelines, because the bowel moves up and down as the infant cries or strains. The decisions regarding management (colostomy or otherwise) is individualized and rests primarily on the findings of physical examination.

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in premature infant. It is a common, serious and sometimes fatal disease. The major risk factor is prematurity. It is seen as a complication in Hirschprung's disease and other congenital bowel obstructions. It's precise aetiology is unclear and is thought to be multifactorial. The ileo-caecal region is commonly affected, though any portion of the gut may be involved.

Once NEC is suspected on clinical grounds, abdominal radiographs are obtained. Unfortunately the radiographic findings are often non-specific especially in the early stages. In early NEC there is a diffuse non-specific gaseous distension. This is the most common pattern, similar to that seen in many premature infants without NEC. This pattern reflects the functional immaturity of the gut in many preterm infants and is difficult to distinguish from those with early NEC. In doubtful cases it is safer to err on the side of overdiagnosis because a delay in diagnosis and institution of treatment may prove catastrophic. A more useful sign of early NEC is distension localized to focal loops only. A dilated loop that remains relatively unchanged (in serial films) is a feature of advanced disease. The more definitive radiographic findings are pneumatosis intestinalis (intramural air) (Fig.10a), portal venous gas and pneumoperitoneum. A characteristic of NEC is linear or cystic intramural air with submucosal and/or subserosal air. The cystic collections are usually subserosal, where as the linear form is usually submucosal. Diffuse pneumatosis usually is a marker of advanced disease. Another pathognomonic sign of NEC is portal venous gas. It is seen as finely branching radiolucency extending from the portahepatis to the periphery of the liver. It is picked up early on ultrasound as bright, shifting echogenic foci within the portal vein (Fig.10b). Pneumatosis intestinalis and portal venous gas are not as ominous as they were thought to be. Pneumoperitonium implies perforation. It is the only universally accepted indication for surgery.

As both the clinical and radiographic signs of early NEC are non-specific; a high index of suspicion based on the risk factors is mandatory for the early diagnosis and management of NEC.
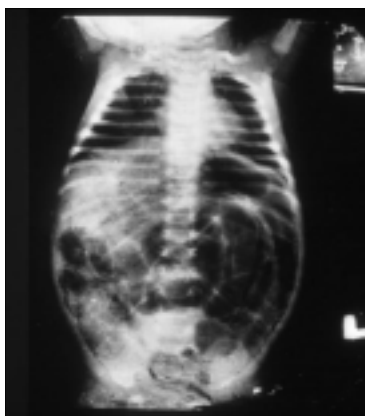
Fig 10a. Pneumatosis - intestinalis

Fig 10b. Air in portal radicles - USG

With all the current imaging modalities available, the plain x-ray of the abdomen is still a valuable study. Even in an emergency, the study can be carried out at the bedside with least effort and minimal stress on the sick neonate.

The abdominal radiograph provides a great deal of information. It is excellent in the evaluation of bowel gas patterns, looking for evidence of obstruction.It does well in the detection of abnormal intraabdominal gas like, extraluminal gas in pneumoperitonium, intramural gas (pneumatosis intestinalis) and portal venous air.

The film can also be evaluated for metabolic bone disease and dysplasias. Abnormal calcifications and intraabdominal fluid can be assessed. Plain films are important in the evaluation of various venous and arterial catheters/lines.

Key points to remember

1. *Plain x-ray of abdomen is a valuable study, especially at the bedside.*

2. *Evaluation of the bowel gas patterns and intraabdominal gas are the key in GI tract diseases.*

3. *Look for association (eg. duodenal atresia and Down's syndrome).*

4. *In the evaluation of NEC a high index of suspicion is mandatory.*

NEWS AND NOTES

CIPP VII
7TH INTERNATIONAL CONGRESS ON PEDIATRIC PULMONOLOGY

Date: 8th to 11th July 2006

Venue: Montreal Congress Center, Montreal, Canada.

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NEONATOLOGY

FOLLOW UP OF THE HIGH RISK NEONATE

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The neonatal care in India has improved considerably in the last two decades. With the emergence of excellent tertiary care centers for newborns, we are now seeing many children on follow-up who have been born as premature/low-birth weight baby, or, have been very sick in the newborn period. Neonatal follow-up program should be viewed as an essential component of high-risk newborn care.

The goals of the follow-up program includes:

1. Monitoring growth and nutrition.

2. Identification of early neuro-developmental problems for early effective intervention.

3. Audiological and visual screening and intervention wherever necessary.

4. A valued support for the family whose life is often disrupted by the birth of a premature or critically ill newborn.

High risk neonates who need follow-up includes:

1. Babies with birth weight less than 1500 grams

2. Preterms less than 34 weeks

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3. Babies with neurological complications - Grade III-IV, intraventricular hemorrhage (IVH), hypoxic ischemic encephalopathy (HIE), seizures, periventricular leucomalacia (PVL), neonates with abnormal neurological findings

4. Ventilated babies

5. Neonates with ongoing pulmonary disease, chronic lung disease (CLD)

6. Neonates who have recovered from septicemia.

7. Neonate who had metabolic complications like hypoglycemia, hypocalcemia, hyperbilirubinemia more than 25mg/dL

8. Miscellaneous: Congenital infection, feeding difficulties, failure to thrive, etc.

Assessment of growth

Low birth weight (LBW) infants are particularly at risk for growth problems. Monitoring the growth pattern is a valuable indicator of well-being of the high-risk infant. Poor growth may reflect inadequate nutrition, chronic illness or psycho-social difficulties. Many factors may alter the subsequent growth in a baby like in bronchopulmonary dysplasia (BPD), the caloric requirement is much higher than a normal preterm baby. Neonatal necrotising enterocolitis (NNEC) of greater than stage III may have some degree of mal-absorption. Babies with neurological illness may have feeding difficulties and palato-pharyngeal incoordination resulting in aspiration. Gastroesophageal reflux (GOR) in a preterm baby may also result in poor growth pattern. It is crucial to ensure optimal

nutrition and to monitor growth parameters closely.

When monitoring the growth of a preterm, it is essential to correct or adjust the age of prematurity (correct age equals chronological age minus the number of weeks born prematurely). Growth parameters are usually plotted on a standard growth chart by using corrected age. Monthly measurement of length, head circumference and weight must be plotted on the chart.

To determine if growth in a preterm baby is adequate the original gestational age (GA) must be accounted as the catch-up growth is fastest during 36-44 weeks after conception. Preterm AGA infants will catch up with a term AGA's growth by 2-2½ years of age. Head circumference is the first measurement to catch up, followed by catch-up of weight and linear growth.

Among low birth weight infants, small for gestational age infants have less catch up growth than appropriate for gestational age infants. They tend to have less than normal weight and length at 3 years.

Nutritional assessment

Many low birth weight (LBW) infants have feeding problems. Caloric intake, fluid intake and vitamin and mineral supplementation should be monitored during weekly visits. For most healthy preterm infants, 110-130 Kcal/kg/day helps to achieve adequate growth. Some infants with chronic disease such as BPD may need as much as 150 Kcal/kg/day. Increase in the caloric density over 24 Kcal/oz may predispose to hyper-osmolar dehydration.

Vitamins and minerals

Vitamin D, calcium, phosphorus, iron, folic acid and zinc are specially important for low birth weight infants. All breast fed infants should probably receive vitamin supplementation during the first year of life. Recommended daily allowance of multivitamins may be administered. Iron supplementation should be started two weeks to two months after birth, and continued for 12-16 months. Supplemental iron is given in the dosage of 2-4 mg/kg/day. Zinc should be given in the dose of 0.6 mg/kg/day. Calcium supplementation in the dose of 200 mg/kg/day and phosphorus in the dose of 100 mg/kg/day should be given with supplemental vitamin D 400 IU/day to all infants discharged home on breast to milk.

Immunization

Immunization should be given to the preterm neonates at the appropriate chronological age as soon as feasible. Pertussis vaccine/component should not be withheld in any child with CP or muscle tone abnormality as long as there is no underlying seizure disorder or progressive neurological illness. The acellular pertussis vaccine is preferred over the whole-cell pertussis vaccine in infants with neurological problem with seizures. Pertussis component should not be withheld in babies with BPD as they may have serious consequences. Oral polio vaccine should be administered at appropriate postnatal age.

Other vaccines, such as those against haemophilus influenza type B, hepatitis B, measles, mumps, and rubella, should be given at the standard chronological age.

RSV immune globulin: Intravenous use of respiratory syncytial virus immune globulin should be considered for use in infants under the age of 24 months of age with CLD who required oxygen therapy in the preceding six months and in infants of a gestational age of 32 weeks or less.

Pneumococcal conjuate vaccine (PCV): All preterm and low birth weight infants are considered at increased risk for pneumococcal disease. These infants should receive full dose

of PCV beginning at two months of chronological age.

Influenza: All preterm infants should be offered influenza vaccine beginning at six months of age and as soon as possible before the beginning, and during influenza season.

ROP Screening

It has been estimated that the incidence of ROP is 30% among infants with less than 1500 g birth weight and 31 weeks of gestation. All babies less than 2000 g birth weight who have been ventilated and given oxygen need retinal examination in the early post-natal period. It is best to do the first examination between 4-6 weeks after birth. If no ROP is detected, and if vascularisation of retina is completed, no further examination is needed. If peripheral retina is avascular, re-examination is needed every week until normal vascularisation occurs or ROP develops. If ROP is present, staging is done. If threshold disease is noted, treatment is advised within 48 hours. If sub-threshold disease is noted, re-examination is done weekly till either disease regresses or progresses to threshold stage.

Following resolution of ROP, yearly eye examinations are suggested to look for refractory errors. Rare complications like nystagmus, late retinal detachment, glaucoma, cataracts and vitreous membranes may be seen; early laser therapy to the retina can avoid many of these complications.

A fixed strabismus at any age is abnormal and needs a referral to ophthalmologist. A child with intermittent strabismus at 1 year of age should also be referred. Simple screening tests for visual acuity in the first year of life include: infant's ability to follow examiner's face at 1-2 months, response to stimuli with a reciprocal smile, observing the infant during spontaneous play for eye tracking, reaching for objects and attentiveness to visual stimuli at 3-4 months.

Hearing screening

1-3% of infants in NICU develop hearing loss. TORCH infection, meningitis, anatomical malformation of head and neck, hyper-bilirubinemia, neonatal seizures, mechanical ventilation, HIE, PPHN, ototoxic drug usage, prematurity, VLBW, NICU stay and family history of sensorineural hearing loss (SNHL), are some of the risk factors associated with hearing loss in neonates. Audiological screening by BERA should be done at 3 months of age to identify any hearing loss and intervene by 6 months if any. Hence repeat evaluation should be done at 6 months if first screening is abnormal. Hearing aid can be used early in infancy and is the primary method of treatment so that there is no delay in speech development.

Developmental screening

The main aim of neurological assessment is to find out the effect of pre-natal and peri-natal events on the brain and to assess the functional integrity of the complex nervous system. The single most important point concerning development is that the infant's abilities will correspond more closely to the post conceptional age than post delivery age.

Neurological assessment

Awareness of the pattern and changes of motor function within the first year of life allows us to separate the normal from the abnormal and to assess whether motor abnormalities are transient or persistent. The evaluation of neuromotor function is of paramount importance in establishing links between perinatal events and later outcome.

Amiel-Tison Method of Assessment: Evaluation of muscle tone is a fundamental part of this assessment. There is a waxing and waning pattern of muscle tone from 28 weeks of gestation to the end of first year of life. From 28 to 40

weeks of gestation, acquisition of muscle tone and motor function spreads from the lower extremities towards the head in a caudo-cephalic direction. After 40 weeks, the process is reversed so that relaxation and motor control proceed downwards from the head to the lower extremities in a cephalo-caudal direction in the next 12-18 months (Fig. 1 and Fig. 2).

Examination should be done at three, six, nine and twelve months. For preterms, corrected age or post-conceptional age should be used rather than chronological age. During examination, infants should be awake and not crying, lying straight with head in midline.

At the end of first year, motor development may be normal, transiently abnormal or permanently abnormal.

Cognitive assessment

Early and effective means of monitoring cognitive development is crucial in the management of high-risk infants. Cognition in infancy can be best described as combination of multiple factors including infant's sensorimotor status, gross-fine motor development as well as social and language development.

The widely used developmental scales are:

1. Trivandrum Developmental Screening Chart (TDSC): It is an acceptable simple tool for a busy practitioner and at community level. 17 test items in it include motor, mental, hearing and vision and given a range of 3-97th centile. A vertical line is drawn at that chronological age. If the child fails to achieve any items short of 3rd centile, the child is considered to have developmental delay.
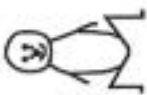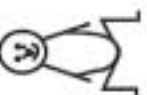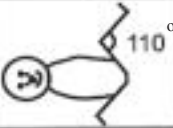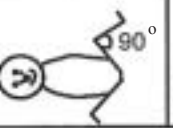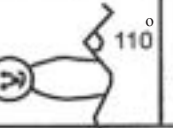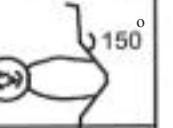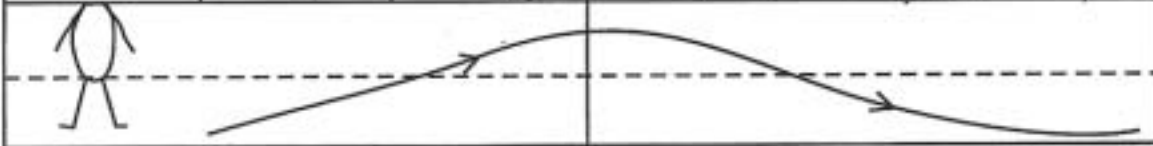
Fig 1. Assessment of passive tone
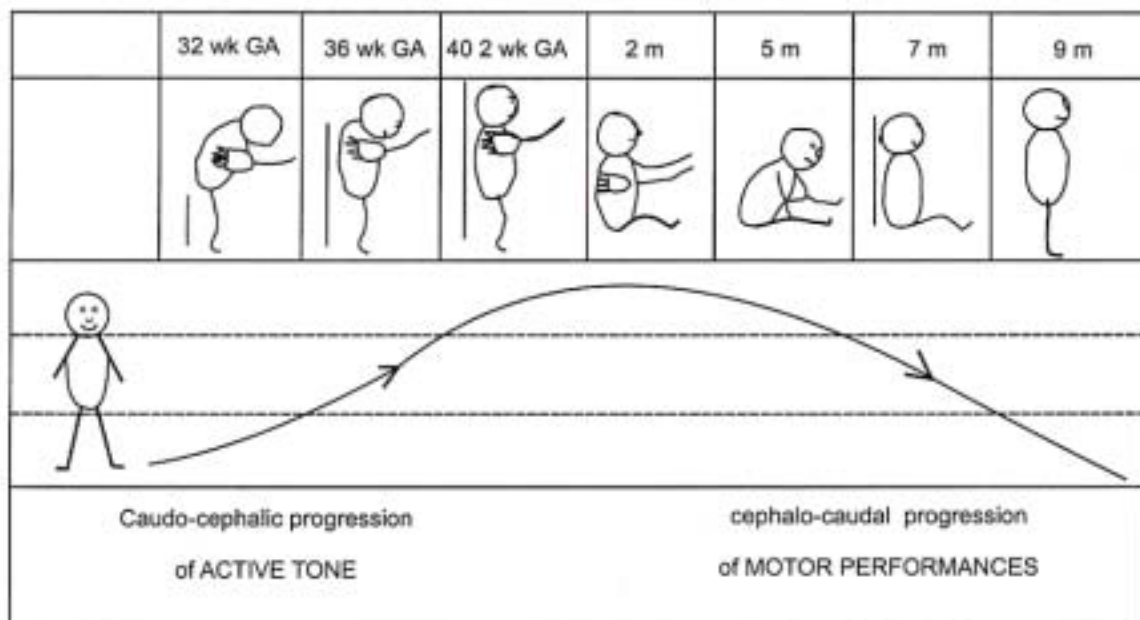
Fig 2. Assessment of active tone

2. Baroda Development Screening Test (BDST): This simple screening test has 22 motor and 32 mental items. They are grouped age wise monthly up to 12 months, 3 monthly till 18 months and 6 monthly till 30 months. A child who fails requires a detailed assessment.

3. Gessell Developmental Schedule: Offers procedure for evaluating observed behavior of children from 1 month-6years of age composed of 4 scales motor development, adaptive behaviour, language and personal social behaviour. It is a screening tool.

4. The Bayley Scale of Infant Development (BSID): Comprises of mental, motor and infant behavior scale. It is for children 2-30 months of age. It is most often used to characterize the infant's developmental status.

5. Denver Developmental Screening Test (DDST). There are four scales assessing fine and gross motor abilities, language and personal social development for upto 6 years of age. It is a sensitive indicator for developmental delay in preterms.

Behavioral problems

The behavioral problems causing concern to parents of premature infant include negativism, temper tantrum, head banging, hyperactive, and/or attention deficit. Behavior problems can contribute to difficulties in relation to both school performance and other health issues.

Early intervention and physical therapy

Ideally all babies discharged from NICU need some form of special care. One of the main aim of follow-up service is to identify delayed or abnormal development so that early intervention can be started. Early intervention consists of identifying a baby who already has or is at potential risk for developing one or the other handicap and subsequently providing remedial measures to lessen its effects.

The goal of the physical therapy is to optimize the motor function of an infant with emphasis on establishment of functional movement by modifying abnormal movement patterns and postures into functional effective patterns, providing appropriate motor experiences, and providing adaptations to compensate for motor deficits. Both transient and long term motor problems in infants require assessment and treatment by physical therapist. Treatment can be given through early intervention program by physical therapist and speech therapist.

Neonatal care is incomplete without adequate follow-up. So, both the neonatal intensive care and follow-up services have to be developed together. Follow-up of these children in the hospital setting and in the community will help them to achieve their maximum potential.

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NEONATOLOGY

FETAL DIAGNOSIS AND THERAPY

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Abstract:Advances in medical technology have made the fetus accessible for diagnostic assessment as well as therapy by various invasive and non invasive tests and procedures. This article will review the current status of the screening and diagnostic technologies that are applied in fetal medicine as well as the therapeutic modalities available.

Key words: *Prenatal diagnosis, Fetal therapy, Fetal transfusion, Amniocentesis*

Congenital malformations are assuming increasing importance in bringing down the perinatal mortality in India. With the advent of surfactant therapy and state of the art neonatal units the survival of neonates with respiratory diseases and other major medical problems has seen a quantum improvement. The prevalence of a major congenital malformation is about 2 – 3 % and not all of them are treatable[1]. Identifying the at risk foetus and wherever possible initiation of therapeutic measures targeting the fetus assumes prime importance in reducing the mortality and morbidity due to congenital malformations. The concept of fetus as a patient and foetus personhood and the question of fetus's right to life versus the right of pregnant women are ethical questions that are hot debates in fetal medicine. This article will summarize the current status of fetal diagnostic techniques and fetal therapy.

Fetal diagnosis or prenatal diagnosis

Fetuses with chromosomal aneuploidy (Trisomy 21, Klinefelter's syndrome 47XXY, Turners 45 XO), those with isolated major structural malformations (cardiac defects, neural tube defects, defects of abdominal cavity etc) and certain inherited genetic disorders (cystic fibrosis (CF), thalassemia, haemoglobinopathies, Tay sach's disease, Gaucher's disease etc) are the ones that can be identified using the available fetal screening and diagnostic techniques (Table 1).

Who should be offered prenatal screening?

1. Fetuses at high risk of genetic disorders as suggested by clinical criteria like singleton pregnancy at >35 years age, dizygotic twin pregnancy at age > 31 years, previous sibling with autosomal trisomy, Klinefelter's syndrome or Turner's syndrome, parents with chromosomal anomalies like translocation etc and those fetuses with an identified major structural malformation by ultrasound.

2. Sibling with a cardiac defect places the foetus at a high risk of similar defect (atrioventricular defect recurred in 80%, other septal defects in 60% and outflow tract defects in 47% in a recent study[2]). Targeted echocardiography is offered at 20-22 weeks to these fetuses.

3. Screening for neural tube defects (NTD) is

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offered to those with family history of NTD, those with exposure to teratogens like hyperglycemia in mothers with type 1 diabetes mellitus, hyperthermia and drugs like valproate, carbamazepine and isotretinoin and to those belonging to high risk ethnic groups like India, China, United Kingdom and Egypt.

4. Screening for certain genetic disorders is done in the relevant ethnic groups like cystic fibrosis in Caucasians, Tay Sach's, Canavan's disease and Gaucher's disease in Jews and hemoglobinopathies in certain Asian and African ethnic groups.

The screening techniques

1.Maternal serum alpha fetoprotein (AFP)

AFP is the major serum protein of the embryo analogous to albumin and its concentration in the fetal serum steadily increases upto 13 weeks and then decreases. It leaks into the amniotic fluid by diffusion and then into the maternal serum wherein it is detected in steadily increasing quantities after 12 weeks. Open fetal body wall defects augment the AFP leak and result in raised amniotic and maternal serum AFP levels.

Maternal AFP estimation is done between 14th and 22nd weeks and results expressed as Multiple of Median (MoM) of the unaffected population values. A MoM of 2.5 is considered the upper limit of normal. Levels between 2.5 to 3.5 MoM are indiscriminate and a repeat sample is advised. Levels greater than 3.5MoM indicate a fetus at high risk and warrants a high resolution ultrasound which can identify a neural tube defect or other causes of raised maternal serum AFP (Table 2). Where a diagnosis is not possible by sonographic examination, amniotic fluid AFP estimation is done coupled with acetyl cholinesterase assay and the presence of latter enzyme is confirmative of the presence of an open

Table 1. Techniques used for fetal diagnosis

1. Screening techniques:
   a) Maternal alpha foetoprotein (AFP) assay
   b) Second trimester Down's syndrome screening [Maternal serum AFP, hCG, oestradiol and Inhibin]
   c) First trimester screening [maternal serum hCG, Pregnancy associated plasma protein (PAPP-A) and Nuchal translucency]
   d) High Resolution ultrasound scan
   e) Fetal Echocardiography

2. Diagnostic techniques:
   a) Second trimester (14 – 20 weeks) amniocentesis
   b) First trimester (11 – <14 weeks) amniocentesis
   c) Chorionic villus sampling (CVS) 10 – 13 weeks
   d) Percutaneous Umbilical Cord Blood Sampling (PUBS)
   e) Fetal tissue biopsy (liver, skin, muscle)
   f) Pre-implantation genetic diagnosis
   g) Fetal cells in maternal circulation

NTD. Karyotyping is offered to those with elevated amniotic fluid (AFP) levels but absent acetyl cholinesterase enzyme, as the incidence of chromosomal abnormalities is increased five fold in such fetuses.

Since 95% of NTD occur in mothers with no previous history, it is recommended that maternal serum AFP screening be offered to all pregnant women in the second trimester.

2. High resolution ultrasound

High resolution ultrasound can identify major structural malformations of the fetus but the results are operator dependent and in the largest trial to evaluate the usefulness of sonography in detecting the major fetal anomalies in 15,151 low risk pregnant women, (RADIUS trial, Routine Antenatal Diagnostic Imaging with Ultrasound), only 17% of major anomalies were picked up by routine sonography at 15 – 22 weeks gestation and a second scan at 31-35 weeks gestation[3]. Currently the major usefulness of sonography lies in estimation of Nuchal Translucency (NT) which is used in Down's syndrome screening. Fetal echocardiography is offered to those at risk of congenital heart defects and again its results are operator dependent. Recently real time Magnetic Resonance Imaging(MRI) of the fetus has been used to identify defects that cannot be detected by sonography like isolated cleft palate[4].

3. Down's syndrome screening

Triple test or Multiple Marker Screening: Mothers carrying a fetus with Down's syndrome has low levels of AFP and estriol and elevated levels of hCG. The analysis of these three analytes in the maternal serum together with maternal age has been validated as a useful second trimester screening test to identify Down's syndrome fetuses with a 60-75% detection rate. Some centres include a fourth analyte, inhibin. Women with a positive screening test are offered amniocentesis for karyotyping and confirmation of the diagnosis.

First trimester screening: Identification of trisomies in the first trimester offers more choices of safe pregnancy termination and thus it is advantageous to the mother. Combination of maternal serum hCG and Pregnancy Associated Plasma Protein A (PAPP-A) with Nuchal Translucency (NT) measurement done at 10-13 weeks gestation identifies 85% of Down's syndrome cases at a false positive rate of 9.4% (BUN Study)[5]. While hCG levels are raised, the PAPP-A levels are reduced in Down's pregnancies when compared to normal pregnancies.

Table 2. Conditions with abnormal maternal serum AFP levels

Elevated levels:
1. Neural tube defects
2. Abdominal wall defects – omphalocoele, gastroschisis
3. Multi foetal gestations
4. Foetal death
5. Congenital skin defects
6. Cystic hygroma
7. Oesophageal or intestinal obstruction
8. Chorioangioma of placenta
9. Urinary obstruction
10. Renal anomalies (polycystic or absent kidneys)
11. Underestimated gestational age
12. Maternal hepatoma or teratoma

Low levels:
1. Chromosomal trisomies (Down's syndrome)
2. Gestational trophoblastic disease
3. Fetal death (later stages)
4. Overestimated gestational age

4. Carrier screening in genetically inherited disorders:

Parents at high risk of cystic fibrosis (those with CF affected first or second degree relative and Caucasians) are offered carrier testing to identify common CF mutations including the △F508 and if both parents are tested positive then foetal DNA testing is offered.

Diagnostic techniques

Diagnostic techniques are used to confirm the diagnosis in at risk fetuses identified by screening techniques discussed above and also to reassure the parents in cases of false positive screening test results.

1. Second trimester amniocentesis

This procedure is performed between 14 to 20 weeks and amniotic fluid (20 cc) is obtained under sonographic guidance using a 20 – 22 G spinal needle for fetal karyotyping. Complications are fetal loss in 0.3 - 0.5%, vaginal spotting or amniotic fluid leakage in 1-2% and chorioamnionitis in less than 0.1%.

2. First trimester amniocentesis

This procedure is done between 11 and 14 weeks of gestation and although the technique is similar to traditional amniocentesis, less fluid can be withdrawn usually only 1 ml for each week of gestation. Complications include a fetal loss rate of 0.4 – 0.9%as compared to a 0.3- 0.7% for mid trimester amniocentesis and 1.5 % for chorionic villus sampling and an increased incidence of positional foot deformities 0.75- 1.6% versus a 0.1 % background rate. Membrane rupture is also more likely after early amniocentesis and significantly more cell cultures fail necessitating an additional amniocentesis. For this reason, this procedure is not performed in many centres.

3. Chorionic Villus Sampling (CVS)

Placental villi are obtained either transcervically or transabdominally at 10-13 weeks of gestation. Since results are obtained early in pregnancy it alleviates parental anxiety in case of normal results and also offers earlier and safer choices of pregnancy termination in case of abnormal results. Transabdominal CVS is safer than transcervical CVS, has a fetal loss rate of 1.5% as compared to 0.3-0.7% with mid trimester amniocentesis.

4. Percutaneous Umbilical Cord Blood Sampling (PUBS) or cordocentesis

This procedure is used to obtain fetal blood by puncturing the umbilical vein at or near its origin from the placenta with a 22 G needle under sonographic guidance. Its uses are

a) In the assessment, treatment and follow up of red cell and platelet allo- immunization (see later)

b) Karyotyping of fetal blood obtained can be accomplished within 24-48 hours and thus obviates the delay associated with culture of skin fibroblasts obtained by amniocentesis. Hence it can be used when amniocentesis or CVS results are confusing and when rapid diagnosis is necessary.

c) Fetal blood thus obtained can be used for immunological studies, viral cultures, metabolic and hematological studies and acid base analysis

Complications include fetal loss in 1.4%, cord vessel bleeding in 50%, cord haematoma in 17%, feto maternal bleeding in 66% with anterior placentation and 17% with posterior placentation. Most of them are transitory.

5. Fetal tissue biopsy

Fetal tissue can be obtained by ultrasound guided biopsy; for example muscle biopsy to diagnose muscular dystrophy or mitochondrial myopathy and skin biopsy to diagnose epidermolysis bullosa.

6. Preimplantation genetic diagnosis

Either polar body or a totipotent stem cell obtained by blastomere biopsy is subjected to genetic tests like Fluorescent in situ hybridization (FISH) analysis. Only healthy embryos are then implanted into the womb. Diseases like cystic fibrosis, thalassemia, sickle cell disease, X linked disorders can be prevented by this advanced but still experimental technique.

7. Fetal cells in maternal circulation

A small number of fetal cells circulate in the blood stream of pregnant women and these can be isolated using cell sorting techniques and used for evaluation of genetic diseases like hemoglobinopathies and fetal red cell D – antigen typing. Nevertheless it is difficult to obtain a pure uncontaminated specimen of fetal cells from maternalcirculation.

Fetal therapy

Therapeutic options available are

1. Pregnancy termination: Single fetal termination or multifetal reduction
2. For twin to twin transfusion syndrome
3. Fetal transfusion
4. Fetal medical therapy (Table 3)

5. Fetal surgery (Table 4)
6. Stem cell transplantation
7. Gene transfer

Pregnancy termination

This is offered to fetuses with irremediable structural anomaly or chromosomal disorder. Prenatal diagnosis allows parents to make an informed decision after consultation with a multidisciplinary team that comprises of the pediatrician, genetic consultant and the appropriate pediatric sub specialist. For techniques of pregnancy termination readers can refer to any standard text book of obstetrics.

Twin to Twin transfusion syndrome

This can complicate about 15% of monochorionic twin pregnancies. The donor twin is anemic, growth restricted with oligohydramnios while the recipient twin is plethoric, plump with poly hydramnios. The therapeutic options available are therapeutic amniocentesis (for recipient twin), septostomy, and laser occlusion of placental anastomosis and selective feticide of the donor twin.

Fetal transfusion

Rh D Alloimmunization: Two significant

Table 3. Fetal medical therapy

Medical disorders	Treatment and rationale
1. Congenital adrenal hyperplasia	Maternally administered cortisol to minimize virilization of female fetus
2. Congenital hypothyroidism	Intra amniotic thyroxine which will be ingested by the fetus.
3. Fetal thyrotoxicosis	Maternally administered propyl thiouracil
4. Fetal supra ventricular tachycardia	Maternally administered digoxin, flecainide or amiodarone is given to fetus through umbilical vein or intramuscular injection into the buttock
5. Fetus at risk of congenital syphilis or toxoplasmosis	Maternal treatment with appropriate antibiotics

advances have influenced our management of Rh alloimmunized fetuses. One is the ability to non-invasively identify the Rh D genotype of the foetus by typing the fetal cells circulating in maternal blood using the polymerase chain reaction assay. The other is the advent of velocimetry of fetal middle cerebral artery to predict foetal anemia which has superceded the traditional Liley's nomogram[6]. Peak systolic velocities (PSV) greater than 1.5 multiples of median (MoM) of the specific gestational age identifies a fetus with moderate or severe anaemia with 100% sensitivity and 12% false positive rate. PSV shows a good correlation to the Liley's nomogram which uses serial optical density measurements of amniotic fluid at 450nm that reflects the bilirubin content of amniotic fluid and hence fetal hemolysis[6].

If monitoring of PSV of middle cerebral artery indicates fetal anemia then fetal blood sampling and transfusion are mandated. The earliest agreed gestation wherein this can be initiated is 18 weeks. Either cordocentesis or intra hepatic vein puncture can be used. The latter is technically difficult but has a lesser incidence of fetal distress. Fetal loss due to the transfusion is 1 – 2 % in uncomplicated cases but it can be as high as 20% in hydropic fetuses. Group O negative, cytomegalovirus negative and irradiated (to prevent graft versus host disease) packed RBCs with a hematocrit of 75 – 90% to minimize volume of transfusion is used aiming at a post transfusion fetal hematocrit of 55 – 60%[6]. Weekly measurement of PSV of middle cerebral artery is indicated in follow up of these fetuses to assess the need for further transfusions.

The same principles are applied in the management of red cell alloimmunization due to minor group incompatibilities as well as anaemia due to parvo virus B19 infection. A single transfusion is all that is needed in most cases of fetal parvo virus infection although viral myocarditis adversely influences the outcome[1].

Fetal medical therapy

Fetal medical conditions can be treated by

Table 4. Fetal surgery

Surgical disorders	Procedures performed
1. Obstructive uropathies	Vesico amniotic shunts to decompress the collecting system and prevent progressive hydronephrosis.
2. Hydrothorax or thoracic masses leading to pulmonary hypoplasia	Thoraco amniotic shunts
3. Cystic adenomatoid malformation causing hydrops fetalis	Open fetal lobectomy, thoracic shunts
4. Congenital diaphragmatic hernia	Ex-utero fetal surgery but this is strictly investigational as outcomes are suboptimal and postnatal outcomes are improving
5. Sacro coccygeal teratoma	Debulking surgery
6. Cleft lip and palate[7]	Feto endoscopic approach and repair which obviates numerous orthodontic, dental and plastic surgeries that are needed after birth.

maternal medications that cross placenta. The conditions and the treatment modalities are given in Table 3.

Fetal surgical therapy

The major advantages of fetal surgery are scarless wound healing and callus free bone healing. The risk of fetal loss due to surgery should be weighed against the chances of fetal death without surgery and informed consent be taken. Percutaneous shunt placements are the commonly performed procedures (Table 4). Fetoscopy and video endoscopic surgery promise to be less invasive and hence are more acceptable than open surgical techniques.

Stem cell transplantation

As fetus is immunoincompetent until 18 weeks, it is theorized that it would be tolerant to foreign antigens before that time. Stem cell transplantation may offer a life time cure to many hemoglobinopathies, severe combined immunodeficiency syndrome etc. This therapy is experimental.

Gene therapy

This is the ultimate panacea for the genetically inherited disorders that will otherwise necessitate termination of pregnancy. Anderson proposed certain criteria for gene therapy in 1984[8] which have not been met so far and hence fetal gene therapy is still in its nascent stages confined to experimental trials. The criteria for therapeutic gene transfer are

1. The normal gene can be inserted into the target cells and remain there long enough to have the desired effect.

2. The level of gene expression in the new gene will be appropriate

3. The new gene will not harm the cell or the individual.

Points to remember

1. Measurement of various analytes in the maternal serum, high resolution ultrasonography and carrier screening in genetic disorders are the main screening tools available in prenatal or fetal diagnosis.

2. Maternal serum alpha fetoprotein (AFP), estriol and human chorionic gonadotrophin constitute the triple screen that is performed in the second trimester to identify the fetus at risk of Down's syndrome

3. First trimester screening for trisomies consists of maternal serum AFP, Pregnancy Associated Plasma Protein–A and Nuchal Translucency

4. Mid trimester amniocentesis and trans abdominal chorionic villus sampling are the recommended diagnostic techniques to assign a diagnosis following positive screening tests

5. Fetal anemia severe enough to warrant intervention is identified by Peak Systolic Velocity in Middle Cerebral artery of greater than 1.5 multiples of median for the specific gestational age and this has replaced traditional Liley's nomogram in the management of Rh alloimmunization.

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NEWS AND NOTES

CME ON "COMMON EMERGENCIES IN CHILDREN"

Date: 19th March 2006

Venue: Chandigarh

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12th East Zone Pedicon & 20th Assam State Pedicon

Date: 19-20 November, 2005

Venue: Guwahati, Assam

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NEONATOLOGY

FREQUENTLY ASKED QUESTIONS IN NEONATAL OFFICE PRACTICE

1. **Is phimosis normal in newborn? What are the indications for circumcision?**

   At birth the prepuce and glans penis are adherent and cannot be retracted. Phimosis therefore is physiological in newborn up to the age of 1 year. This per se is not an indication for any intervention. Circumcision can be advised after 5 years if the prepuce cannot be retracted after a trial of cortico steroid local application. If the infant has ballooning of the prepuce, recurrent balano posthitis and recurrent UTI, circumcision may be considered at an earlier age.

2. **What are the important causes for scrotal swelling in a newborn baby and when is surgery recommended?**

   In a baby scrotal swelling can be due to hydrocoele or hernia. Hydrocoele is accumulation of fluid in tunica vaginalis. In hernia the content of scrotal swelling is bowel loop. In majority, hydrocele is non communicating and disappears by 1 year of age. In some, hydrocele is communicating (persistingly patent processus vaginalis connecting the scrotum to peritoneal cavity) and is likely to persist. If hydrocele is large and tense (early surgery) or persisting beyond 12-18 months, surgical repair is indicated. On the other hand, hernia should be operated at the earliest, as there is a risk of incarceration or strangulation.

3. **What are the various anterior abdominal wall hernias?**

   Umbilical hernia is very common and is considered normal, especially in preterm babies. The vast majority of them spontaneously resolve. It is not advisable to do strapping since it delays, rather than help closure. Umbilical hernias usually disappear by 5 to 6 months, but they may persist until the age of four or five. Incarceration is common, strangulation is extremely rare though it has been documented. If the ring is more than 2 cm it is less likely to close spontaneously and surgery is advocated. Supra umbilical hernias may require surgery, although only for cosmetic reasons. An epigastric hernia may not get corrected on its own, but does not require treatment unless it causes discomfort. Divarication of the recti is a self-limiting condition and is obvious between the ages of three and six years, it disappears without treatment by about ten years.

4. **How do we detect squint in the baby?**

   The eyes of a healthy neonate are frequently not aligned and intermittent squint is common in the first few weeks of life. Squint may be due to transient sixth nerve palsy, birth trauma and transient disorders of vertical gaze. If it persists beyond six weeks, ophthalmological opinion is essential.

5. **What are the causes of watery / sticky eyes in a neonate?**

   Nasolacrimal duct obstruction is common in neonates and may lead to persistent watery/

sticky eyes. This usually clears spontaneously by 12 months of age. Frequent gentle massaging at the inner angle of the eyes on the nasal side may be helpful. If symptoms persist beyond 12 months, probing of the duct may be necessary to establish tear drainage. Rarely it may be due to acute dacryocystitis.

6. What are the common causes of papular facial lesions in a newborn?

Eruptions similar to acne vulgaris such as comedones, papules, pustules may be seen over the face and are due to the effect of maternal androgens on the pilosebaceous unit. They are usually seen predominantly in boys and resolve spontaneously without treatment. Mild keratolytics like salicylic acid may be used in severe cases. If lesions persist, virilising syndrome should be suspected.

7. What are the various presentations of 'nappy rash' and its management?

Erythema, edema, papules, blisters, followed by scaling can be seen in the nappy area with maximum intensity over the convex surface of the thighs and buttocks sometimes also over the genitalia. It is due to various factors like irritant effect of ammonia liberated from the fecal organisms in wet napkin, maceration, sweating, high humiditiy, bacterial and candidal colonization and sometimes even frank infection. The treatment is to keep it clean, dry and well aerated. Anti barrier cream like vaseline and topical steroid / antibacterial / anti fungal can be applied in severe cases.

8. What is cradle cap?

Greasy scaling over the vertex of the scalp is called a cradle cap. It usually denotes an increase in normal scaling and may be due to infantile ichthyosis or seborrhoeic dermatitis. It responds well to liquid paraffin and washing, rarely requires topical steroids or antibacterial agent.

9. What is miliaria and why does it occur?

Miliaria or prickly heat or sweat rash is caused by obstruction of sweat ducts. The lesions occur when sweat is unable to escape on to the surface and over which bacterial colonization occurs. Neonates are usually prone to miliaria due to immaturity of the sweat ducts and nursing being done in a warm environment. Eruptions are either tiny vesicles or erythematous papules, which develop around sweat ducts. They are usually seen over the chest and areas of friction, but may be seen elsewhere. Erythematous lesions may produce itching. The treatment is to reduce the humidity and sweating.

10. What are Mongolian spots?

Mongolian spots are benign pigmented lesions often found at birth. These lesions may be small or large, grayish blue or bluish black and irregular in shape. They are never elevated or palpable, most commonly seen in lumbo sacral region, but upper part of the back, buttocks, shoulders, arms, legs and face are occasionally involved. They result from an infiltration of melanocytes deep in the dermis. They usually fade by the first year of life, probably due to decreasing transparency of the overlying skin rather than a true disappearance of the lesions.

11. What is the common skin rash seen in a neonate in the first 2 days of life?

The common skin rash seen during the first 2 days of life is erythema toxicum. It presents as a scattering of macules, papules and sometimes vesicles that usually occur on the extremities and face. It affects 50- 70% of term infants and the cause is not known. The rash usually appears on the first or second

day after birth and is self-limiting. The newborn is active, alert and feeds well. It may cause alarm when the vesicles and papules are numerous and if the lesions are pustular. If the vesicles are punctured and the fluid examined eosinophils are seen. The incidence of erythema neonatorum decreases with decreasing gestational age. Rarely seen in infants < 30 wks.

12. What are the causes of bowing in a neonate?

Mild bowing of the lower extremities is a normal finding in a baby up to 18 months of life. Generally the bowing is 15° and confined to the tibia (genu varum) but occasionally it can be noted in the distal femur also. It is often symmetrical and accompanied by internal tibial torsion. Pathological bowing is rare in a neonate and can be due to metaphyseal dysplasia, Blount's disease and rickets, which can be distinguished radiologically.

BOOK REVIEW

Name	:	Flexible fiberoptic bronchoscopy in children
Editor	:	Dr. D. Vijayasekaran
Review	:	The book on 'Flexible fiberoptic bronchoscopy in children', the first book by an Indian author dwells on the fundamentals of flexible bronchoscopy. Beginners in this field will find it very useful when they are proceeding onto do flexible bronchoscopic procedure. The author has not only given, the indications but also has elaborated on the how to do the procedure under local anesthesia. The author also gives details on how to clean and maintain the instrument properly. The book also has case scenarios with bronchoscopic pictures. The clinical scenarios could have been discussed more elaborately. The picture quality could be improved further in subsequent editions.
Publishers	:	M/s. Kural Publications 18, Harris Road, Chennai - 600 002. India
Price	:	Rs. 500/-

Name	:	Breastfeeding: A guide for new mothers
Editor	:	Dr. Meenakshi Krishnan
Review	:	The book covers issues like reasons to breastfeed, facts about breast feeding and problems faced by nursing mother. Added attraction is the frequently asked questions related to breastfeeding. As additional information, the book also covers the nutrition while nursing, medication and nursing mother, as well as how to continue breastfeeding while working. The facts are delivered in a simple language for the mothers to understand and will be of immense help for paramedicals also who are involved in the promotion of breastfeeding.
Publishers	:	East West Books (Madras) Pvt. Ltd., New Delhi - 110 002. India
Price	:	Rs. 120/-

NEPHROLOGY

SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDREN-CLINICAL SPECTRUM AND MANAGEMENT

* Uma Sankari Ali

Abstract : Systemic lupus erythematosus is an autoimmune multisystemic disease whose etiology is unknown. The etiology of lupus is unknown. Lupus in children tends to present acutely with multisystem involvement. A disciplined approach to the evaluation of every symptom and sign along with appropriate laboratory evaluation leads to the correct diagnosis. When treated adequately the natural history is favorably altered to produce a good outcome with improvement in the histopathology. Leading cause of death in almost all series then and now remains infections followed closely by renal failure.

Keywords : Systemic lupus erythematosus, Children, Clinical features, Management

Systemic lupus erythematosus (SLE) is an autoimmune, multisystemic, potentially fatal disease that predominantly affects young post pubertal women. 20% of all cases of SLE begin in childhood usually after 5 years of age. The predominantly female involvement is not so apparent when lupus occurs in prepubertal children, the female to male ratio being 2:1 as compared to 8:1 in adults[1,2].

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The etiology of lupus is unknown. It may be triggered by one or more known or unknown environmental factors in a genetically predisposed host. There is a multigenic predisposition to the development of SLE that may contribute to the susceptibility at different checkpoints involving immune dysregulation, enhanced apoptosis, production of autoantibodies and decreased clearance of immune complexes.

Although rare, patients with genetic deficiencies of complement components C1q, C1r, C1s and C4 and C2 are highly predisposed to develop SLE. Complement deficiencies probably predispose to SLE because of disturbance in the processing and clearance of immune complexes.

Hormonal factors play an important role in the expression of SLE with androgens suppressing and estrogens and prolactin aggravating SLE. Environmental factors that precipitate SLE include ultraviolet light, drugs, toxins and infections [3].

Clinical manifestations

Lupus in children tends to present acutely with multisystem involvement. Fever with musculo skeletal symptoms, weight loss, anorexia and fatigue are the common presenting features. Arthiritis which is non-erosive and non-deforming is found in 60 to 75% of children and is often a presenting feature[1,3,4]. The well known malar rash is neither pathognomonic nor found consistently in patients. It is seen in not more than 50% of the cases and is less commonly seen in Indian children [4]. Anemia is a common finding seen in almost 75% of the Indian children.

Pleuritis with or without obvious signs is present in 25%-45% of the children. Overt pericarditis or pericardial effusions are uncommon but 2D echo detection of pericarditis is seen in one-third of the patients[1,3,4] (Table 1).

Photosensitivity is common, though the information is not often volunteered by the patient. Raynaud's phenomenon and discoid lupus are rare but significant findings. Alopecia is seen in many children with active disease and in the given setting highly suspicious of lupus. Oral and genital ulcers are painless and may be easily overlooked.

Renal involvement is very common and is one of the main determinants of the long-term outcome. It is seen in about 60% of the patients at presentation. The cumulative incidence is much higher and renal involvement eventually occurs in more than 75% of the cases. Clinical manifestation may be initially silent with asymptomatic proteinuria or hematuria detected only on routine urinalysis. With progression there may be acute nephritis, nephritic syndrome, tubulo-interstitial diseases, hypertension and rarely acute renal failure. Findings on urinalysis vary with the severity of the disease. There may be just leucocyturia, hematuria and / or proteinuria in milder cases. In classical lupus nephritis the urine shows not only massive proteinuria but also shows telescoped sediment with RBCs, WBCs and a variety of casts characteristic of different stages of glomerulonephritis. The presence of nephritic-nephrotic features, a telescoped urinary sediment with low C3 along with elevated titres of ANA and ds-DNA makes the diagnosis of lupus fairly certain even when renal involvement occurs as an isolated feature[5,6]

Renal biopsy is essential as it determines the aggressiveness of the therapy as well as the long term prognosis. The WHO classification describes six histological varieties. Diffuse proliferative glomerulonephritis (WHO class 4) carries the worst prognosis with a high risk of progression to chronic renal failure.[7]

The presence of crescents, endocapillary proliferation, karyorrhexis, neutrophilic infiltration, fibrinoid necrosis are indices of activity and warrant intensive therapy. The presence of tubular atrophy, fibrosis and sclerosis are indicators of chronicity that may not benefit from immunosuppression.[8] Although there is a fair correlation between the clinical severity and the histopathology, this is not absolute. Children without overt nephritic syndrome and with milder urinary findings can sometimes reveal severe diffuse proliferative glomerulonephritis on histopathology (Table 2).

CNS involvement is not a common presenting manifestation but is seen overall in 30 to 45% of the patients. Manifestations may be seen in the form of seizures, altered behaviour, focal deficits or frank psychosis. Though it may be difficult to diferentiate it from steroid induced psychosis and infective causes can be a cause of major diagnostic difficulties. Rapid investigation to exclude infections is needed before instituting aggressive immunosuppression as a mistaken, diagnosis can have a disastrous outcome [9]

Infectious complications are extremely common and are the major cause of death. They occur in both treated and untreated lupus and can pose serious diagnostic and management problems. In the presence of fever, respiratory symptomatology or CNS involvement consider infection. Blood cultures and cultures from involved sites are a must before starting treatment. High WBC counts and neutrophilic leucocytosis are not features of SLE and generally indicate the presence of infections. However counts are often not elevated despite infections. Apparently normal counts may represent

infection induced elevation from previously low counts. A highly elevated CRP titre is also indicative of infection. Tuberculosis, fungal and other opportunistic infections also should be kept in mind. Prophylactic antibiotics should be strictly avoided[3]

Diagnosis

Although lupus is a multisystemic disease the organ involvement need not be simultaneous; it can occur sequentially at any interval of time. Therefore it is not uncommon for a child to present with predominantly single organ involvement posing diagnostic difficulties. Mistaken and missed diagnosis is the rule rather than the exception.

A high index of suspicion is required to diagnose lupus. Fever with arthritis is often diagnosed as rheumatic fever or rheumatoid arthritis. The associated anemia is often not investigated in detail and is presumed to be nutritional. Another common mistaken diagnosis is tuberculosis because of the prolonged fever, constitutional symptoms and accompanying pleuritis. It is very uncommon to have a negative mantoux test in a child with pleurisy due to tuberculosis and hence one should be very wary of treating a child with pleurisy as TB in the absence of mantoux positivity. Children presenting mainly with fever are often treated as enteric fever or empirically with antimalarials. The widal test may be falsely positive due to an anamnestic reaction.

A disciplined approach to the evaluation of every symptom and sign along with appropriate laboratory evaluation leads to the right diagnosis. Detailed assessment of anemia including a reticulocyte count and a Coomb's test as well as routine urinalysis helps to point out to the presence of multisystemic involvement. 2D echocardiogram is a useful adjunct to detect the presence of a silent myopericarditis.

It must be remembered that although multi organ involvement is common it is not unusual for a child to present with a single organ involvement. Presentation with a hemolytic anemia or thrombocytopenia or a nephritic nephrotic syndrome may pose diagnostic difficulties unless unusual features are taken note of. The ACR (American College of Rheumatology) criteria of 1982 needs 4 out of 11 criteria to be met for making a diagnosis of lupus[10]. This has been shown to have a sensitivity of 96% and a specificity of 100% in the diagnosis of childhood lupus. The revised 1997 criterion has substituted false +ve VDRL with false +ve VDRL for >6 months and the presence of LE cell phenomenon is no longer included as a criterion. This has been substituted by antiphospholipid antibodies. The diagnostic specificity of these revised criteria is yet to be validated. [11]

Although not part of the ACR criteria, measurement of serum complement is a useful adjunct investigation. It is invariably lowered during active disease especially in those with renal involvement. Reduction of C3 usually precedes the development of a clinical relapse.

The loss of recognition of self, leading to the production of auto antibodies against nuclear antigens is the hallmark of SLE. Most notable amongst these antibodies is the anti nuclear antibody (ANA) which is so consistently found in more than 95% of all active untreated SLE that it constitutes one of the 11 criteria for diagnosis. However, it has low specificity as it is found in a number of viral infections as well as drugs. Antibodies to double stranded or native DNA is highly specific for lupus. Antibodies against Ro and La are important, as their presence in pregnancy is associated with the development of neonatal lupus and congenital heart block. They are the only antibodies that can cross the placenta. The presence of antiphospholipid

antibodies-lupus anticoagulant and anti cardiolipin antibodies is associated with a high incidence of intravascular thrombosis, spontaneous abortions and fetal death. However they are not specific for lupus and can be found in many other conditions [3].

Treatment

The treatment of SLE requires a careful evaluation of the presence as well as severity of the organ and systems involved. It must be remembered that SLE is a dynamic disease. When treated adequately the natural history is favorably altered to produce a good outcome with improvement in the histopathology. If inadequately treated it can progress either overtly to a more aggressive disease or insidiously to silent destruction of organs.

Non-steroidal anti-inflammatory drugs have a limited role in childhood SLE. Their main use is in children with predominant musculoskeletal symptoms without organ or system involvement. Such a situation is rarely encountered in childhood SLE. Close monitoring is needed in patients treated without immunosuppression to detect the insidious development of systemic involvement. Regular CBC and urinalysis is required along with careful clinical evaluation.

For the vast majority of patients steroids form the mainstay of therapy. Children with systemic involvement and those with constitutional symptoms such as fever, anorexia, fatigue and weight loss require steroid therapy. The standard steroid induction therapy consists of prednisolone 1-2 mg/kg/day in divided doses for 4-6 weeks till clinical, laboratory and serological remission is attained. This is indicated by normalizing C3 and negative ANA, dsDNA.

Children with only constitutional symptoms or those with mild systemic involvement can be treated with lower doses of prednisolone, 0.5-1 mg/kg/day in divided doses. However, the response may take several weeks or even months to occur.

In children with life or organ threatening disease, a more rapid induction can be attained with IV methylprednisolone at 15-30 mg/kg/dose once daily for 3 to 6 doses. Some of the indications for high dose steroids are CNS disease, acute renal failure, acute hemolysis, severe thrombocytopenia and pulmonary hemorrhage.

Maintenance therapy

Once remission is attained it needs to be maintained with lower doses of steroids to avoid steroid toxicity while maintaining a disease free state. Steroids need to be maintained at a dose sufficient to maintain clinical, serological and laboratory remission. Steroids need to be continued for several years (not less than 3 years) and in many cases indefinitely.

Tapering should be done very slowly by 10 mg if the patient is on > 50 mg/day; by 5 mg if the patient is on 20-40 mg/day and by 2.5 mg if the patient is on less than 20 mg/day. Tapering can be done monthly if the patient is taking daily steroids and 2 to 3 monthly if the patient is taking alternate day steroids. Not all children can maintain total control on alternate day steroids[3].

Second line drugs

All second line drugs are additives to corticosteroids and not substitutes. The indications for second line therapy include steroid unresponsiveness, poorly controlled disease, relapse while tapering steroids, steroid toxicity, presence of CNS involvement, serve renal disease or life threatening organ involvement.

The various drugs that have been used as second line are

Table 1. Clinical manifestation in childhood SLE

	Cassidy (58 cases)	Cameron	Ali (50 cases)
Arthritis	72%	76%	60%
Malar rash	51%	56%	30%
Alopecia	16%	20%	25%
Oral ulcers	12%	16%	10%
Anemia	43%	47%	75%
Thrombo-cytopenia	22%	27%	10%
Pleuritis / Pericarditis	31/40%	36/45%	25/30%
Renal inv	84%	86%	75%
CNS inv	9%	31%	45%

Cyclophosphamide

Azathioprine

Cyclosporine

Methotrexate

Mycophenolate mofetil

Cyclophosphamide is the drug of choice for severe renal or CNS involvement. The high risk of toxicity precludes its use in less severe disease. When indicated, it should be used under the supervision of a pediatric nephrologist or a person experienced in its use. The NIH trial in adults with SLE and renal involvement found a better long term outcome with a lower incidence of progression to CRF in the group that received cyclophosphamide when compared to those receiving prednisolone alone or prednisolone with azathioprine[12]. IV cyclophosphamide is given as 500 mg to 750 mg/m^2 monthly for 7 months followed by three monthly infusions. Its long term use is associated with secondary amenorrhea with ovarian failure in 100% of adult females above the age of 30. Similar therapy has been recommended for children with class 4 lesions. However their place in the management of childhood lupus nephritis needs to be better defined. The risk of gonadal toxicity with pulse cyclophosphamide in prepubertal children has not been defined[13]. It must be remembered that incidence and severity of SLE varies in different ethnic groups. SLE favourable results are not always found with this regime in all ethnic groups. A less toxic and gonad sparing alternative would be to treat initially with oral or IV cyclophosphamide followed by maintenance immunosuppression with azathioprine[14]. Indiscriminate use of cyclohosphamide in children whose disease severity could be managed with less toxic approaches should be strongly condemned.

Azathioprine is the oldest second line drug used to treat SLE. It is well suited for treatment of less severe disease as a steroid sparing drug or to prevent relapses while tapering steroids and as maintenance therapy after the disease is well controlled with steroids and cyclophosphamide.

Although not widely used, three drugs that may be useful in selected cases are methotrexate, cyclosporine and mycophenolate. All three could have a steroid sparing role in steroid dependent SLE permitting reduction in steroid dosages without inducing a lupus flare. Mycophenolate has also been tried in cyclohosphamide resistant lupus. Methotrexate may have a beneficial role in resistant arthritis or skin lesions and in interstitial lung disease [15,16].

Hydroxychloroquine is a useful adjunct and should be used in all patients needing steroid therapy. It has a steroid sparing effect and attenuates some of the adverse effects of long term steroids on lipid metabolism. Regular ophthalmic check up is essential to detect retinal toxicity [17].

Table 2. WHO histopathological classification and clinical correlations

Class	Description	Clinical features
1.	Normal	No renal involvement
2.	Mesangiopathic	Asymptomatic hematuria, proteinuria
3.	Focal proliferative	Nephritis, nephrotic syndrome
4.	Diffuse proliferative	Nephrotic syndrome, nephritic features, azotemia
5.	Membranous	Nephrotic syndrome
6.	Sclerosing	Chronic glomerulonephritis, CRF

Autologous bone marrow transplantation has been used with short term success in adolescents with SLE. However the long term outcome is not yet known. The use of biological modulators such as IV immunoglobulin or plasmapheresis is largely anecdotal and at present has no place in the routine management of SLE.

General measures

General measures play a very important role in the successful management of lupus. These include good nutrition, avoidance of fatigue, protection from sun exposure and avoidance of drugs that could trigger SLE.

Exposure to sunlight or UV radiation should be strictly avoided not only in children with photosensitivity but in all cases of SLE. Sunscreen with a sun protection factor (SPF) of at least 15 should be used daily when going out during the day even if it is not sunny. Ultraviolet B results in photo degradation of native DNA in the skin thereby increasing its immunogenicity. Light induces apoptosis of keratinocytes which may develop small surface blebs that may contain lupus auto antigens such as Ro rendering them available as immunogens which may trigger activity of SLE[3]. Drugs such as chlorpromazine which has a similar action should be avoided.

Pubertal girls should avoid oral contraceptives.

One of the vital requirements for managing lupus is the continuity of care by a team of physicians with experience in the management of SLE and in the use of immunosuppressive therapy. Continued close surveillance with the aim of total control of the disease and the inclusion of a pediatric nephrologist in the care of the patient from its inception to provide ongoing renal surveillance and care are important ingredients for a successful outcome.

Outcome

The mortality has dropped from 42% seen in the 60s to less than 20% today. The mortality in our setup has been about 28%. However, the leading cause of death in almost all series then and now remains infections followed closely by renal failure [1,3,6,18,19].

The quality of life of long term survivors is reasonably satisfactory. In our own follow-up of 12 long term survivors (5-17 years follow-up) 7 are in remission with normal renal function and are off therapy. Three of the 7 had WHO class 4 on histopathology. Five are still on therapy, 3 of whom are in good control with normal renal function. One patient with class 4 is inadequately controlled and has hypertension. She is intermittently non-compliant. Only one patient is in CRF. This patient was transferred 10 years ago to an adult care where his monitoring and treatment had been very inadequate.

The social adjustment of these patients has been good. Barring one girl who has dropped out of school, the remaining are either in college doing well in studies or working. Two girls are married, one has had 2 successful pregnancies and the other is now seven months pregnant and doing well. Lupus may flare during pregnancy and requires close monitoring.

Points to remember

1. *Multisystemic, potentially fatal disease.*

2. *A high index of suspicion is required to diagnose lupus.*

3. *Steroids form the mainstay of therapy. Second line drugs are additives to corticosteroids and not substitutes. General measures play a very important role in th successful mnagemnt of lupus.*

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RADIOLOGIST TALKS TO YOU

ACUTE ABDOMEN IN THE CHILD - I

*** Vijayalakshmi G**
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***** Ramalingam A**

We have already dealt with recurrent abdominal pain in a child in earlier issues. This article will focus on a child with acute abdominal pain. When faced with a distressed, anxious parent and a history of events, which is not clear imaging of the abdomen can help you to evaluate the patient. Ultrasound will address your primary concern – whether a surgical procedure is indicated or not. It may not always give you the exact answer, but it will definitely help to narrow down possibilities.

One catastrophic event is perforation. An x-ray of the abdomen is a more sensitive modality for the presence of free air and it is easy to identify air under the domes of diaphragm. The other surgical emergency is intestinal obstruction. The x-ray will show dilated loops of bowel upto the point of obstruction but it will not always show the cause for the block. Other modalities like barium meal series, ultrasound or CT will help to delineate the cause.

The imaging algorithm for acute abdomen therefore includes the x-ray of the abdomen as a first step. This is followed by ultrasound. CT can be of some help but the disadvantage is the enormous radiation that it entails which is not good for a growing child.

The commonest cause for acute abdomen is acute appendicitis. The ultrasound features are a thickened, non-compressible appendix. This is seen as a blind ending, aperistaltic tube in the RIF. (Fig.1). Sometimes it is distended with fluid with a bright fecolith within it. The mesenteric fat surounding it is swollen and bright. A thickened oementum may protectively drape over it and is seen as a horizontally placed echogenic band just under the anterior abdominal wall. All these appearances are seen well with a high frequency probe of 5 or 7 MHz. Ultrasound may not help in diagnosing appendicitis if it is very mild or if the examination is done very early in the course of the disease. The technique of graded compression with the probe may not be possible due to the presence of pain. The associated ileus may result in gas filled loops of bowel in the RIF that may block the ultrasound. Therefore, practically speaking, it is reasonable to proceed with surgery when there is a classical presentation of RIF pain and tenderness even if ultrasound does not produce clear evidence. The value of ultrasound in these instances is more to rule out other problems.

As inflammation proceeds peri-appendiceal fluid may collect. Abscess formation is seen as a fluid loculation with a gas component that is seen as white specks within. The appendicular mass consists of thickened aperistaltic bowel loops and omentum surrounding an appendix that is now ill-defined. (Fig 2).

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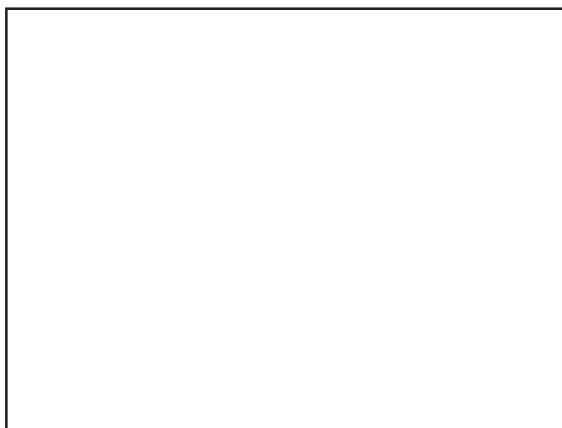
Fig. 1 Fluid filled, non-compressible appendix
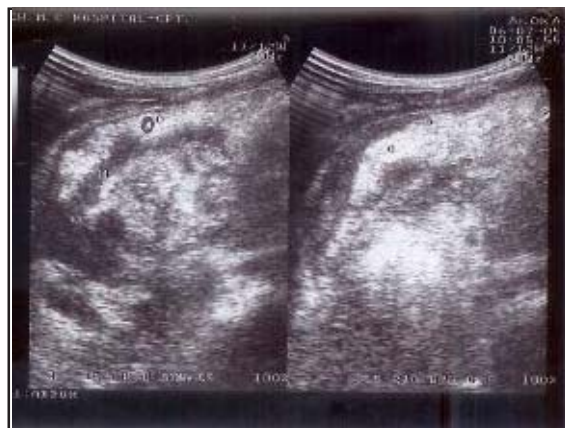
Fig. 2 Appendicular mass. W is wall of the bowel. O is omentum

Fig. 3 Mesenteric adenitis

Fig. 4 Perforated Meckel's

The same process of walling off an inflammatory process is seen with Meckels diverticulitis also. A mass of thickened aperistaltic bowel loops with small localized peritoneal fluid collections seen in the suprapubic or umbilical region should lead to a suspicion of Meckel's. In other words a mass like an appendicular mass seen medial to the usual location of the appendix should also prompt a diagnosis of Meckels. Fig.3 is that of a 19 year old boy who was diagnosed as appendicular mass which later turned out to be perforated Meckels.

Another problem in children that can lead to a false diagnosis of appendicitis is mesenteric adenitis. Mesenteric adenitis is part of a systemic viral infection. There is a cluster of enlarged nodes in the RIF with surrounding mesenteric (Fig 4) thickening and hyperperistaltic bowel loops. Enlarged nodes and mesenteric thickening can also occur in appendicitis but local ileus rather than hyperperistalsis is seen. This may be the differentiating feature. However it is practically difficult to rule out appendicitis totally and it is better to be careful before reporing appendicitis as mesenteric adenitis.

In the next issue we will continue to see more instances of how imaging will help in evaluating the acute abdomen.

CASE STUDY

AMNIOTIC BAND SYNDROME - A CASE REPORT

* *Thiraviam Mohan M*
* *Gopal Subramoniam*

Introduction

Amniotic Band Syndrome (ABS) is a set of congenital anomalies attributed to amniotic bands that stick, entangle and disrupt fetal parts. In view of its rarity, we report a case of newborn with multiple constriction bands.

Case report

A term, small for gestational age, female baby weighing 2.2 kg was born to a 31 years old primi by elective ceasarean section for breech presentation. There was no history of consanguinity miscarriages in mother, or congenital deformities in the family, The baby was not asphyxiated. She was noticed to have multiple congenital anomalies talipes equinovarus deformity of left foot, absent right foot and syndactyly of both hands. Her head circumference was 32.5 cm and length 48 cm. There was no facial anomaly. There were multiple constriction bands observed in the left hand and both legs. The other systems were within normal limits. The ultra sonogram of abdomen and cranium was normal. With these findings a diagnosis of amniotic band syndrome was considered.

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Discussion

Amniotic Band Syndrome is a set of congenital anomalies caused by entrapment of fetal parts in fibrous bands[1]. It is also called as annular constriction bands, intrauterine amputation, Streeter's dysplasia, ADAM Complex (Amniotic deformity, adhesion, mutilation), amniotic band sequence.

The incidence of Amniotic Band Syndrome is 1:1200 births[2]. It is not a genetic disorder but thought to be due to amniotic rupture in early pregnancy which exposes baby to the fibrous bands originating from the chorion.

Two theories have been suggested to explain the mechanism of fetal anomalies. Endogenous theory suggests that the defects result from focal development errors in formation of limb connective tissue. Exogenous theory by Torpin[3] suggests these bands result in entanglement of fetal parts reduced blood supply, leading to constriction rings and amputations.

The clinical features include distal ring constriction, limb deformity, intrauterine amputaion, syndactyly, progressive lymphodema and peripheral nerve palsy. Associated anomalies include cleft lip, cleft palate and clubfoot in 50% of cases. In the case of asymmetric fetal anomalies regardless of presence or absence of fibrous bands, Amniotic Band Syndrome should be considered.

The diagnosis can be made by ultrasound. During the first trimester an appearance of a "Cobweb containing a fetus" is suggestive of ABS[4]. Visualisation of amniotic bands attached

Fig 1. Showing constriction bands in (L) index finger, (L) leg & (R) leg (shown by arrows)

to the fetus and the restriction of fetal movements is another observation[5]. If there is foetal death the diagnosis is confirmed by autopsy.

Treatment options for this include surgery[6] in which the amniotic bands that threaten to amputate limbs are separated. Syndactyly needs plastic surgery to correct the webbed fingers. In case of growing hands, distraction augmentation

manoplasty is done. Cleft lip and palate and strabismus also need correction.

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