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DR. PRADEEP KUMAR DEBATA

Professor
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President NNF Delhi

Dear NNF Delhi Members

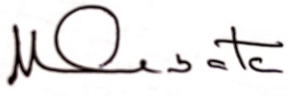
Wish you all a happy and healthy new year on behalf of NNF Delhi. May this year bring new accolades to our most loved NNF Delhi branch.

It's a feeling of pride that we are coming with our new edition of NeoClips (Neonatal Clinical Practice) for the 2nd year. In this occasion, I am feeling privileged to congratulate our Editorial Board Members, chaired by Dr. T J Antony and our Editor in chief Dr. Naveen Parkash Gupta, who are working tirelessly, to make each edition of NeoClips to see the light.

NeoClips is the platform for the Neonatologist to publish their studies, review articles and their clinical experience as case reports which help adding to the current knowledge. I am thankful to the authors who are contributing with their research works for publication and request all our Esteemed Members to contribute their research works and experience in a big way to enrich it further.

We all, as Neonatologists, are contributing towards the better survival of neonates. Many national and international programs are being launched to decrease neonatal mortality and we are approaching our set target by reducing the deaths among extremely preterm and asphyxiated neonates. Is this enough? The mere survival of neonates is not the solution. I feel we have to rethink our current strategy not only to decrease neonatal mortality but also to have the intact survival of our children. In this year of 2023, let us all focus on the intact survival of neonates rather than just decreasing Neonatal mortality.

With Regards



Dr. Pradeep Kumar Debata
President, NNF Delhi

From Secretary's Pen

DR KUMAR ANKUR

Secretary, NNF Delhi

Dear friends,

Warm greetings from National Neonatology Forum, Delhi!

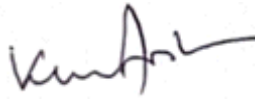
It gives me immense happiness to see the success of NNF Delhi's monthly E-Bulletin launched in February 2022 with the name '***NeoClips' (Neonatal Clinical Practice)***. I congratulate the NeoClips team under the able leadership of Dr T J Antony and Dr Naveen Parkash Gupta for bringing out 11th edition.

The monthly newsletter tries to cover some interesting review articles, cases, images and pictures. OSCE always remain an important highlight. In the current issue, OSCE is on mixed bag.

Based on reviews from postgraduate students and neonatal fellows, we can proudly say that the newsletter has been of tremendous use to them for exam preparation and learning (especially the OSCE section).

We are requesting all the esteemed members to contribute to these E-bulletins. We shall be giving the due credits to all the contributors.

We eagerly look forward to your feedback and hope to give you an experience that you will cherish forever!



Dr. Kumar Ankur
Secretary, NNF Delhi

Editor's Desk

DR NAVEEN PARKASH GUPTA

Chief Editor, Neo Clips

Dear Friends,

Greetings from the NeoClips team.

As Editor, I would like to start by thanking the editorial team for the effort and the authors for their contribution to the current (11th issue) and previous issues.

We have covered some interesting topics in the present issue.

The case report covers an interesting case of transient lactic acidemia in a newborn.

Enteral nutrition is an important aspect of preterm care that has long-lasting effects on the neurodevelopment outcome of these babies. The current issue covers recent ESPGHAN guidelines about enteral feeding and supplementation in these babies.

An interesting case of neonatal erythroderma has been covered in the picture of the month.
The image section describes an MRI image of a baby with Maple syrup urine disease.

This issue OSCE is a mixed bag having few interesting questions.

We hope that you will enjoy reading this issue. Please share your feedback with us. It will help us improve the journal.

Dr Naveen Parkash Gupta

Transient Lactic Acidemia in a Preterm: A Case Report

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Case Details A female preterm baby was delivered as second twin to a naturally conceived primigravida mother out of a non-consanguineous marriage at gestational age of 26 weeks 2 days and birth weight of 835grams. Baby was delivered by caesarian section due to preterm labor with unfavorable lie after prior antenatal steroid and magnesium sulfate coverage. Baby cried immediately after birth and developed respiratory distress soon after birth for which delivery room CPAP was initiated. At admission, baby was started on mechanical ventilation and surfactant was given as respiratory distress persisted on CPAP and the baby required an FiO2 30 % to maintain SpO2>90%. Baby was continued on mechanical ventilation for 48 hours, then extubated to NIMV and weaned to HHHFNC by 5th DOL. In 2nd week of life, echocardiography was done which was suggestive of hemodynamically significant PDA for which iv paracetamol was given, repeat echocardiography suggested tiny closing PDA. Initially, baby was started on parenteral nutrition and minimal enteral nutrition followed by incremental feed. Baby had feed intolerance on day 12 of life which was managed conservatively and feed restarted to reach full feed with fortification by 3rd week. In 3rd week of life, investigations were done in view of suboptimal weight gain for consecutive 5 days despite of adequate caloric intake. Investigations revealed presence of lactic acidemia without associated dyselectrolytemia, sepsis and anemia. Blood gas analysis: pH-7.34, PCO2-41, HCO3-20.9, Lactate-7.8 mmol/l. Baby was kept NPO & additional investigation for secondary causes of lactic acidemia like necrotizing enterocolitis, PDA, hidden foci of sepsis were done. X-ray Abdomen, USG abdomen, echocardiography, stool for occult blood & blood culture were normal. After 5 days of nil per oral, baby was restarted on feed as no obvious secondary causes of lactic acidemia detected and lactate normalized. Lactate level again started to rise as baby reached full feed. Differential diagnosis of lactic acidosis was kept as following: spurious lactic acidemia, primary lactic acidemia (pyruvate metabolic defect, electron transport chain defect), secondary lactic acidemia (hypoxia/tissue damage- NEC, sepsis, Shock), inborn error of metabolism (fatty acid oxidation defect, Organic Acidaemia). Geneticist opinion was taken and investigation for metabolic causes of lactic academia were done. Serum ammonia-39mg/dl, serum lactate-26mmol/l, TMS-normal, Urine GCMS-normal, whole genome exome sequence – no pathogenic variant detected. Baby was managed by keeping nil per orally, restarted with protein free formula along with medication as carnisure, biotin, multivitamin upon normalization of lactic acidemia. As metabolic work up was normal, mother's own milk feed was restarted along with fortification which was tolerated well. Lactate levels remained normal subsequently. Baby was weaned of respiratory support at day 63, discharged at day 70 of life at 1800 gram weight and is thriving well on mothers milk on follow up till 6 month of life.

We found this baby to have severe lactic acidemia at 3rd -5th week of life after initial normal metabolic phase for

which repeated investigation were inconclusive of any secondary or primary cause of lactic acidemia. This led to diagnosis of transient severe lactic acidemia in an extreme preterm neonate.

REVIEW OF LITERATURE:

Neonatal lactic acidosis is most common cause of metabolic acidosis in hospitalized patients and it is generally defined as a plasma lactate concentration greater than 4 mmol/L. Acidosis typically becomes concerning around lactate levels of 45 mg/dL (5.0 mmol/L). (1) It is taken as a surrogate marker of acute instability of a patient in intensive care. Lactic acid is normally created from pyruvate which is end product of glycolysis. Pyruvate then enters Krebs cycle to generate reducing equivalents (NADH/FADH) which in turn gets processed by Electron transport chain (ETC) to produce ATP in presence of oxygen. Lactate and pyruvates are in equilibrium which depends upon utilization of pyruvate by TCA and Urea cycle & NAD+ - NADH redox pool by ETC. In absence of oxygen at tissue level or dysfunctional ETC machinery, depletion of reducing equivalent shifts equilibrium towards lactic acidemia. (2)

As lactate is very sensitive molecule, spurious elevation is quite common secondary to faulty collection technique and handling of the sample after collection. Sample should be drawn as a free-flowing source without a tourniquet to avoid local tissue hypoxia and hemolysis. Collected sample should be kept on ice to prevent further cell lysis and measurement should be done as soon as possible.(3) An identified lapse in collection or handling, a lactate elevation less than twice the upper limit of normal, a normal or low pyruvate value, a normal repeat value, absence of metabolic acidosis, and normal plasma amino acids point towards diagnosis of spurious lactic acidemia. Once spurious lactic acidemia is ruled out, it is either increased lactate production or primary decrease in lactate utilization.

Secondary lactic acidemia is noticed when presence of tissue hypoxemia leads to depletion of reducing equivalents for ETC functioning and anaerobic metabolism causing shifting of equilibrium to lactate accumulation. Identification of underlying condition is important as normalization of lactic acidemia results from restoration of tissue oxygenation and also serves as prognostic marker. Necrotizing enterocolitis, bronchopulmonary dysplasia, shock, sepsis and congenital cyanotic heart disease are some of the causes of secondary lactic acidemia. Inborn error of metabolism like organic acidopathies and oxidation defect are also secondary causes of lactic acidemia.

Disorders that elevate lactate levels directly due to either ETC dysfunction or pyruvate metabolism are considered as primary lactic acidemia. Pyruvate dehydrogenase complex (PDHC) deficiency is the most common primary lactic acidemia. Other such defects include pyruvate carboxylase deficiency gluconeogenesis defects, and Krebs cycle defects. Mitochondrial electron transport chain defects elevate lactate level due to increased reliance on glycolysis process and is associated with other associated defects like cardiomyopathy, cataract, and seizures. Primary differentiating feature in ETC is highly elevated lactate: pyruvate ratio unlike pyruvate metabolism disorders where the ratio is normal. Table 1 summarizes characteristic of differential diagnosis of lactic acidemia.

Diagnostic evaluation should include blood gas analysis with anion gap, evaluation of secondary causes such as sepsis, liver disorder, cardiac pathology, hypoxia, drugs, and evaluation of primary metabolic disorder including serum ammonia, lactate, pyruvate, urine organic acid quantification, TMS- acylcarnitine profile, plasma amino acid quantification, molecular diagnosis (whole exome sequencing) (4,5).

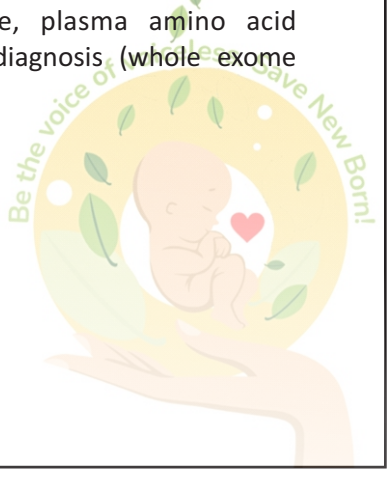

Table 1: Common differential diagnosis of lactic acidosis and their characteristics

Types	Feature	S.Lactate (in mmol/l)	Lactate/ Pyruvate Ratio	Remark
Spurious	Well appearing baby, delayed processing of sample	<4	High	
Hypoxia/tissue damage	Hypotension and/or poor tissue perfusion	<5	High	↑ Amino acid
Inborn error of metabolism	Sudden decompensation after a phase of previously well period	5–10	High	Organic aciduria, ketonuria Acylcarnitine
Pyruvate Metabolic defect	Illness present apparent around 24HOL. Associated structural brain anomalies	10–20	Normal	↑Amino acid
Electron transport chain defect	Presence of Hypertrophic cardiomyopathy, structural anomalies, cataracts; intrauterine growth restriction	10–20	High	Hyperammonaemia ↑ Plasma amino acids: Urine organic acids:

Adapated from Ganetzky RD, Cuddapah SR. Neonatal lactic acidosis: a diagnostic and therapeutic approach. NeoReviews. 2017;18(4):e217–27.

Management of neonatal lactic acidemia follows acute stabilization of airway, breathing, circulation, correction of acid base derangement, bicarbonate supplementation after fluid /circulatory repletion and management of underlying disease.(6) Cocktail therapy can be used in unknown secondary cause of lactic acidemia. Empirical management includes glucose at a glucose infusion rate to maintain euglycemia, the remainder of caloric needs being provided using balanced TPN.

In addition nitrogen scavengers for hyperammonemia, vitamins that act as cofactors for common enzymatic defects such as Thiamine and biotin for are also administered.

Mitochondrial cocktail including Riboflavin, Vitamin C, Vitamin E, and Coenzyme Q10 can also be given.

The prognosis in primary lactic acidosis is grim, while secondary lactic acidosis is excellent if reversal is done as early as possible. Gene sequencing assists in prognostication.

Key messages:

- Severe lactic acidosis is life threatening and indicative of underlying sickness
- Secondary causes of lactic acidosis are more common and needs to be investigated thoroughly
- Primary lactic acidosis should be considered strongly in differentials if spurious and secondary causes are ruled out.

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Enteral Nutrition in Preterm Infants: A Summary of updated ESPGHAN 2022 Recommendations

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Introduction

This article summarizes the updated conclusions and recommendations for nutrient intake and nutritional management of preterm infants. These are the revised recommendations made by the Committee of Nutrition (CoN) of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) based on 12 years of active research on neonatal nutrition. The guidelines focus on pre-discharge nutrition of preterm infants who are less than 1800 grams in birth weight.

The nutritional challenges faced by very low birth weight infants include insufficient nutrient stores and increased demand due to high postnatal growth rate or prematurity-related complications. Inadequate nutritional support can result in poor growth and serious consequences such as increased risk for sepsis, necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), osteopenia, and poor neurodevelopment. (1)

Recommendations

The updated recommendations go beyond nutrient requirements and additionally cover optimal feeding practices, growth monitoring, and dietary considerations for enteral feeding in preterm infants.

The recommendations are organized into four categories: nutrient requirements, feeding practices, clinical management, and diet.

(i) Nutrient requirements

Fluid and macronutrient requirements:

The recommendations for fluid and macronutrient requirements in enterally fed preterm infants are summarized in Table 1. The recommendations are mostly unchanged, except for energy requirements which have a slightly higher upper limit than in ESPGHAN 2010. (2, 3) This is due to assumptions of higher growth rates and fat deposition. It is important to note that these recommendations do not factor in alterations in energy requirements caused by acute illness or chronic diseases. The ideal total energy intake range for healthy preterm infants with normal growth is 115-140 kcal/kg/day. However, if growth is not within the recommended range, energy intakes exceeding 140kcal/kg/day may be necessary, but only after ensuring sufficient protein and other nutrients. The maximum energy intake should not exceed 160kcal/kg/day.

The guidelines suggest providing preterm infants with protein at 3.5-4g/kg/day and sufficient macro and micronutrients to meet intrauterine growth rates. Protein intake can be increased to 4.5g/kg/day only in case of slow growth, with monitoring of plasma urea levels. Low levels suggest an increase in protein intake, while urea levels >34mg/dl indicate the need for lowering protein intake in the absence of fluid or renal disturbances.

Table 1: Fluid and macronutrient recommendations for enteral nutrition in preterm infants

	ESPGHAN 2022	ESPGHAN 2010	Units
Fluid	(135) 150-180 (200)	135-200	ml/kg/d
Energy	115-140 (160) With PER 2.8-3.6g/100kcal	110-135	kcal/kg/d
Protein	3.5-4.0 (4.5)	<1kg- 4-4.5 1-1.8kg-3.5-4.0	g/kg/d
Fat	4.8-8.1	4.8-6.6	g/kg/d
Carbohydrate	11-15	11.6-13.2	g/kg/d

The carbohydrate recommendations in the new guidelines remain unchanged.

Essential fatty acids:

Essential fatty acid (linoleic and alpha-linoleic acid) recommendations remain unchanged.

Docosahexaenoic acid (DHA) and arachidonic acid (ARA) accumulate in the brain during the third trimester of pregnancy, but preterm birth can lead to reduced levels. This deficiency is linked to increased risk of severe ROP, BPD, and septicaemia. Thus, considered as conditionally essential in preterm. Enteral supplementation of these fatty acids appears desirable. However, the efficacy of enteral DHA supplementation (with/without ARA) in improving clinical outcomes and neurodevelopment remains inconclusive based on data from meta-analyses and RCTs. (4) It is recommended to keep daily intakes of EPA (eicosapentaenoic acid) through enteral supplementation below 20mg/kg/day due to concerns regarding toxicity and insufficient data on its effectiveness. These recommendations are summarized in **Table 2**.

Table 2: Recommendations for essential fatty acids

	ESPGHAN 2022	ESPGHAN 2010	Units
Linoleic acid	385-1540	385-1540	mg/kg/d
Alpha-linoleic acid	>55	>55	mg/kg/d
DHA	30-65	12-30	mg/kg/d
ARA	30-100	–	mg/kg/d
EPA	<20	–	mg/kg/d

Minerals:

The recommendations for mineral requirements in enterally fed preterm infants are summarized in **Table 3**. Breastmilk with fortifiers may not provide enough sodium to meet the needs of preterm infants, as breastmilk's sodium content declines over time and preterm infants may lose up to 7mmol/kg/day through urine. The recommended range for sodium (Na) intake is between 3 to 8 mmol/kg/day. It is noteworthy that the upper limit of Na intake has been slightly raised compared to earlier recommendations, particularly in infants who are receiving high energy and protein intakes or have significant sodium loss, and should be taken into account. Sodium additives should be distributed over 24 hours to avoid increasing feed osmolarity. When oral salt supplementation is used, chloride intake closely follows that of Na. It is recommended that infants receive 3-8 mmol/kg/day of chloride.

Parenterally fed preterm infants with high protein and energy intakes are more likely to develop hypokalemia. (5) A potassium intake of ≥ 2 mmol/kg/day is recommended for infants receiving ≥ 3 g/kg/day of parenteral amino acids. The optimal potassium intake for enteral fed infants with higher protein intakes (>4.5g/kg/day) is unknown. It is recommended that preterm infants receive 2.3-4.6 mmol/kg/day of potassium, with consideration for the upper limit in growing infants with high energy and protein intakes.

Human milk alone is insufficient for meeting the mineral needs of preterm infants, leading to poor bone mineral content and fractures. Enteral absorption rates for calcium, phosphorous, and magnesium vary based on milk type and mineral supplementation. (6) New guidelines recommend higher calcium and phosphorous intake and a lower Calcium: Phosphorous molar ratio for better calcium retention. The recommended intake for calcium is 3.0-5.0 mmol (120-200 mg)/kg/d, while the recommended intake for phosphorous is 2.2-3.7 mmol (70-115 mg P)/kg/d. Regular monitoring of Ca and P status is recommended, but not routine use of bone imaging or direct BMC assessments.

Table 3: Recommendations for mineral requirements in enterally fed preterm neonates

	ESPGHAN 2022	ESPGHAN 2010	Units
Sodium	3-5 (8)	3-5	mmol/kg/d
Potassium	2.3-4.6	1.7-3.4	mmol/kg/d
Chloride	3-5 (8)	3-5	mmol/kg/d
Calcium	120-200	<1.4/<1.8	120-140
C:P molar/mass ratio	<1.7/2.0	mg/kg/d	
Phosphorous	70-115	60-90	mg/kg/d
Magnesium	9-12.5	8-15	mg/kg/d

Selected micronutrients and vitamins:

Most recommendations for micronutrients and vitamins remain unchanged, as summarized in **Table 4**.

For iron supplementation, the starting dose is 2-3mg/kg/day, and early supplementation at 2-3 weeks has shown to decrease the need for blood transfusion in VLBW infants. However, infants receiving erythropoietin may need up to 6mg/kg/day iron. Supplementation should be guided by serum ferritin levels, with an increase in iron dose recommended for ferritin <35-70 µg/L, for a limited period. Prolonged intake of >3 mg/kg/day iron should be avoided due to possible adverse effects. If ferritin is >300 µg/L, iron supplementation should be discontinued until ferritin falls below this level. Iron supplements or intake of iron-fortified formula should be continued until 6-12 months of corrected age. (7)

In preterm infants, zinc is generally safe with minimal adverse effects. A minimum of 2.0-2.25 mg/kg/d enteral zinc is recommended, with up to 3 mg/kg/d for extremely preterm infants due to faster growth rates. Higher doses have been associated with better weight gain and linear growth. (8,9) Zinc levels should be monitored in preterm infants with poor growth and low ALP levels, particularly if high GI fluid losses are present.

To support bone health and possibly immune function in preterm infants, sufficient vitamin D intake is crucial. Current recommendations suggest a daily intake of 400-700 IU/kg/d (10-17.5 µg/kg/d) in the first few months, with a maximum dose of 1000 IU/day (25 µg/d). (10) To ensure adequate supplementation, serum 25(OH)D levels should be measured at 3-4 weeks of life and monitored monthly until discharge to adjust vitamin D intake according to individual needs.

Table 4: Recommendations for micronutrients and vitamins

	ESPGHAN 2022	ESPGHAN 2010	Units
Iron	2-3	2-3	Mg/kg/d
Zinc	2-3	1.1-2.0	Mg/kg/d
Copper	120-230	100-132	µg/kg/d
Selenium	7-10	5-10	µg/kg/d
Manganese	1-15	<27.5	µg/kg/d
Iodine	11-55	11-55	µg/kg/d
Chromium	0.03-12.25	0.03-12.25	µg/kg/d
Molybdenum	0.3-5	0.3-5	µg/kg/d
Vitamin D	400-700 (1000 max)	800-1000*	IU/kg/d

(*IU/d)

(ii) Feeding practices

Initiation of feeds:

Start small volume feeds in preterm with normal dopplers, as soon as possible after birth and advance as tolerated. No clear benefit of fasting or minimal enteral nutrition. (11)

Feed advancement:

Advancement of feeds should be based on routine daily increments of 18-30ml/kg/d. Faster increments decreases time to full enteral feeds, duration of hospital stay, and incidence of invasive infections. (12)

Gastric residual monitoring:

Routine gastric residual monitoring is not recommended. (13) Gastric residua should only be assessed if clinical signs of feed intolerance or NEC are seen.

Standardized feeding protocol:

Each unit caring for preterm neonates should have standardized feeding guidelines and protocols for enteral nutrition. This has been shown to achieve full feeds faster, shorten parenteral nutrition days/hospital stay, decrease NEC rates, and improve growth and development. (14)

Feeding mode:

Nasogastric (NG) vs orogastric (OG) feeding tubes- NG and OG feeding tubes both have potential adverse effects, and the choice of tube should be based on individual patient needs and risks. There is no clear preference for either method in preterm neonates. (15)

Bolus vs continuous feeds- Bolus feeding (2-3hourly) may be slightly preferable over continuous feeding for preterm infants, but more studies are needed. (16,17)

Non-nutritive sucking (NNS)- NNS prior to oral feeding can shorten hospital stay. (18)

Direct feeds- Oral feeding should be guided by the infant's competence and stability, and can begin at 32 weeks postmenstrual age.

(iii) Clinical management

Growth:

The optimal growth velocity for preterm infants is unclear.

Regular monitoring of weight, length, and head circumference is recommended, with a goal of regaining birth weight by 7-10 days and following a target centile.

Nutritional management and growth assessment should be the same for IUGR/SGA infants as AGA infants, and rapid catch-up growth should be avoided.

NICUs should have a standardized approach to managing growth faltering while balancing the risks of nutrient deficiencies and rapid catch-up growth.

Monitoring should be done on accepted growth charts. Gradual transition to WHO growth charts before or at 44weeks postmenstrual age (PMA). (19)

(iv) Diet

Breast Milk:

Role of Colostrum- Regular application of buccal colostrum has not consistently shown to reduce mortality or morbidity in premature infants. (20) Although it is safe and appealing from both emotional and immunological perspectives, its clinical benefits in high-resource settings remain unclear.

Type of milk- Compared to donor human milk (DHM) pasteurized with the Holder method, fresh mother's own milk (MOM) has higher levels of macronutrients and immunoreactive/trophic factors. Fortified pasteurized DHM reduces NEC rates in preterm infants compared to preterm formula, but other morbidity and mortality rates are similar. (21, 22) MOM is strongly recommended as first choice for feeding all infants, with fortified DHM conditionally recommended for preterm infants (< 32 weeks PMA, <1500g birth weight) if MOM is insufficient. (23)

Cytomegalovirus (CMV) Risk with MOM- During lactation, there is a possibility of reactivation of (CMV) which may cause it to be present in breast milk. However, it is not recommended to pasteurize the milk of CMV-positive women as routine practice since it can result in the loss of important nutrients. (24) Although CMV can be transmitted through breast milk, it is important to weigh the potential risks against the benefits of breastfeeding.

The osmolarity of feed- Based on the available evidence, it is currently not possible to establish a specific upper safety threshold for the osmolality of enteral feedings in preterm infants. To avoid excessive osmolality, supplements should be added to the largest possible volume of milk feed, and multi-component fortifiers should be used for breastmilk fortification instead of multiple individual nutrient supplements. (25)

Supplemental bio-nutrients:

No update on the recommendation for daily enteral choline supplementation in preterm infants. Milk formula providing 8-55mg/kg/day of choline is enough, no extra supplementation is necessary.

No role of other bioactive supplements like lactoferrin, human milk oligosaccharides and inositol.

Human milk Fortification:

Type of fortification- Commercially available fortifiers may have insufficient protein content to meet recommended intake levels if enteral feeds are limited. The variation in nutrient content among fortifiers can affect growth and health outcomes. To compensate for variation in human milk macronutrient composition, adjustable and target fortification strategies may be used, but the optimal strategy is unclear. Individualized fortification strategies may be appropriate.

Initiation of fortification- Multi-component fortifiers are recommended to enhance nutrient content and promote growth, starting when enteral intakes reach 40-100 ml/kg/d. (26,27)

Human milk vs bovine milk fortifiers- Fortifiers derived from human milk may reduce the risk of NEC, but the optimal strategy is unclear due to insufficient data. Routine use of human milk-derived fortifiers is not recommended until more high-quality data is available. (28)

Limitations

The updated guidelines have some limitations, including recommendations that are based on low-quality evidence and emphasize the importance of considering local contexts and individual infants in decision-making. Additionally, the guidelines do not account for changes in energy requirements due to acute illness or chronic disease states.

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Image section– Netherton syndrome with hypernatremia

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Case – A late preterm(34wk) appropriate for gestational, female baby with a birth weight of 2.5 kg was referred to us on day 6 for hypernatremia serum sodium(165meq/l). On admission to our NICU on examination, there were multiple areas of dry scaly skin with peeling and associated redness (ichthyosis erythroderma) (Figure 1). The child was in some dehydration with 10 %weight loss from birth (wt at admission was 2250gram as against the expected weight of 2235 Grams). Serum sodium levels were corrected gradually over the next 30 hours as per protocol. In view of skin lesions emollients application was started and genetic analysis (Whole exome sequencing) was planned after consultation with a pediatric dermatologist to rule out primary immunodeficiencies (PID). However, parents decided to do it on follow-up if skin lesions persist. Baby did well on follow up but skin lesions persisted. She was readmitted at 3 months of age in view of a lower respiratory tract infection. Whole exome sequencing was done at that time.

Investigation -Whole exome report showed a mutation in SPINK-5 gene variant- c.1292_1295(p.Ala431Valfs*3) and c.1410C>A (p.cys470Ter).

Diagnosis- Netherton syndrome with hypernatremia.

Review of literature

Netherton syndrome (NS) is a genetic, multisystemic disease that classically have a triad of congenital ichthyosiform erythroderma, hair shaft abnormalities, and immune dysregulation. (1) It's a rare disease with an incidence of 1/200,000. Netherton syndrome results from mutations in the serine protease inhibitor Kazal-type 5 (SPINK5) gene. (2) Deficiencies of serine protease inhibitor leads to excessive serine protease activity which leads to premature stratum corneum detachment and defect of skin barrier function. (3)

Outcome

During their first year of life, patients with Netherton's syndrome undergo a period of life-threatening infections, hypernatremic dehydration, diarrhoea, and failure to thrive, with a mortality of 30–40% during this period. Later in life these babies are very prone to infections due to underlying immunodeficiency (3).

Management and genetic counselling

These babies should be started on ammonium nitrate based emollient therapy. Workup for primary immunodeficiencies (Serum IgE) should be done. These babies should receive age-appropriate vaccines and additional vaccinations for pneumococcal and meningococcal. Family should be counselled regarding inheritance patterns (most cases follow autosomal recessive inheritance) and future risk of recurrence in the next sibling and also need to do chorionic villous sampling or amniocentesis in next pregnancy.

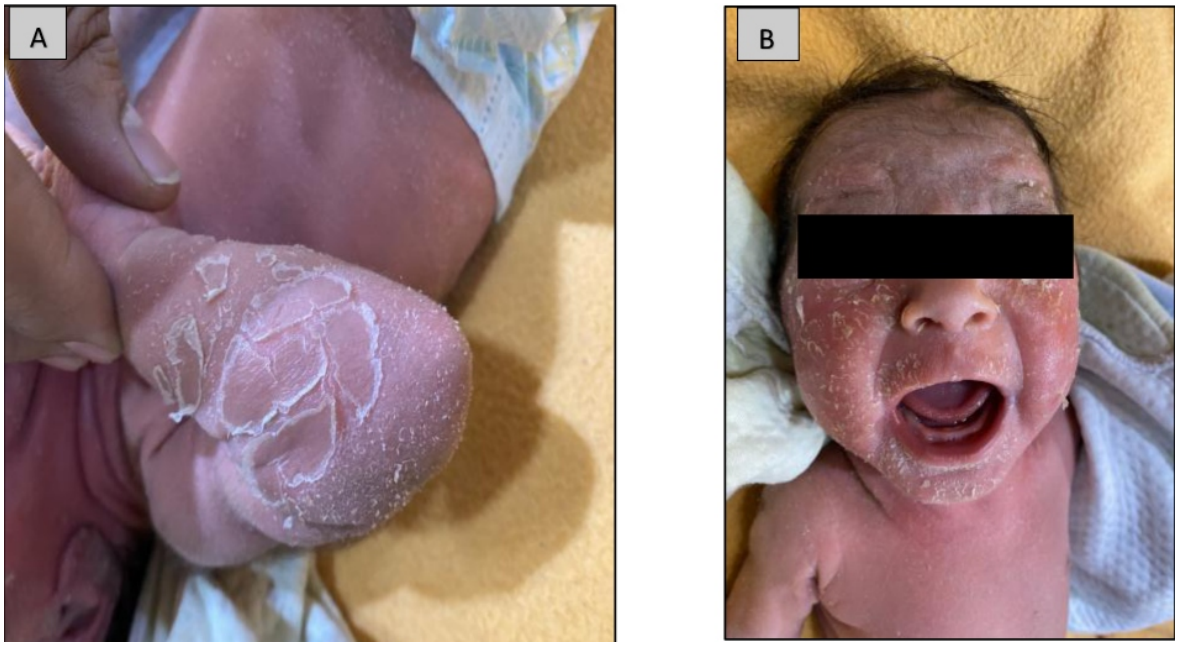

Fig.1. A and B shows multiple areas of dry, scaly skin lension with skin peeling (lcthyosis Erythroderma)

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Newborn with Generalized Hypotonia and Seizures

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Clinical presentation: Term Baby, outborn, delivered at 38+6 weeks of gestational age, LSCS in view of non-progression of labour, APGAR-unknown, with a birth weight of 3055 gms and no perinatal complications. The baby was shifted to the mother's side after birth and was started on direct breastfeeds, passing urine and stools normally and was discharged on day 3 of life. On day 7 of life, the baby became symptomatic with an episode of vomiting followed by noisy breathing and one episode of seizure in the form of tonic posturing and staring look. With the above complaints, the baby was admitted to a higher centre, where he continued to have recurrent seizures, became encephalopathic and was mechanically ventilated. The baby was managed conservatively with antiseizure medications (phenobarbitone) and supportive care before being transferred to our hospital on day 12 on a transport ventilator.

Suspicion: Inborn error of metabolism (organic acidurias/ aminoacidopathies)

Course: On examination, the baby was encephalopathic with no eye-opening, no motor response to painful stimuli and flaccid with signs of raised intracranial tension. Neuroprotective measures were initiated along with titration of antiseizure medications (levetiracetam, phenobarbitone) in view of continuing seizures. Sepsis parameters were negative. A basic metabolic workup was done. Blood gas showed pH 7.49/pco2 26/po2- 31/lactate- 3.26. Serum ammonia was 167 micromoles/L. Urine for ketone bodies were negative and blood glucose levels were within normal limits. TMS/GCMS was sent in view of a strong clinical suspicion of inborn errors of metabolism (IEM). MRI reveals symmetrical diffusion restriction in myelinated areas in the posterior limb of internal capsule, corticospinal tracts, thalami and posterior aspects of midbrain and pons and cerebellar white matter, likely due to intramyelinic edema. Also diffuse cerebral edema is present with effacement of sulcal spaces and basal cisterns. These findings likely indicate possibility of Aminoaciduria (?Maple Syrup Urine Disease) (Figure 1). The baby was planned for peritoneal dialysis and a trial of thiamine supplementation was planned.

Outcome – Baby continued to be in encephalopathy, had absent brain stem reflexes and signs of raised intracranial tension. Parents refused permission of any active intervention on the baby owing to severe encephalopathy and poor prognosis. The baby continued to remain sick and expired on 3rd day of admission. TMS and GCMS report was confirmatory of Maple syrup urine disease with elevated branched-

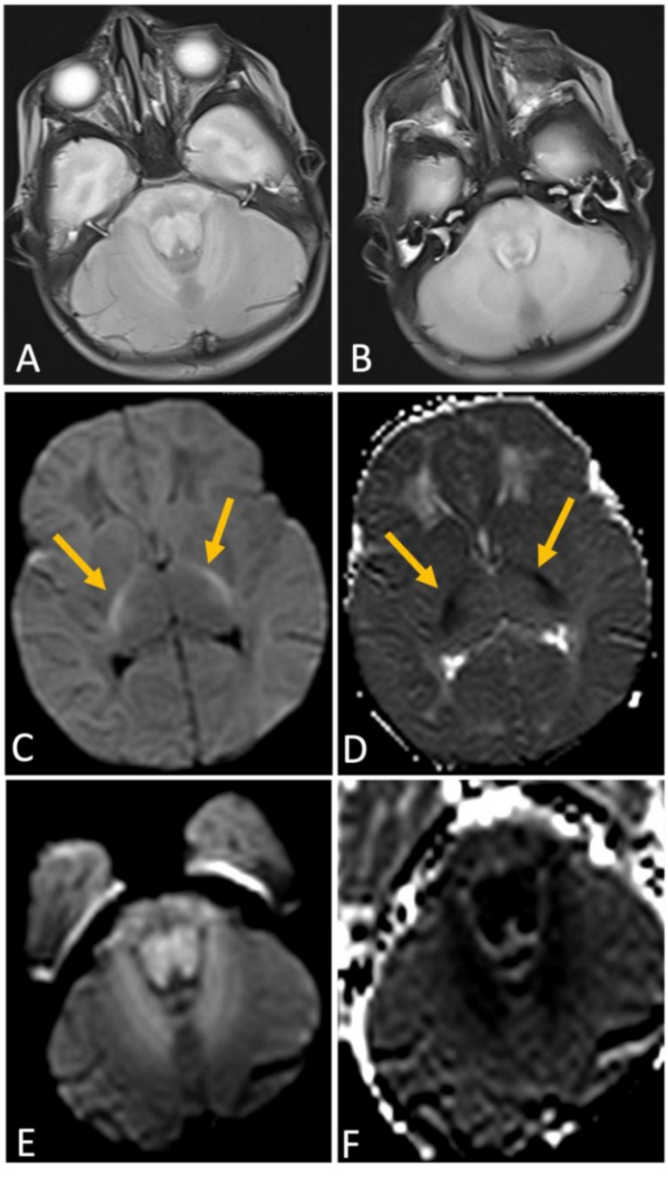

Fig.1. MRI Brain: Axial T2-W images show cerebral edema with hyperintensity in brainstem and cerebellar white matter (A, B). DWI and corresponding ADC maps show diffusion restriction (cytotoxic oedema) involving posterior limbs of internal capsules (C, D – yellow arrows), medulla and cerebellar white matter (E, F).

Review of Literature:

Maple syrup urine disease (MSUD) occurs in approximately 1 in 86,800 to 185,000 live births. It is an inborn error of metabolism of autosomal recessive inheritance caused by defects in the branched-chain α-ketoacid dehydrogenase complex, which results in elevations of the branched-chain amino acids in plasma, α-ketoacids in urine, and production of the pathognomonic disease marker, alloisoleucine. (1) There are five distinct clinical phenotypes of Maple syrup urine disease (2) (refer to table 1), that can be categorised based on age at onset, severity of symptoms, response to thiamine supplementation, and biochemical findings. No clear phenotype-genotype correlation exist nor these clinical phenotypes correlate with residual enzyme activity. The classic and E3-deficient forms ofMSUD usually become symptomatic in the neonatal period or early infancy, whereas the other variants may manifest at any point during childhood, often triggered by a catabolic event like an intercurrent illness or injury/fasting/surgery. (1)

Diagnosis:

Positive newborn screening: Classic MSUD in newborn infants is readily detected by tandem mass spectrometry. Confirmatory testing includes, plasma amino acids, urine organic acids, and urine ketones. Newborn screening may not detect milder or variant forms of the disorder. (2) Confirmation of the genetic diagnosis can be obtained by next generation sequencing based tests (clinical / whole exome sequencing). (3)

Mutational analysis can be performed in a newborn with a family history of MSUD if the specific gene defects are known. If pathogenic variants are not known, high-risk newborns can be evaluated with for *BCKDHA, BCKDHB,* and *DBT* gene variants. Plasma for amino acid analysis should be obtained between 18 to 24 hours of life in these high-risk newborns.

Prenatal diagnosis can be performed by measuring branched-chain alpha-ketoacid dehydrogenase complex (BCKDC) enzyme activity in cultured amniocytes or chorionic villus cells or by mutation

MSUD TYPE	AGE OF ONSET	GENES	CLINICAL FEATURES	BIOCHEMICAL FEATURES
Classic Type	Neonatal	BCKDHA BCKDHB DBT	Most common form of MSUD. Initial 2-3 days of life: Non-specific signs like irritability, poor feeding , vomiting and hypersomnolence. Days 4-7 of life: Neonatal encephalopathy and signs of cerebral edema with apnea, seizures, opisthotonos, bicycling or fencing movements and maple syrup odour in urine. Ultimately, coma and central respiratory failure sets in if left untreated.	Elevated BCAAs, alloisoleucine in plasma. Elevated branched-chain ketoacids in urine
Intermittent	Variable	BCKDHA BCKDHB DBT	Second most common form. Normal growth and development. May present with metabolic decompensation during episodes of catabolic stress -any intercurrent illness/ increased protein intake/ surgery.	BCAA levels are normal. Elevated levels as in classic form can be seen in stress situation.
Intermediate	Variable	BCKDHA BCKDHB DBT	Rare form, variable presentation.	Elevated BCAAs, alloisoleucine in plasma. Elevated branched-chain ketoacids in urine (Less severe than classic form)
Thiamine	Variable responsive	DBT	Same presentation as in intermediate form	Improvement of leucine tolerance and levels of BCAAs when on thiamine supplementation.
E3- Deficient Type	Variable	DLD??	Early-onset neurologic phenotype: hypotonia, developmental delay, emesis, hepatomegaly, lethargy, seizures, spasticity, Leigh syndrome, failure to thrive. Hepatic phenotype: nausea, emesis, hepatomegaly, hepatic encephalopathy	Elevated BCAAs, alloisoleucine, lactate, pyruvate, and alanine in plasma Elevated branched-chain ketoacids and α-ketoglutarate in urine

analysis if the specific gene defect is known.

Abbreviations: MSUD- Maple syrup urine disease, BCAA- Branched chain Aminoacids, BCKDHA- Branched chain keto acid dehydrogenase E1 subunit alpha, BCKDHB- Branched chain keto acid dehydrogenase E1 subunit beta, DBT- Dihydrolipoamide branched chain transacylase E2, DLD- Dihydrolipoamide dehydrogenase.

Management:

- The goals of dietary therapy are to reduce toxic metabolites, achieve plasma concentrations of branched-chain amino acids (BCAAs), especially leucine, that are within the target range, support normal growth and to improve intellectual function and development. (1)
- Restricting intake of BCAAs is done using

commercially available formulas. Patients are also started on a low-protein diet providing sufficient protein, calories. Additional valine and isoleucine supplementation may be required to prevent low plasma concentrations, which would be rate limiting for protein synthesis, and to promote anabolism. Dietary restriction is maintained throughout life. Plasma leucine concentrations should be maintained between 75 to 200 micromol/L in children under five years of age. Plasma valine and isoleucine concentrations should be maintained between 200 to 400 micromol/L.Thiamine supplementation is started at a dose of 50 to 200 mg/day. Plasma BCAAs and tolerance for dietary BCAAs should be monitored to evaluate thiamine responsiveness, which is expected to reduce plasma BCAAs and increase dietary tolerance. (4)

- Episodes of metabolic decompensation must be treated aggressively. Plasma and tissue concentrations of leucine should be lowered rapidly by inhibition of protein catabolism and enhancement of protein synthesis.
- Liver transplantation is done for classic MSUD. Indications for liver transplantation include poor metabolic control and poor quality of life as indicated by significant psychomotor disabilities and more frequent acute metabolic decompensations and related hospitalizations. (4)

Outcome –. Outcome is better in patients who begin therapy before they become symptomatic or are treated rapidly after symptoms develop. Cognitive outcome appears to be related to plasma leucine concentration.

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Journal Scan

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ORIGINAL ARTICLE

Trial of Erythropoietin for Hypoxic–Ischemic Encephalopathy in Newborns

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Research question?

Do high doses of erythropoietin along with therapeutic hypothermia have neuroprotective effects on infants with hypoxic-ischemic encephalopathy?

Hypothesis

Population	36 weeks or more of gestation with one or more signs of perinatal depression with moderate to severe encephalopathy and therapeutic hypothermia started within 6hrs and continuing for 72 hours.
Intervention	Intravenous Erythropoietin (1000 U per kilogram of body weight) administered within 26 hours after birth, as well as at 2, 3, 4, and 7 days of age.
Control	Equal volume of placebo given intravenously
Outcome	Death or neurodevelopmental outcome at 22-28 months of age

Methods

Design Multicenter randomized control trial

Allocation Concealment - Neonates were randomly assigned with computer-generated to either erythropoietin or placebo

Blinding - Double-blinded trial

Settings Level 3 neonatal intensive care units in 15 centers across the United States.

Inclusion Criteria

36 weeks or more gestation with Apgar score < 5 at 10 minutes, cardiopulmonary resuscitation received beyond 10 minutes of age and a pH less than 7 or a deficit ≥ 15 in the umbilical cord or obtained within 60 minutes after birth. Moderate to severe encephalopathy according to Sarnat criteria during 1st 6 hours of birth. Receipt of active or passive hypothermia that was started within hours after birth and continued for 72 hours.

Exclusion criteria

1. Birth weight less than 1800.

2. Head circumference less than 30 cm.
3. Genetic or congenital condition affecting neurodevelopmental outcomes.
4. Hematocrit is more than 65%.
5. Parents considering redirection to palliative care.
6. Encephalopathy attributed to postnatal event.
7. Surviving twin undergoing hypothermia.
8. Anticipation that child would be unavailable for evaluation at 2 years of age.

Sample size - The estimated outcome (death or neurodevelopmental impairment) was 49% in placebo group. Assuming a 90% follow-up rate at 22 -26 months, the estimated sample size was 500 with 90% power and a two-sided alpha error of 0.05 with the ability to detect a relative risk difference of 33%.

Results - 500 patients were enrolled. Death or neurodevelopmental impairment at 22-36 months of age was 52.5 % in the erythropoietin group and 49.5% in the placebo group. (RR 1.03;95 % CI 0.86 to 1.24; P 0.74).

The percentage of children who had any single type of serious adverse event did not differ substantially according to the trial group. However, the mean number of serious adverse events per child was higher in the erythropoietin group than in the placebo group (0.86 vs. 0.67; RR 1.26; 95% CI, 1.01 to 1.57), as was the percentage of children with at least one serious adverse event (53.3% vs. 43.6%; RR 1.21; 95% CI, 1.00 to 1.45).

Reviewer comments: The incidence of HIE 6 in 1000 term infants and incidence of death or neurological impairment is 1 in1000. As of now, therapeutic hypothermia is the only neuroprotective therapy that improves outcomes. However, cooling therapy only helps in 1 in 7 infants with HIE. Therefore additional treatments are needed to further improve brain function and recovery after HIE.

It was hypothesized in this study that high dose erythropoeitin given to cooled infants with moderate /severe HIE will reduce the primary outcome of death or neurodevelopmental impairment at age 24 months from 49%to 33%. Multiple high doses of erythropoietin do not significantly affect death or neurodevelopmental impairment at 2 to 3 years of age. Infants who received erythropoietin were more likely to have serious side effects and had a greater number than those with the placebo(2). Higher incidence of behavioural abnormality was found among erythropoietin group at 2 years of age. No appreciable group differences in MRI brain or functional outcome.

Strengths of the study: This is the largest trial to test the high doses of erythropoietin in infants undergoing therapeutic hypothermia for moderate to severe HIE. The primary outcome had specified the criteria and admissions also reviewed and confirmed it. Multivariate imputation using chained equations algorithm used for missing data.After 125,250 and 375 infants had been enrolled, the data and safety monitoring board compared mortality rates and rates of serious adverse events.

Limitations of the study: Unable to address the usefulness of erythropoietin in the absence of therapeutic hypothermia. Some children were evaluated in a delayed fashion owing to covid 19 pandemic. Babies sample representative of infants with hypoxic-ischemic encephalopathy in the United States.

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Question 1.

An infant is diagnosed with a primary immunodeficiency disorder after persistent skin infections. The patient also has severe eczema and very high total immunoglobulin (Ig) E

levels and eosinophilia. Which of the following is the most likely diagnosis?

A. Hyper IgM syndrome.

B. Wiskott-Aldrich syndrome.

C. Hyper IgE syndrome.

D. DiGeorge syndrome.

Question 2.

A) Diagnosis?

B) What drug is to be given to the mother of this baby in the next pregnancy?

C) What percentage of neural tube defects can be prevented by this drug in the periconceptional period?

Question 3.

Corticosteroids are attractive therapeutic agents for BPD prevention because of their potent anti-inflammatory properties and dexamethasone has been the most studied. Which of the following statements regarding the use of dexamethasone is correct?

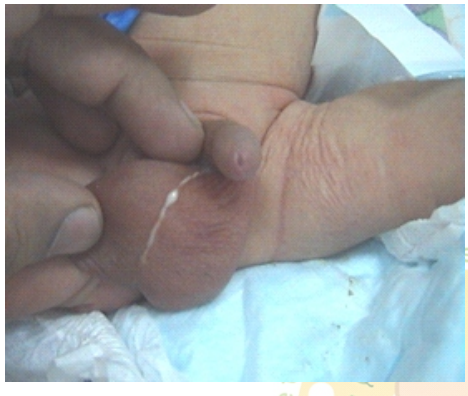
A. Early dexamethasone is defined as treatment initiation within 14 days of birth.

B. Early dexamethasone treatment is associated with an increased risk of gastrointestinal perforation and hypertrophic cardiomyopathy, but not cerebral palsy.

C. Based on a meta-regression study by Doyle et al, late dexamethasone should be considered in infants in whom the risk for BPD exceeds 80%.

D. In the Dexamethasone: A Randomized Trial (DART) study, low-dose dexamethasone did not result in lower BPD risk.

Question 4.



A) What is the diagnosis?

B) What are the other sites where these lesions are commonly found?

C) What is the treatment?

Question 5.

An infant born at 39 weeks' gestational age is noted to have mild respiratory distress and echocardiography leads to a diagnosis of hypoplastic left heart syndrome.

A. What screening tool can help in the diagnosis of subclinical hypoxemia during transitional physiology in certain critical CHDs soon after birth?

B. Prostaglandin is started to maintain patency of the ductus arteriosus. Arrangements for transport to a higher centre are made. Which of the following is an important consideration for transport of this infant receiving prostaglandin?

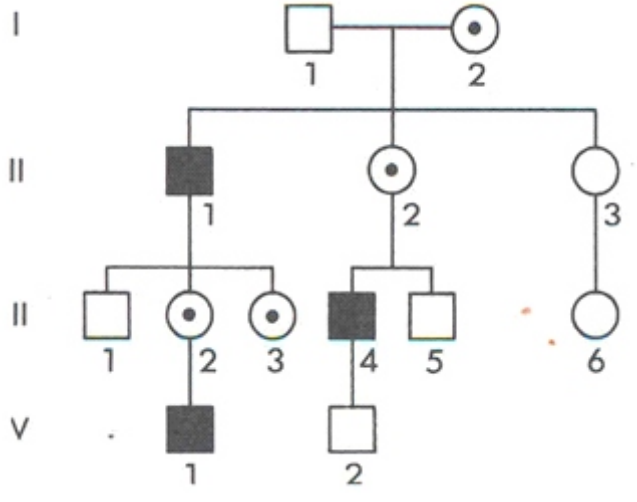
   a. Avoidance of intubation is suggested because of the high risk of pneumothorax in this population.

   b. Inhaled nitric oxide is an important consideration for supplementing current therapy to improve pulmonary vascular dilation.

   c. The most frequent side effect of prostaglandin in newborns is seizures.

   d. Because hypoventilation and apnea are common side effects, establishment of a secure airway before initiating prostaglandin therapy and transport should be considered to decrease the risk of transport complications.

Question 6.



A) Identify this pedigree

B) Name a disorder with this type of disorder that presents in neonatal period.

C) Name the mechanism by which a carrier can manifest the disease.

Question 7.

Hemophagocytic lymphohistiocytosis (HLH) is associated with poor prognosis, emphasizing the need for early diagnosis and intervention in affected patients. Which of the following statements regarding the diagnosis of HLH is correct?

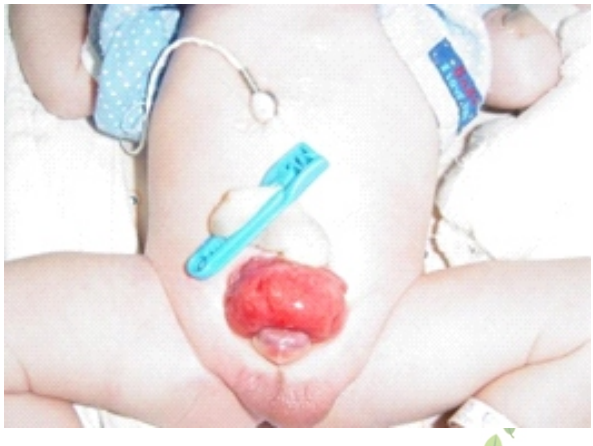
A. High natural killer cell activity is a diagnostic criterion for HLH.

B. Hypertriglyceridemia is the most helpful criterion in neonatal HLH.

C. Hyperferritinemia represents one of the criteria for the diagnosis of HLH.

D. The presence of low concentrations of soluble interleukin 2 receptor represents one of the criteria for the diagnosis of HLH.

Question 8.



A. Identify this condition

B. Characteristic X ray abdomen finding

C. Urethral anomaly universally associated with it?

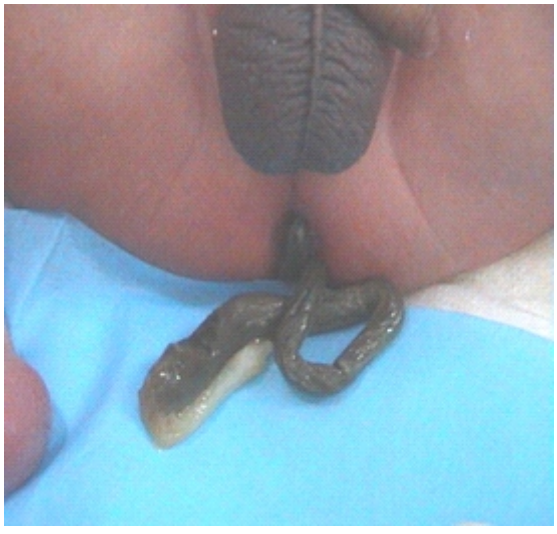
Question 9.

Which one of the following is the most useful tool in the prediction of neurodevelopmental outcomes for a baby with moderate encephalopathy secondary to hypoxic-ischemic encephalopathy (HIE)?

A. Doppler of cerebral arteries
B. MRI
C. Bedside amplitude integrated EEG
D. Neurological examination

Question10.

A) Diagnosis?
B) What co-morbid condition should be suspected in this?
C) What is the treatment offered?



Answer 1 – C (Hyper IgE syndrome)

Hyper-IgE syndrome (HIES) is a rare, primary immunodeficiency distinguished by the clinical triad of atopic dermatitis, recurrent skin staphylococcal infections, and recurrent pulmonary infections. Furthermore, there are elevated IgE levels of early-onset in primary childhood.

The HIES is classified into 2 types.

Type I: Autosomal dominant hyper-IgE syndrome (AD-HIES), in which patients have abnormalities in different systems, including the immune system, connective tissue, skeletal and vascular among others

Type II: Autosomal recessive hyper-IgE syndrome (AR-HIES), which also affects the immune system, manifesting in high IgE, recurrent skin and lung infections, sensitivity to viral infections such as molluscum contagiosum, and central nervous system (CNS) involvement, but does not have musculoskeletal alterations

The main diagnostic feature is an increase in serum IgE levels of more than 2000 U/mL, and often 500 U/mL. A clinical score has been developed to define the probability of diagnosis. A total IgE concentration greater than 1000 IU/mL and a weighted score of greater than 30 indicate an AD-HIES of the defect in STAT3, and a dominant-negative heterozygote mutation in STAT3 confirms the diagnosis. Eosinophilia is observed in more than 90% of the patients. The WBC count can be normal, elevated, or reduced in number(neutropenia)

The most effective treatment, for now, for this condition is the long-term, sometimes continuous, use of antibiotics (penicillinase-resistant penicillins, cephalosporins, antifungal agents, and others) by adapting the treatment to the infections occurring in these patients and sometimes using surgical procedures during abscess development. Interferon-gamma has shown no clinical benefit in this condition. Thanks to the antibiotics, and if the diagnosis is made early, patient survival can be increased. The management of non-immunological manifestations must be interprofessional. It aims to treat complications. Thus, scoliosis, depending on its severity, as well as bone fractures and degenerative joints diseases may require orthopedic surgery. Dental abnormalities require adequate stomatological treatment. Cardiovascular complications are managed in a specialized environment. Bone-marrow transplantation has been associated with mixed results in these patients.

Answer 2

A. Encephalocele

B. Folic acid

C. 75%

Prevention of up to 75% of NTDs can be achieved by supplementation with 4 mg/day of folic acid. However, two points should be emphasized: i) the preventive effect of folic acid is greater in women with lower serum folate, and ii) higher folate intake is related to higher risk reduction. Supplementation with 0.4 mg/day is associated with a 36% risk reduction. Higher risk reduction (up to 70%) can be obtained with a tenfold dosage of folic acid (4 mg daily). However, a dose of more than 1 mg of folic acid daily might mask a clinical condition caused by vitamin B12 deficiency. For all those reasons, the recommended folic acid supplementation in the normal population is 400 mcg (0.4 mg) daily.

Answer 3 - D

The potent anti-inflammatory properties of corticosteroids make them a logical therapeutic agent for BPD prevention. Of all corticosteroids, the use of dexamethasone to prevent BPD has been studied in the largest number of RCTs. Meta-analyses of steroids typically group studies evaluating dexamethasone initiated within the first 8 days of age ("early use") separately from those initiating therapy after this time point ("late use"). Evidence suggests that early dexamethasone therapy reduced BPD risk; it increased the risks for gastrointestinal perforation,

hypertrophic cardiomyopathy, cerebral palsy (CP), and major neurosensory disability. Because of these unacceptable side effects, early dexamethasone therapy is not recommended.

The risks and benefits of "late" dexamethasone are less well-established. Meta-analysis of the available trial data shows that initiation of dexamethasone after the first week of age reduces BPD risk, but carries the short-term side effects of hyperglycemia, glycosuria, and hypertension. A meta-regression conducted by Doyle et al provides the best means for clinicians to balance these competing risks where he showed that when the risk for BPD in the control population (akin to an infant's baseline BPD risk) was less than 33%, corticosteroids significantly increased the risk for death or CP.Alternatively, when the risk for BPD exceeded 60%, corticosteroids reduced death or CP risk.

A Randomized Trial (DART) study (0.89 mg/kg administered over 10 days) is one such approach. In this trial of 70 very preterm infants receiving invasive mechanical ventilation, compared with placebo, dexamethasone significantly improved rates of successful extubation. However, the risk for BPD was not significantly reduced in the dexamethasone treated infants.

Answer 4

A) Epstein pearls

B) Hard palate

C) No treatment required

Alois Epstein first described Epstein disease as the presence of small nodules in the oral cavity of newborns. However, it was not until 1967 that Alfred Fromm undertook the largest study on oral inclusion cysts, where 1367 newborn infants were evaluated. Fromm classified the cysts according to their location and composition as Epstein pearls, Bohn nodules, and dental lamina cysts and concluded that these lesions were common among infants. Epstein pearls result from epithelium entrapment during the palate development; Bohn nodules are believed to be remnants of salivary glands; gingival cysts arise from the rests of the dental lamina. However, because of their most common location (junction between the hard and soft palate near the midline), it is hard to verify clinically if a palatal cyst arises from entrapped epithelium after palatal fusion or from developing salivary glands. Epstein pearls resemble the equivalent of milia (white papules produced by retention of sebum and keratin in the hair follicles), which are frequently seen on the faces of neonates. Palatal and gingival cysts of the newborn are diagnosed based on their clinical features alone. No laboratory or imaging is required as they do not involve bone. No treatment or removal is required as they spontaneously regress within a few weeks or months. They are seldom observed after three months of age. Parental apprehension should be alleviated by reassurance and follow-up appointments.

Answer 5

A. Pulse oximetry screening done at either 24 hrs or more

Sites – Preductal (right hand) and either of feet

According to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children SACHDNC protocol, an infant would have a positive (failing) screen if at ≥ 24 hours of life: 1) A pulse oximeter reading was <90% in either the right hand or either foot. 2) Both readings from the right hand and either foot were <95% on three measurements each separated by 1 hour. 3) A persistent >3% difference in the right hand and either foot measurement on three measurements each separated by 1 hour.

B-D. Evaluation for a suspected congenital heart disease remains a common reason for neonatal transfer to a tertiary care center. A continuous prostaglandin E1 infusion is vital in maintaining the patency of the ductusarteriosus in ductal dependent heart lesions. Common side effects of prostaglandin E1 are hypoventilation and apnea, affecting around one- fifth of babies. Hence, establishment of a secure airway before inter-facility transport should be considered to decrease the risk of transport complications.

Answer 6

A) X linked recessive disorder

To start reading a pedigree: Determine whether the trait is dominant or recessive.

If the trait is dominant, one of the parents must have the trait. Dominant traits will not skip a generation. If

the trait is recessive, neither parent is required to have the trait since they can be heterozygous.

Determine if the chart shows an autosomal or sex-linked (usually X-linked) trait. For example, in X-linked recessive traits, males are much more commonly affected than females. In autosomal traits, both males and females are equally likely to be affected (usually in equal proportions).

B) G6PD deficiency

C) Lyon's hypothesis states that the phenotypic effect of the X chromosome is the same in the mammalian female which has two X chromosomes as it is in the male which has only one X chromosome. One out of two X chromosomes in females is inactivated early in embryonic development. It is called as the Barr body. The Barr body is highly condensed and does not have any phenotypic effect.

Answer 7 - C

Hemophagocytic lymphohistiocytosis (HLH) belongs to a group of disorders known as histiocytosis, which is characterized by an overabundance of tissue macrophages or histiocytes. Histiocytes are phagocytic cells present in connective tissue, which normally participate in the innate immune system by triggering cell signaling and activation. HLH can concisely be defined as a hyperinflammatory syndrome of pathologic immune activation. This syndrome could be either familial or sporadic, which can be difficult to differentiate at the time of initial presentation. The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000.

The terms “familial” (fHLH) or “primary HLH” are often used to indicate cases of HLH caused by an underlying genetic disorder. The genetic mutation can be autosomal recessive or X-linked, based on whether the gene mutation occurred within the fHLH loci or in a gene responsible for an immune deficiency. Of all cases of fHLH, 70% to 80% present before 1 year of age. Of the numerous genes associated with HLH, few gene mutations have been linked to HLH in children younger than 1 month. According to a review of neonates with HLH, the only genes found to be associated were PRF1 and UNC13D. Of the 2, PRF1 was found to be the predominant gene and more likely to be found in black and Hispanic patients, whereas mutations in UNC13D were more common in white patients.

The term “secondary HLH” is used to indicate HLH acquired after a strong immunologic activation resulting from severe infection, rheumatoid disorders, malignancies, metabolic disorders, or prolonged intravenous nutrition (fat overload syndrome). (5) Infections known to cause excessive immune stimulation include Epstein-Barr virus, parvovirus B19, and cytomegalovirus. Bacteria, parasites, and fungi may have similar effects as well.

Diagnosis

Homozygosity or compound heterozygosity for verified HLH-associated mutations (eg, PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, HPS) or gene defects of other immune regulatory genes (identified by whole exome sequencing)

OR

Five of the following nine findings:

1. Fever ≥38.5°C
2. Splenomegaly
3. Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL
4. Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph node, or liver
6. Low or absent NK cell activity
7. Ferritin >500 ng/mL (the authors prefer to consider a ferritin >3000 ng/mL as more indicative of HLH
8. Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms
9. Elevated CXCL9

Primary goal of therapy is to maximize T-cell function while decreasing inflammation until SCT can be performed. The antineoplastic etoposide is used to inhibit topoiso- merase II, which is crucial for DNA replication and repair. Etoposide causes breaks in the

DNA when interacting with the DNA/topoisomerase II complex, preventing further replication of DNA in the late S and early G2 phases and inhibiting cell proliferation. The glucocorticoid dexa- methasone is used to decrease inflammation by modulating protein production intracellularly. Cyclosporine A sup- presses cell-mediated immune reactions by blocking tran- scription of cytokine genes in activated T cells.

Answer 8

A) Ectopia vesicae (bladder exstrophy)

B) Separation of pubic symphysis

C) Epispadias

Answer 9 - B

The change that best predicts a bad outcome is an abnormality in signal intensity in the posterior limb of the internal capsule (PLIC) and basal ganglia with 90% sensitivity and 100% specificity, and positive predictive value of 100%. Impaired cerebral blood flow is often found in severe cases of HIE but is not the most useful tool in predicting outcome. A number of EEG changes have been reported and are associated with adverse outcome; however, MRI is the most useful predictor. Neurological findings can change quickly in cases of moderate HIE.

Answer 10

A) Meconium plug syndrome

B) Cystic fibrosis

C) Conservative management

Instructions for Authors

Review Article	**The article should be approximately 2-3 pages long with a word count of 2000-2500 words. Author should summarize key practice points at the end. Please include 5-6 references as suggested reading.**
Case Report	**This would be a summary of the case discussed in that months clinical meeting. Interesting cases even if not presented may also be submitted. It should include the clinical presentation and a brief discussion about the condition. Word count should be 1000-1500. Please include 2-3 references at the end.**
Journal Scan	**Some recent research paper of interest to pediatricians and neonatologists. The structure should include Introduction, Research question, Hypothesis, Methods, Results, Limitations and strengths of study, Reviewers comments. Word count should be approximately 1000 words. Please include 2-3 references if needed at the end.**
Picture of Month	**An interesting case related to neonatal practice. It should have a brief case history and a commentary, all fitting on one page along with the pictures.**
Image section	**Any interesting Xray, Ultrasound, CT or MRI of clinical interest. Brief clinical presentation and about the condition should be summarized on one page along with image.**
OSCE	**About 10-12 questions would be included in this section along with answers.**

Contact Us

On behalf of committee, I request all members of NNF, Delhi to actively contribute to various sections of the newsletter.

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