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CONTENTS

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DR. PRADEEP KUMAR DEBATA

Professor
Division of Neonatology
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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 up with 12th issue of NeoClips. I feel priviledged 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 light of the day

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 the 12th issue.

The monthly newsletter tries to cover some interesting review articles, cases, images and pictures. OSCE always remain an important highlight.

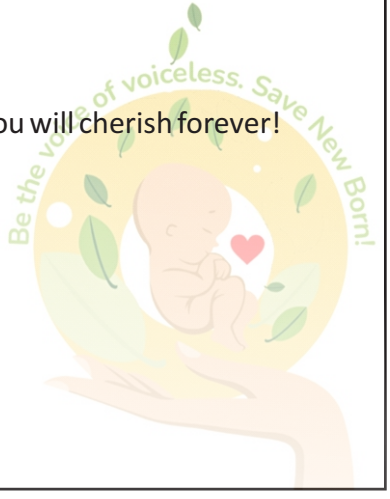
The current issue covers a few interesting cases like methemoglobinemia, collodion baby and intracardiac calcifications.

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 (12th issue) and previous issues.

We have covered some interesting topics in the present issue.

The case report covers an interesting case of transient neonatal methemoglobinemia.

The dilemma continues in the management of neonatal shock. The review article covers which inotrope to be given to which baby.

An interesting case of neonatal erythroderma (Collodion baby) has been covered in the picture of the month.

The image section describes an echocardiographic image of intracardiac calcifications.
OSCE is covering a few interesting questions on neonatal neurology.

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

Unusual Life Threatening Cyanosis in Neonate

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Case

A 30 days male infant presented with loose watery stools for 3 days, lethargy and poor feeding for 1day and bluish discolouration of lips and extremities for the last 3-4 hours. There was no history of fever, vomiting, rash, blood or mucus in stool, breathing difficulty, excessive sweating while feeding, similar bluish discolouration of body in past. There was no contact with a sick patient and no intake of any medications.

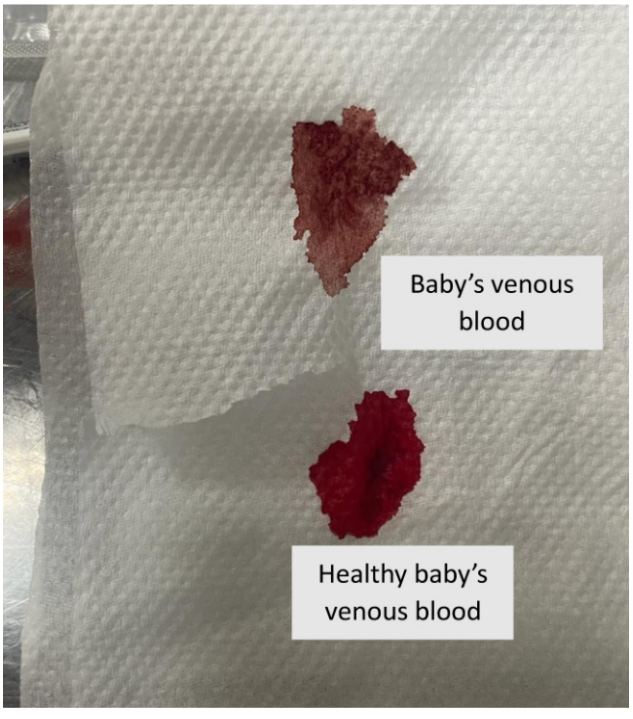
He was born with a low birth weight (2kg) at term gestation to a primigravida mother with a history of pregnancy-induced hypertension (on Tab Labetalol). The perinatal period was uneventful and he was discharged home on breastfeeding. But the baby was fed with diluted cow milk at home for the last 20days (the source of water was pipe water). His weight one week prior to illness (DOL 23) was 2.470kg.

At admission, baby was acutely ill, lethargic, dehydrated with acidotic breathing, impaired peripheral perfusion, and central cyanosis. Admission weight was 2kg with loss of 19% in one week. Pulse oximeter saturation was 83-84% on room air and 88% on noninvasive respiratory support with FIO2 50 %. There was no increase in saturations on increasing FIO2. A diagnosis of term, small for gestation with acute gastroenteritis with severe dehydration with hypovolemic shock and late onset sepsis (to rule out meningitis) was made. The differential diagnosis of cyanosis that were considered were cyanosis secondary to shock, pneumonia with respiratory failure, ARDS and cyanotic congenital heart disease.

Initial blood gas showed severe metabolic acidosis with raised lactate. Chest X-ray was normal. Blood investigations showed haemoconcentration, leucocytosis and thrombocytosis, positive C-reactive protein and impaired blood urea and creatinine. He was managed with invasive ventilation support, intravenous fluid boluses and dehydration correction over 48hours, and intravenous antibiotics for sepsis. CSF examination showed raised proteins suggestive of meningitis. Blood culture and CSF culture later came sterile. Stool routine examination was normal. The baby had high ventilator requirements (oxygen saturation was 85-88% over a wide range of Fio2 25 to 95%); there was no pre and post ductal difference in oxygen saturation (SpO2). Echocardiography was within normal limits. Clinically he had refractory hypoxemia, but surprisingly arterial blood gas showed hyperoxia (paO2 >100) with hypocarbia and metabolic acidosis. As baby clinically improved with good respiratory efforts, and high paO2, he was extubated to non-invasive support by 18hours of admission.

After ruling out the common aetiologies of cyanosis, a differential of abnormal Hb was kept. Infant's blood appeared chocolate brown in colour on absorbent paper as compared to healthy infant blood. Blood gas analysis by co-oximetry revealed methemoglobin (MetHb) concentration of 32.9% (normal range <5%) and a diagnosis of acute methemoglobinemia was established. Glucose-6-phosphate dehyrogenase level was sent and meanwhile he was started on oral ascorbic acid for 24hours. Genetic test to rule out congenital cause was planned but family refused. A packed red cell transfusion was given at Hb of 8.5gm% with cyanosis at 36hrs of admission. By 48hrs, dehydration and acidosis corrected, also SpO2 and cyanosis rapidly improved. MetHb level rapidly declined by 50hours to 3.6%. G6PD level came normal. By 72hours of admission baby was weaned to room air, maintaining target saturation, loose stools improved, started on oral feeds with formula milk, skin colour was pink. Most probable cause of methemoglobinemia in this case could be acquired, secondary to severe sepsis with gastrointestinal inflammation, dehydration and acidosis.

He was treated with intravenous antibiotics for total 14 days. At discharge he had normal oxygen saturation and colour, neurologically normal, gained good weight, sent home on breast milk and formula milk .



Discussion

Pathophysiology

Methemoglobinemia is a rare disorder and an unusual cause of cyanosis in neonates. It is an altered form of hemoglobin oxidized from its ferrous state to ferric state. It binds irreversibly to the heme portion. There are two protective enzymes (NADH-cytochrome b5 reductase and NADPH methemoglobin reductase) for reducing MetHb in erythrocytes. MetHb has a high affinity for oxygen, and causes a leftward shift in the oxygen dissociation curve and causes functional anemia, hypoxemia and lactic acidosis. Cyanosis occurs when the total concentration of methemoglobin (MetHb) is more than 1.5gm/dl

Methemoglobinemia can be congenital or acquired. Congenital form is due to deficiency of cytochrome b5 reductase enzyme, Hemoglobin M disease (pathogenic variant affecting globin gene) or rarely deficiency of cytochrome b5.

Acquired form can occur due to some drugs or food such as anesthetic agents, inhaled nitric oxide, dapsone and sulfonamides; or nitrate contaminated water or food; or Neonates with gastroenteritis, dehydration, sepsis, urinary tract infections, sepsis, milk protein intolerance and organic acidemias are at high risk of developing methemoglobinemia.

Why infants are at risk?

Neonates and infants are more vulnerable for developing methemoglobinemia than children and adults due to certain predisposing factors.

1. Gastric pH of the infants is less acidic which leads to greater bacterial proliferation of the intestinal flora that can convert the ingested nitrate to nitrite.
2. Fetal hemoglobin is oxidized more readily to MetHb by nitrite.
3. Cytochrome b5 reductase activity is reduced 50 percent in infants when compared with older children and adults.

Intake of cow milk in infancy is commonly associated with cow milk protein allergy and can present as diarrhoea associated with methemoglobinemia. Kurian S et al reported a case of diarrhoea and cyanosis and was diagnosed with a high MetHb level of 33%. His condition improved and MetHb level returned to normal following fluid resuscitation and methylene blue administration. He was later managed with breast feeding and elemental formula. The index case was also on cow milk and developed sepsis and gastroenteritis which made him susceptible to this disease.

Methemoglobinemia Associated with Late-Onset Neonatal Sepsis

The probable mechanism for methemoglobinemia in sepsis is release of large amounts of nitric oxide (NO) by activated endothelial cells. NO interacts with Hb, forming MetHb and nitrate (NO3) which can be transformed into nitrite (NO2) and subsequently to other NO in the presence of nitrate reductase producing bacteria, initiating a vicious circle of severe MetHb.

A retrospective observational study of hospitalized newborns over a 2-year period revealed that MetHb-positive patients had a high rate of clinical or culture-proven sepsis and MetHb can be an indicator of an infectious process linked to nitrate-reducing bacteria.

Diagnosis

Methemoglobinemia can be suspected clinically in infants with pale, gray or blue coloured skin, lips or

nail beds; cyanosis out of proportion to pulse oximetry readings, in the presence of normal partial pressures of oxygen (paO2) and the symptoms do not improve with oxygen. Discoloration of blood (dark red to chocolate brown) is noted on an absorbent paper. Confirmatory diagnosis is made by assaying the MetHb on blood gas (MetHb >5%) by measurement of absorption spectrum using co-oximetry. MetHb has a peak absorbance at 630nm.

Management

Treatment involves removal of any oxidative stress or offending drug, supportive care, treatment of ongoing sepsis and administration of intravenous methylene blue and ascorbic acid. Specific therapies are indicated in severely symptomatic cases with Methb level>30%. Methylene blue is contraindicated in G6PD deficient patients. The response to therapy is rapid, within few minutes to 24 hours depending on the MetHb level. In mild cases, withdrawal of offending drug is the only indicated treatment modality. Persistent methemoglobinemia requires exchange transfusion or hyperbaric oxygen therapy.

KEY MESSAGES

- Methemoglobinemia is a rare medical emergency.
- It should be considered in the differential diagnosis of cyanosis and hypoxia in neonates.
- A high index of clinical suspicion and early treatment in such cases can be life-saving.
- Diagnosis is rapid and treatment is easily available and very effective.

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Approach to Neonatal shock

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Shock is a pathological state with imbalance between oxygen delivery and demand leading to tissue hypoxia. When we talk about tissue hypoxia or low organ perfusion, there is a '*functional threshold*' of blood pressure/ organ perfusion below which the neuronal function is impaired. It is the lower limit of blood pressure where we should act. There is an '*ischemic threshold*' of perfusion/ blood pressure below which permanent organ damage starts to happen. These thresholds vary from baby to baby and are affected by gestation, post menstural age, acidosis and duration of hypotension. Various studies have shown that approximately 30% of VLBW babies have hypotension during their NICU stay. Between 16-52% require treatment with volume expansion and 30% require vasopressors.

The main causes of shock in the newborn period are hypovolemic (hemorrhage, sepsis, dehydration), distributive (sepsis, asphyxia, dysregulation as in extreme PT), cardiogenic (asphyxia, myocarditis, arrhythmias, large PDA) and obstructive (pneumothorax, obstructive lesions). Various factors that cause low cardiac output can be decreased preload, structural injury leading to decreased contractility and increased afterload (Table 1). Shock can be initially in compensated phase where blood flow to vital organs are maintained and BP is maintained in normal range. Signs would be tachycardia, prolonged CFT and decreased urine output. Second phase is uncompensated phase where there is decrease in vital and non-vital organ perfusion, development of lactic acidosis, cellular disruption and multiorgan dysfunction (MODS).

Table 1: Common causes of shock in newborn period

Etiopathology	Causes	Clinical clues
Hypovolemia	Blood loss (placental bleed, IVH, pulmonary hemorrhage, DIC)	APH, delivery events, pallor, revealed bleed
	Plasma loss (low oncotic pressure, capillary leak)	Hydrops, suspicion of NEC, sepsis
	ECF loss (insensible water loss, polyuria)	Extreme prematurity, excessive Weight loss
Cardiogenic	Obstructive (AS, CoA)	Onset towards end of 1st d
	Myocardial dysfunction (asphyxia, SIRS, myocarditis, cardiomyopathy)	Asphyxia, infant of diabetic mother, sepsis,
	Arrhythmia	HR >220, in ECG rhythm disturbances
	Others (high PEEP, tension pneumothorax , cardiac tamponade)	Hyperexpanded chest, ↓ ed air entry, CO_2 retention
Abnormal vasoregulation	Peripheral vasodilatation (sepsis, drugs, neurogenic)	Wide pulse pressure
	Shunts / transitional circulation / inotropic – afterload imbalance	(1st 24 h in ELBW)
Mixed Vasoregulative + Cardiac dysfunction	Sepsis	Suggestive clinical features

Clinical features

The cardinal features of neonatal shock are:

- Signs of poor perfusion like cool and pale extremities, prolonged capillary refill time (CRT) (more than 3-4 seconds).
- Tachycardia is a non-specific early sign of shock, while bradycardia is often a pre-terminal finding.
- Non-specific signs like lethargy, irritability etc.
- Hypotension is a late sign of shock. The definition of neonatal hypotension is not clear.
- Poor end organ perfusion may lead to low urine output, intestinal ischemia leading to increased risk of NEC etc.

Operational definition of hypotension in newborns

There is no single universally accepted definition for hypotension in newborns. Generally, hypotension is defined as blood pressure less than 5th percentile for the age. This could be defined as mean BP less than gestational age in weeks for a particular baby in the first 48-72 hours of life. But gradually the mean blood pressure increases with age and therefore, corrected or postnatal gestation should be considered for the definition.

A number of non-invasive bedside parameters like perfusion index (PI), plethysmography variability index (PVI), functional echocardiography measurements and laboratory parameters like blood pH, lactate levels, mixed venous oxygen saturation measurements are used for the detection and management of shock. However, no single measure has been found to be sensitive and specific for detection of shock. Recently, PI and PVI measured by pulse oximeter have been suggested as an objective assessment of pulsatile flow of blood in peripheral arteries and the flow variability during breathing.

Sometimes, particularly in ELBW neonates, the mean blood pressure is low but other parameters of systemic perfusion like pulse volume, CRT, pH, lactate, base excess etc. are normal. We often ignore the blood pressure readings for such babies acknowledging the fact that we don't have nomograms for normal blood pressure for newborns and these values maybe within the normal range. We call this '*permissive hypotension*'. Such hypotensive infants who have but with evidence of good perfusion have as good outcome as normotensive patients.

Investigations

The investigations would vary with the clinical condition of the baby and suspected etiology. Broadly, following investigations should be offered-

1. Complete blood count- Hemoglobin, platelet count, total leukocyte count and differential count should be performed to determine infection and degree of concomitant anemia and thrombocytopenia.
2. Coagulation parameters like PT, aPTT should be done when DIC and liver failure is suspected.
3. Electrolytes, blood sugar, blood urea and creatinine should be done if oliguria/anuria is present.
4. If facility is available Functional Echocardiography should be done to assess cardiac function. Generally, left and right ventricular output are equal in children and adults. But in neonates, due to shunting across PFO and PDA, there is unequal output across both the ventricles. Hence, SVC flow is considered a surrogate marker of systemic cardiac output. For preterm neonates, SVC flow of less than 50 ml/kg/min and RVO of less than 150 ml/kg/min is considered a threshold for shock. Echocardiography also helps assessing the preload by measurement of IVC collapsibility and IVC variability. Cardiac contractility can be assessed by fractional shortening and Ejection fraction. Echocardiography also helps in ruling out structural heart diseases in neonates with shock.
5. Chest xray should be done in newborns with respiratory distress and abnormal findings on respiratory examination.
6. Cranial ultrasound should be done in all preterm neonates with abnormal neurological signs and symptoms and/or features of acute blood loss to rule out intracranial bleed.
7. Arterial blood gas should be done to access adequacy of ventilation and oxygenation. Some studies suggest that mixed venous oxygenation less than 70% is associated with poor outcomes in children but evidence is lacking in neonates.
8. Serum lactate is one of the parameters for tissue hypoxia/ hypoperfusion. However, exact correlation between serum lactate and degree of tissue hypoxia is lacking.

9. Blood culture and lumbar puncture should be done for all the babies suspected to have severe sepsis and septic shock.
10. Cross matching and typing of blood should be done for neonates where one is expecting a possible need for transfusion.

Treatment

One should not delay the treatment of shock and it should be done aggressively. In the management of neonatal shock, postnatal physiological variation with postnatal age and gestation should be taken into account.

1. Volume expansion: This has been a first line management for neonatal shock. One has to be cautious especially in preterm neonates where excessive volume resuscitation has been associated with increased risk of PDA, BPD and NEC and poorer neurological outcome. Cautious use of fluids- 10-20 ml/kg should be considered for all neonates with shock. The volume of fluids and the rate of infusion depends on the gestation of the baby (lower volume and slower rate in extreme preterms).
2. Supportive management:

- Early support of airway and breathing as per the need of the baby.
- Appropriate venous access for the baby should be done.
- Correction of metabolic derangements like hypoglycemia, hypocalcemia, hypo/hyper-kalemia and acidosis.
- Antibiotics as per the unit policy should be considered. In case of suspected sepsis, antibiotics should be started without any delay.
- Blood product transfusion where shock is due to blood loss (placenta previa, intraventricular hemorrhage). In emergency situations, O negative PRBC or whole blood can be given.

3. Pharmacotherapy in neonatal shock:

- *Dopamine:* It causes dose dependent stimulation of alpha, beta and dopaminergic receptors. Lower doses (2-4 mcg/kg/min) mainly stimulates the dopaminergic receptors on renal and splanchnic vessels and causes vasodilation. Moderate doses (5-10 mcg/kg/min) cause augmentation of cardiac contractility by stimulating beta receptors on the heart. Higher doses (10-20 mcg/kg/min) act on alpha receptors and increase blood pressure by increasing peripheral vascular resistance.
- *Dobutamine*: It increases cardiac contractility and cardiac output by acting on Beta receptors on the heart. It has minimal effect on blood pressure and afterload. Dose range is 10-20 mcg/kg/min. There is evidence that dopamine is more effective than dobutamine for treatment of hypotension in neonates.
- *Epinephrine:* It is a non-selective alpha receptor and beta 1 & 2 receptor agonist: increases BP and systemic blood flow by increasing SVR and cardiac output. At lower doses (0.01 – 0.1 mcg/kg/min), it increases cardiac contractility and causes slight vasodilation. However, at higher doses (> 0.1 mcg/kg/min) it stimulates alpha receptors and increases peripheral resistance and blood pressure. The available evidence suggests that epinephrine is comparable to dopamine for treatment of hypotension in neonates.
- *Norepinephrine*: It is a potent non-selective alpha agonist with some effect of beta receptors. The recommended dose is 0.1-0.3 mcg/kg/min. The benefit of using norepinephrine over epinephrine is that it does not cause pulmonary vasoconstriction at higher doses and therefore is useful in situations where there is concomitant pulmonary artery hypertension.
- *Vasopressin*: Vascular effects of vasopressin occur by vasoconstriction mediated by stimulation of G-protein coupled V1a receptors. The usual dose of vasopressin is 0.0002 to 0.006 mcg/kg/min. Vasopressin is commonly used in catecholamine refractory shock. One should exercise caution while using vasopressin in babies with myocardial dysfunction. Some recent studies have suggested that vasopressin is non-inferior to dopamine for neonates with hypotension. It rather has some benefits and causes less tachycardia as compared to dopamine.
- *Milrinone*: It is a selective phosphodiesterase III inhibitor. It enhances myocardial contractility without raising myocardial oxygen consumption or increasing afterload and decreases vascular

tone in systemic and pulmonary vascular beds. It is useful for treating low cardiac output states after corrective surgery for congenital heart defects. It is useful as an adjunct to Inhaled Nitric oxide in persistent pulmonary hypertension. The usual dose is 0.5-1.0 mcg/kg/min

- *Steroids*: Steroids cause upregulation of adrenergic receptors and release of vasoactive factors and leads to increase in intracellular calcium concentration. Its use is generally restricted to fluid refractory catecholamine resistant shock. The usual dose of hydrocortisone is 1-2 mg/kg/dose q6 hourly.

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A case of Congenital Icthyosis

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Case - Late preterm(36 weeks + 3 days) appropriate for gestational age male baby with a birth weight of 2500 grams was born through C section in view of cerebral redistribution. He was noticed to have extensive skin lesions with ectropion and eversion of lips (Figure 1). The baby was shifted to NICU, put in a humidified incubator, and started on IV fluids and paladay feeds.

Suspicion – Congenital icthyosis (Collodion baby)

Course - A paediatric dermatology reference was taken and the baby was started on capsule acitretin (oral retinoid) in a dose of 1mg/kg/day. Skin emollients (first ceramide based emollient followed by petroleum jelly) were applied 5-6 times a day. Baseline lipid profile/Liver function tests were done which were normal and whole exome sequence was sent. An opthalmology review was taken and advised topical methylcellulose eye drops. Serum sodium levels were monitored regularly to guide intravenous fluid therapy. IV fluids were tapered and stopped over 5 days. With due course of time, ectropion subsided and skin lesions were better and new skin lesions didn't appear (Figure 2). The baby was discharged on day 15 of life on breastfeeding once mother was confident, on capsule acitretin, on skin emollients.

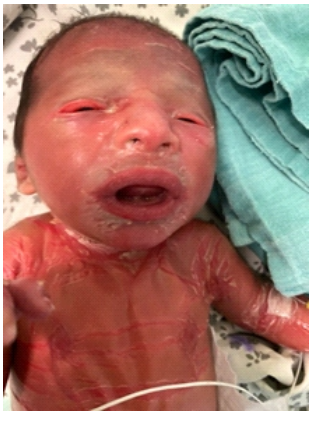

Fig 1 : Skin lesions on Day 1 of life

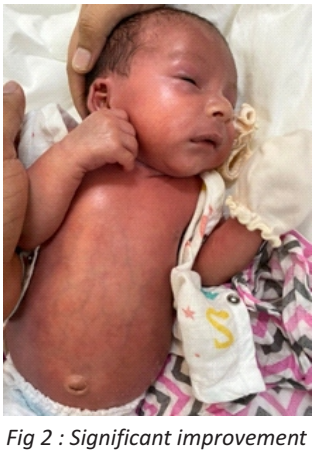

Fig 2 : Significant improvement in skin lesions by Day 20 of life

Condition

Congenital icthyosis is a group of disorders characterized by erythroderma with cellophane/ parchment-like membrane encasing the entire body along with ectropion (eversion of the eyelids), eversion of the lips (eclabion), pseudo-contractures of limbs, and limited joint mobility.

Types:

1. Non-syndromic - Lamellar icthyosis (50%), non-bullous congenital Icthyosiform Erythroderma (20%), X-linked icthyosis, icthyosis vulgaris.
2. Syndromic - Lipid storage disorder, ARC syndrome
3. Metabolic - Holocarboxylase synthase

deficiency , Gauchers type 2 , Congenital hypothyroidism

4. Self healing variant (10%)

Differential diagnosis-

1. Harlequin icthyosis
2. Icthyosis prematurity syndrome
3. Netherton syndrome
4. Sjogren larrson syndrome

Pathogenesis - Most collodion babies (CBs) are autosomal recessive in inheritance. Most of these occur as a result of mutation in TGM1(40%), ALOXE3, or ALOX12B genes. There is deficient cross-linking of cornified cell envelope proteins which leads to increased epidermal germinal cell activity and a failure of stratum corneum cells to separate and disruption of the skin barrier.

Diagnosis - Whole exome sequencing can be done antenatally or postnatally depending on case to case basis. In skin biopsy transglutaminase -1 activity can be assessed though not routinely done.

Complications - Temperature instability , hypernatremic dehydration , sepsis and exposure keratitis.

Management -

1. Admit in NICU.
2. Skin care : Soft bedding , Use of emollients like paraffin dressings and petroleum based jelly. Use of topical antibiotics in areas of fissuring and ulceration. Use of humidified incubators with initial humidity (60-70%) gradually tapered as lesions improved.
3. Monitoring of body temperature and avoidance of hypothermia.
4. Monitoring of water and electrolyte balance.
5. Monitoring for signs of cutaneous or systemic infection, and standard NICU precautions for infection control.
6. Oral retinoids : Acitretin is a 2nd generation aromatic retinoid and Vitamin A Derivative. It affects cell growth and differentiation and alters cellular adhesiveness .Dose: 0.5 to 0.75 mg/kg/d, max (2mg/kg/d) with slow tapering to 0.25 mg/kg/d and then withdrawn. Duration of therapy is usually 3-6 months. Side effects include cheilitis, hair loss, pseudotumor cerebri, liver toxicity and thyroid disorder.
7. Eye care - Topical methylcellulose, antibiotic drops.
8. Feeding – Oral feeding should be encouraged. In case of severe stiffness and pain, orogastric feeding can be given.
9. Analgesia – Non-pharmacological measures should be used. Sometimes child need paracetamol or opiods.
10. No role of prophylactic antibiotics.
11. Parental involvement in caregiving is very important.

Prognosis - Most of them (around 75%) evolve into NBCIE (nonbullous congenital ichthyosiform erythroderma) or LI (lamellar ichthyosis). Although both LI and NBCIE have a normal life span, symptoms of LI remain severe throughout life while NBCIE improves after puberty. The remaining 15% develop into various hyperkeratotic skin disorders.

Key points -

- Collodion baby is a rare and true dermatological emergency
- It may be life-threatening in the early phase with an increased risk of complications which may be prevented by meticulous multi-disciplinary care
- Early use of acitretin is highly beneficial
- Appropriate genetic counselling must be done for all cases

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An Interesting case of Idiopathic antenatally diagnosed intracardiac calcifications

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Case – Term (38 weeks) appropriate for gestational age male baby born to 30 years G2A1 mother through elective LSCS with a birth weight of 3486 grams. Antenatal ultrasound at 33 weeks showed hyper-echoic subchordal shadows with severe tricuspid regurgitation (Figure 1). There was no pulmonary stenosis and ductal velocity was normal. The mother was screened for autoimmune disorders (ANA, Anti Ro, Anti LA antibodies were normal). Her TORCH titer was normal. The baby cried immediately after birth. A postnatal echo was done which showed a hypertrophied right ventricle and multiple hyper-echoic shadows with moderate tricuspid regurgitation (Figure 2, 3)

Possibilities: Cardiac Calcifications
Congenital severe pulmonary stenosis
Restrictive cardiomyopathy

Clinical course:

The baby was started on minimal oxygen in view of respiratory distress after birth. Oxygen was tapered off over the next 24 hours. Baby didn't have any sign of dysmorphism. Serum calcium and phosphorus levels were normal. The baby was shifted to the mother on the second day of life and discharged on day 3rd of life. Possibilities were discussed with the family and the plan was to further investigate the child (TMS/GCMS, Whole Exome Sequence) in case the hyper-echoic shadows persist, or cardiac function deteriorates.

On follow-up echocardiograms, the right ventricle systolic and diastolic function is better, and shadows are persisting (though regressed) (Figure 4). The plan is to do a cardiac MRI, Whole exome sequencing and TMS/ GCMS. There is no hepatosplenomegaly which is evident in these 6 months.

Currently baby is 6 months old, and the growth and milestones of the baby are normal for his age. His cardiac function is normal, and he is not on any medication.

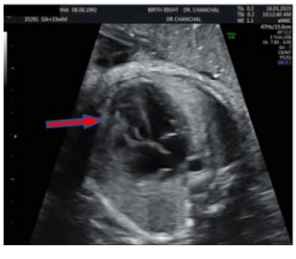

Fig.1

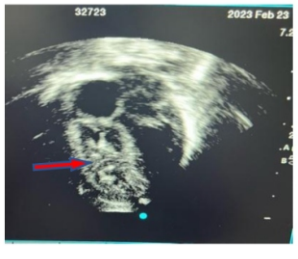

Fig.2

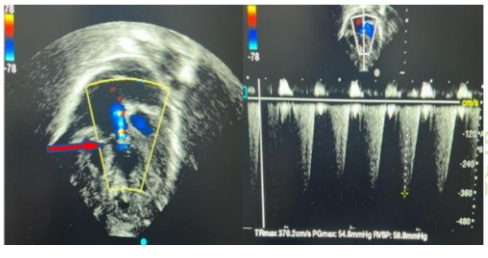

Fig.3

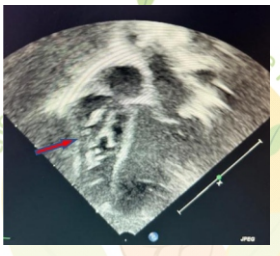

Fig.4

Fig. 1 : Antenatal scan at 33 weeks GA showing hyper echoic shadows in the right ventricle.
Fig. 2 : Postnatal scan on day 1 showing hypertrophied right ventricle and multiple hyper- echoic shadows.
Fig. 3 : Postnatal scan suggestive of severe Tricuspid regurgitation
Fig. 4 : Echocardiography at age of 4 months demonstrating decrease hyperechoic shadows as compared to figure 2.

Condition:

Fetal cardiac calcification is a rare ultrasound finding, defined as diffuse hyperechogenicity affecting mainly the myocardium but can extend to involve the epicardium as well as the visceral pericardium. The calcifications can be diffuse and involve the entire myocardium, or patchy, over large areas of the heart. Due to the indistinct symptoms and very low prevalence, it is difficult to identify the distinctive cause of these lesions. These intracardiac hyperechoic lesions may lead to intrauterine fetal demise, organ dysfunction, and severe developmental delay in living survivors. So, it is of utmost importance to identify and understand the pathological cause which will help in detemining outcome and timely treatment.

Calcifications of the myocardium can result from dystrophic deposition of calcium in areas of necrosis, bleeding or fibrosis of the myocardium. This can occur following decreased perfusion and/or oxygen supply causing hypoxia and infarction, as well as hypo-perfusion from other causes associated with myocardial dysfunction. Chromosomal abnormalities associated with excessive calcium deposits such as trisomy 13 have been associated with myocardial calcifications. Intrauterine infection with associated myocarditis and cardiac dysfunction can also result in myocardial calcifications.

Suggested workup for cases with antenatally diagnosed diffuse intracardiac calcifications:

Detailed structural fetal ultrasound	To look for any structural abnormalities, Signs of intrauterine infection, Fetal hydrops and signs of cardiac failure
Fetal echocardiography	To look for any structural cardiac abnormalities Heart size, Rhythm studies, Functional Doppler studies, and cardiac function.
Amniocentesis/ Chorionic villus sampling	Karyotyping
Infection work up.	TORCH, Parvovirus B19, Coxsackie, Adenovirus
Maternal autoantibodies	Anti- Ro, Anti- La
Vasospastic substances	Cocaine

Possible causes of intracardiac calcifications:

Fetal myocardial infarction based calcification	Associated with intrauterine myocardial infarction. Coronary artery occlusion or glycogen storage disease of the heart can lead to calcifications. Other causes for intrauterine cardiac infarction can be idiopathic, ventricular aneurysms, and twin-to-twin transfusion syndrome.
Thromboembolism based calcification	Thrombus has been reported as a direct factor to cause myocardial necrosis and calcification. Factor V Leiden is the most common inherited form of thrombophilia.
Inflammation based calcification	Autoimmune diseases, such as SLE, scleroderma and rheumatoid arthritis, could cause pericarditis. Autoantibodies like La/SSB antibodies can bind apoptotic cardiomyocytes and may increase the immunoglobulin deposition in the heart. The tissue damage could consequently lead to fibrosis and calcification of the myocardial tissue. Once the AV-node gets involved, complete congenital heart block can occur.
Intrauterine infection associated calcification	TORCH infection in pregnancy, particularly with Cytomegalovirus (CMV), toxoplasmosis, herpes encephalitis, HIV, and rubella, is associated with periventricular calcification of the brain. However, more and more observations and studies have reported that many intrauterine infections could also cause fetal myocardial calcification.

Chromosomal abnormality	Fetal Intracardiac Echogenic Foci (ICEF) by ultrasound was first reported in 1987 and the current understanding of ICEF is micro calcification of the papillary muscles. The presence of ICEF in fetuses represents a high risk for chromosomal abnormalities, particularly with trisomy 21
Familial fetal cardiomyopathy	Isolated cases have been associated with intracardiac calcifications resulting in poor perinatal outcome.
Maternal elicit drug use	Cocaine use is associated with myocardial ischaemia and infarction. Maternal cocaine use has also been implicated as a possible cause of fetal myocardial damage and subsequent calcification

Differential diagnosis:

1. Idiopathic Infantile Arterial Calcinosis (IIAC): IIAC is a rare disease of unknown etiology, which is characterised by arterial calcification. An ultra-sonographic examination can show diffuse arterial calcifications involving the aorta, pulmonary artery, common iliac arteries, renal arteries, and common carotid arteries. IIAC is an example of calcification that occurs primarily in the vasculature rather than the myocardium.
2. Generalised Arterial Calcification of Infancy (GACI): It is a rare genetic disorder consisting of diffuse arterial calcification and intimal proliferation, associated with mutations in ENPP1 in the majority of the cases. It typically results in progressive arterial stenosis and frequently leads to death from myocardial ischemia by 6 months of life. Infants are usually diagnosed before birth or in the neonatal period with symptoms of congestive heart failure.
3. Fetal cardiac tumours: Rhabdomyoma is the most common type of neonatal cardiac tumour. Approximately 40% of rhabdomyomas present in fetal life are associated with tuberous sclerosis. Except rhabdomyoma, the other cardiac tumours which may appear echogenic or calcified include fibromas and pericardial teratomas.

Conclusion:

Fetal myocardial calcification as an unusual pathological finding and potential causes, includes fetal myocardial infarction, autoimmune inflammation and viral infections, maternal drug use, and/or chromosomal abnormalities, etc. Even though most of the neonates with fetal myocardial calcification are ultimately fatal, identification of the possible cause may lead to early diagnosis and management and may significantly contribute to a better outcome and prognosis.

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Journal Scan

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Original research

OPEN ACCESS

A randomised trial comparing weaning from CPAP alone with weaning using heated humidified high flow nasal cannula in very preterm infants: the CHiPS study

Joanne Clements [1], Pernille M Christensen,[2] Michael Meyer[1,3]

Arch Dis Child Fetal Neonatal Ed 2023;108:F63–F68.

Research question -

Should preterm babies be weaned off from CPAP directly or first changed to nasal high flow (nHF)

Hypothesis

P	Preterm infants <30 weeks' gestational age (GA) who were on bubble nCPAP 6 cm water pressure for at least 48 hours and deemed ready to wean
I	Wean off nCPAP support by changing to nHF and progressively weaning the flow
C	Weaning of nCPAP pressure
O	Duration of respiratory support (in hours) from randomisation until weaning was completed.

Study design Single-centre, non-inferiority, randomised controlled trial.

Setting Neonatal Intensive Care Unit, Middlemore Hospital, Auckland, New Zealand.

Study period: 2015-2019

Participants : To be deemed ready to wean preterm infants (<30 weeks) had to meet stability criteria for the 24 hours prior to randomisation. This period could be part of the 48 hours at 6 cm nCPAP.

The stability criteria were as follows:

1. No requirement for oxygen supplementation.
2. Respiratory rate ≤60 breaths/min.
3. No significant desaturation (SpO_2 <80%) or bradycardia (heart rate <100 beats/min) requiring bedside intervention.

Exclusion criteria-

- Infants who had previously been off respiratory support for >7 days
- Significant congenital heart disease
- Surgical conditions
- Chromosomal abnormalities
- Genetic syndromes
- Major congenital malformations

Sample size was determined by using observational data and bootstrapping. A total of 100 infants (50 per arm) would provide a 92% power to conclude non-inferiority of the weaning time (one-sided significance test). A non-inferiority margin of 15% was chosen. 120 infants (60 per group) were recruited

Primary outcome- Duration of respiratory support (in hours) from randomisation until weaning was completed.

Randomisation

The randomisation sequence was computer generated and stratified (≥ 27 weeks' or <27 weeks' GA) with random block sizes (2-10) and allocation

using sequentially numbered sealed opaque envelopes, which clinicians opened immediately prior to study entry.

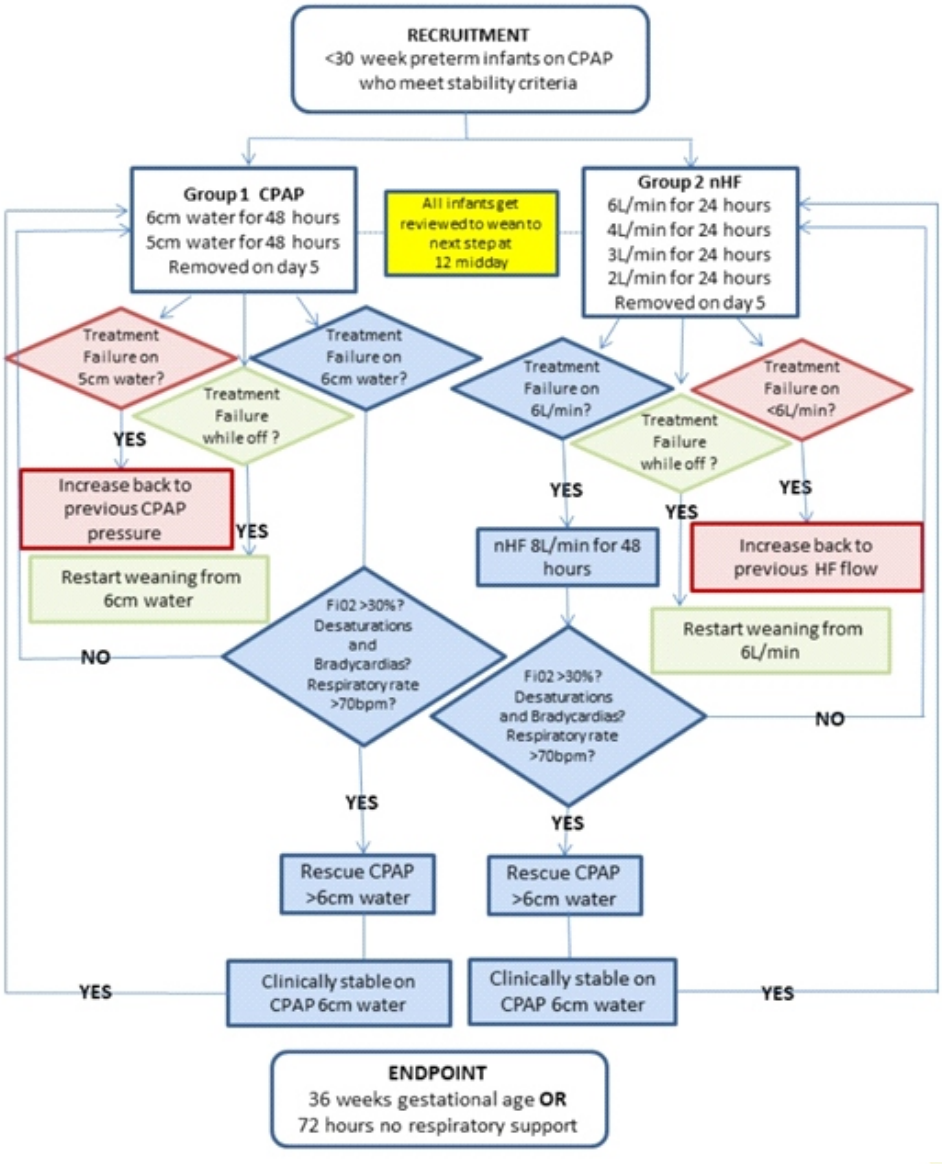
Infants were randomised to wean off nCPAP support either by changing to nHF and progressively weaning the flow compared with weaning of nCPAP pressure. For all infants, the study commenced at 12 midday on the day of randomisation.

96 hours was the minimal time before trialling off. At each step stability criteria had to be met.

Successful weaning-Infants completed weaning by successfully remaining off respiratory support at 72 hours or reaching 36 weeks' PMA.

Failure criteria-

- 6 desaturation (<80% saturation) and associated bradycardia (<100/min) in 6 hours requiring bedside intervention
- 1 episode requiring intermittent positive pressure by t piece



- Respiratory rate >70/min consistently for 30 minutes

Infants could receive increased pressure or flow if they met failure criteria and infants on nHF could be 'rescued' to nHF 8 L/min prior to being placed back on nCPAP. If nCPAP support of >6 cm water or nHF support of >8 L/min were required, then infants received rescue nCPAP until stability criteria were met

and they recommenced their protocol as originally assigned.

Statistical analysis - A non- inferiority one-sided alternative (significance level 2.5%) was used to test the primary hypothesis and a superiority two-sided alternative for secondary hypotheses.

Results

120 infants were randomised; 61 to the nCPAP group and 59 to the nHF group. The cut-point for the restricted mean was 888 hours. The restricted mean hours from randomisation to 72 hours off respiratory support or 36 weeks' PMA was 401 hours in the nCPAP group vs. 375 hours in the nHF group, showing that nHF weaning was non-inferior to nCPAP weaning.

Weaning: The first trial off respiratory support following randomisation was at a similar PMA in the two groups (median 31 weeks).

Infants in the nHF group had a higher rate of escalating flow/ pressure (52.5% vs 34.4%; OR 1.53 (95% CI 0.78 to 2.95)) however, this was not statistically significant. Reduced treatment failures prior to achieving 72 hours in the nHF group compared with nCPAP (24% vs 47.5%; OR 0.49 (95% CI 0.24 to 1.03)). The leading cause of treatment failure in both groups was desaturation/bradycardia.

Secondary outcomes: In the <27 weeks' GA subgroup, we were unable to conclude nHF non-inferior to nCPAP when weaning from nCPAP within a 15% non-inferiority margin. Infants in the nHF arm had significantly less CLD than those in the nCPAP arm (18% vs 36%; OR 0.42 (95% CI 0.18 to 0.99 corrected for gestation and sibling factor). Other outcomes were not statistically significant.

Strengths of study-

- A clear weaning algorithm with predetermined failure criteria
- Inclusion of infants with gestation age < 27 weeks
- Ability for nasal groups to be rescued to nCPAP

Limitations-

- Small sample size of babies born < 27 weeks
- Single center trial
- Weaning occurred at set time during the day
- 15% of study infants were not able to be weaned from support during study.

Reviewer comments

CPAP remains mainstay of non invasive respiratory support in preterm infants. However paucity exists on best practices to wean neonates from CPAP. Prolonged CPAP is associated with complications like nasal septal damage and air leaks whereas early weaning may be associated with atelectasis and failure of weaning.

Options include immediate removal of nCPAP at a predetermined pressure, removing nCPAP for a number of hours each day with increasing time off and stopping nCPAP and starting high flow nasal cannula (nHF) or cycling infants between different modalities of non-invasive support.

Surveys done among neonatologists identified a lack of consensus regarding the optimal method of weaning NCPAP. Only 6% of responders followed set standards within their units, and the majority used a combination of various methods.

Four randomised controlled trials (RCTs) have been published, with the majority of these reporting that weaning from nCPAP using nHF was as effective as weaning from nCPAP alone.

In a systematic review and meta-analysis by Brenda van Delft et al that included 15 RCTs showed that a weaning strategy of progressive reduction of CPAP pressure possibly increases the chances of success at first weaning attempt, but that the weaning process takes more time and discontinuation comes at a later PMA. Stepping down from CPAP to an HFNC shortens the duration of CPAP treatment but is associated with a longer duration of oxygen administration.

While the mainstay of the weaning strategy still remains unclear the ease of use of HFNC stems from less nasal trauma, fewer air leaks and easier bonding with family. However, proper weaning protocols to wean from HFNC are still lacking. The current trial does state a proper weaning algorithm to wean infants from HFNC with intention to treat analysis. Hence, More RCTs are needed with a larger sample size to give a consensus statement for the use of HFNC as a weaning modality from CPAP.

What is already known on the topic

- Continuous positive airway pressure is the mainstay of non-invasive respiratory support in neonatal intensive care units. It does come with

some complications including air leak and nasal septal damage hence early weaning is important but the best way remains unclear.

- There have only been a small number of randomised controlled trials which have explored weaning preterm infants from nCPAP using high flow nasal cannula (nHF).

What this study adds

- Weaning from nCPAP using nHF was non- inferior to weaning from nCPAP alone in stable very preterm infants, when using strict weaning and failure criteria.

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Question 1.

As per the latest ILAE classification of seizures and epilepsies by ILAE Task force on neonatal seizures, which of the follow statements is not true ?

A. Neonatal seizures are considered focal at onset, and thus a division into focal and generalized is not necessary.

B. Seizures are classified by the predominant clinical feature, which may or may not be the first clinical manifestation.

C. Key role of EEG in the diagnostic framework of neonatal seizures which can be either electroclinical or electrographic only.

D. When cEEG / aEEG is not available, observation by an experienced personnel in case of focal clonic and focal tonic seizures can be considered as seizures with "possible certainty" as per algorithm by Brighton collaboration group.

Question 2.

Following an uneventful pregnancy and normal delivery, a 2-day-old term baby boy presented with lethargy, poor feeding and recurrent apneas. Examination revealed hypotonia, poor suck, weak cry, fragmentary myoclonus and jitteriness. EEG showed burst suppression pattern. Basic metabolic and sepsis screens were negative. Refer to Figure 1 for MRI Brain images. MR spectroscopy showed a metabolite peak at 3.5 ppm. Which of the following initial investigations will be most informative in this clinical context ?

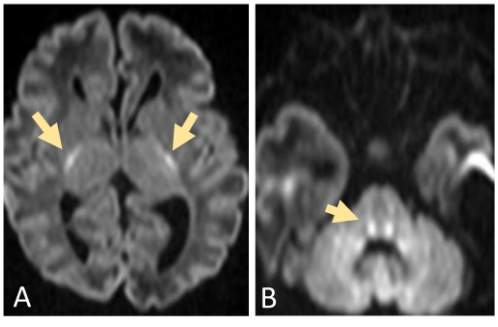


Fig.1: MRI Brain: Axial DWI images

A. Plasma amino acids, urine organic amino acids, total and free acylcarnitine profile

B. Urine sulphite

C. CSF/ plasma glycine ratio

D. Transferrin electrophoresis

Question 3.

One day old term neonate with severe HIE was initiated on therapeutic hypothermia at 3 hours of life with aEEG monitoring. After loading with injection phenobarbitone, no clinical seizures were evident. aEEG tracings at 6 hours (figure 1) and 48 hours (figure 2) of life showed burst suppression and low-voltage respectively. Which of the following statements is correct regarding the predictive value of aEEG on neurodevelopmental outcome ?

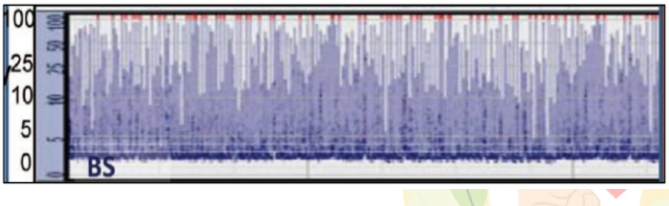


Fig. 1: Burst suppression at 6 hours aEEG

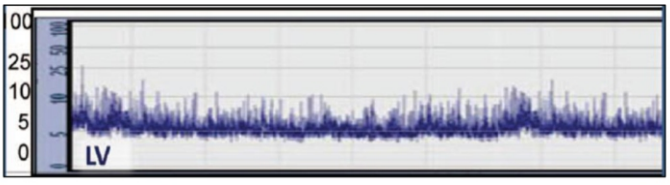


Fig. 2: Low voltage at 48 hours aEEG

A. Burst suppression at 6 hours is always predictive of poor neurodevelopmental outcome

B. Persistent low voltage tracing at 48 hours is more likely predictive of an adverse neuro developmental outcome

C. The positive predictive value of a persistently abnormal aEEG pattern on guarded neurological prognosis decreases over time from 6 hours to 72 hours of life

D. All of the above statements are true

Question 4.

A 5 day old term boy, born out of a normal vaginal delivery with smooth perinatal transition, presented with recurrent episodes of right focal clonic seizures and lethargy. Examination revealed mild encephalopathy and right hemiparesis. Seizures got controlled with levetiracetam. MRI Brain DWI images revealed diffusion restriction in the left middle cerebral artery territory suggestive of acute ischemic infarct. Which of the following statements is wrong?

A. Investigations should include 2Decho, coagulation parameters and sepsis screen

B. MR-Angiography of brain vessels is indicated

C. Thrombophilia testing is not indicated

D. Anticoagulation with low-molecular-weight heparin (LMWH) should be started immediately

Question 5.

A 2 week old neonate, without perinatal complications, with complaints of breathing difficulty and loose stools (Rotavirus positive) in the first week of life, currently presented to the casualty with encephalopathy, tonic seizures and features of raised intracranial tension. Metabolic screen was negative. Sepsis screen was positive. Coagulation parameters were not screened. MRI Brain showed malignant cerebral oedema please refer to figure 1. Which one of the following can be a likely cause ?

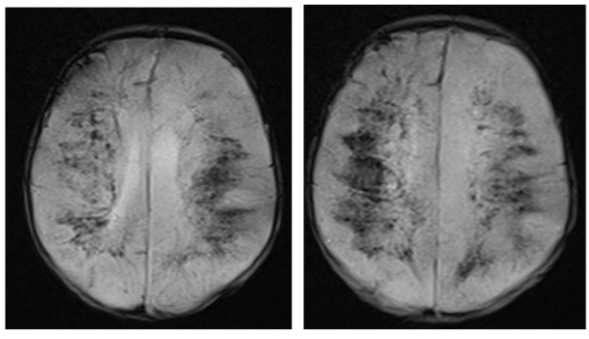


Fig. 1: MRI Brain - Susceptibility weighted imaging (SWI)

A. Infection (rotavirus, sepsis)

B. Inherited thrombophilia

C. Genetic causes (COL4A1, COL4A2)

D. All of the above

Question 6.

Which of the following is not a correct match with respect to landmark randomised controlled trials in therapeutic hypothermia for neonatal HIE ?

A. **Cool Cap trial:** Whole body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic–ischemic encephalopathy

B. **TOBY trial** (Total Body Hypothermia for Neonatal Encephalopathy): At 18 months, children who had been treated with hypothermia had reduced risks of cerebral palsy and improved scores on the Mental Developmental Index, Bayley Scales of Infant Development II (BSID-II) and Gross Motor Function Classification System.

C. **TOBY Children Study:** Moderate hypothermia after perinatal asphyxia resulted in improved neurocognitive outcomes in late childhood.

D. **Whole Body Hypothermia for Term and Near Term New-borns with Hypoxic Ischemic Encephalopathy (NICHD Neonatal Research Network Trial):** This trial determined the effectiveness and safety of moderate whole-body hypothermia in newborns with HIE born in hospitals with and without newborn intensive care facilities or complicated hypothermia equipment.

Question 7.

A term baby boy, with uneventful normal delivery, became symptomatic with breathing difficulty at 4 hours of life. Examination revealed tachypnea, saturation 90% on room air, diminished facial expressions, poor suck/swallow, generalised hypotonia and paucity of antigravity limb movements with preserved muscle stretch reflexes. Mother has history of variable dropping of eyelids and one spontaneous 1st trimester abortion. Which of the following statements doesn't hold true for the above clinical condition ?

A. A possibility of transient neonatal myasthenia can be considered in the clinical context

B. Serum acetylcholine receptor (AchR) antibody testing is indicated in both mother and baby

C. Repetitive nerve stimulation test should be performed in the neonate

D. A positive therapeutic response with anticholinesterase medication (neostigmine sulphate) can aid in arriving at the diagnosis

Question 8.

Which of the following is not true as per the latest guideline and consensus based recommendations by neonatal TASK force of ILAE for the management of neonatal seizures?

A. Phenobarbital should be the first-line ASM regardless of etiology (including HIE, stroke, and haemorrhage).

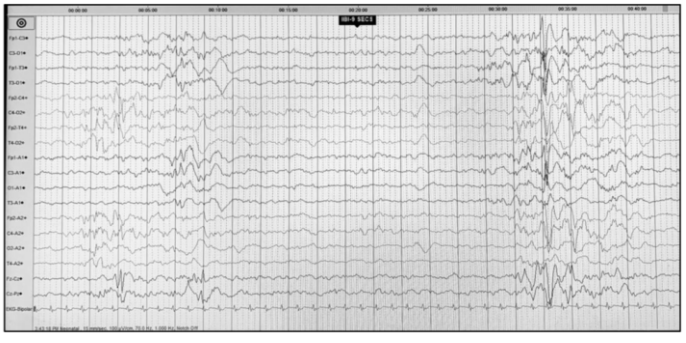
B. Following cessation of acute provoked seizures, ASMs may be continued after discharge based on MRI or EEG findings.

C. If channelopathy is the likely cause for seizures due to family history, then phenytoin or carbamazepine (sodium channel blocker) may be the first-line ASM.

D. In neonates with seizures not responding to first-line ASM, phenytoin or levetiracetam or midazolam or lidocaine may be used as a second-line ASM for most aetiologies.

Question 9.

Figure 1 depicts the EEG epoch (quiet sleep) of a 39 weeks, boy without any perinatal complications. EEG was advised in view of suspicion of recurrent paroxysmal events. Which of the following interpretations is correct ?



A. EEG is normal as bursts can be seen in quiet sleep till 44 weeks of age

B. EEG is abnormal as interburst interval is prolonged for a term neonate

C. Burst- suppression pattern suggestive of hypoxic ischemic injury

D. None of the above

Question 10.

Which of the following drugs is undergoing research as a neuroprotective strategy in neonatal HIE to mitigate the effects of secondary energy failure of developing brain?

A. Topiramate

B. Melatonin

C. Magnesium sulphate

D. All of the above

Answer 1. (D)

Newborns have been shown to have seizures with exclusively focal onset, thus the initial division into focal and generalized is unnecessary. Nevertheless, in some rare conditions, seizures may rapidly engage bilaterally distributed networks such as spasms or myoclonic seizures, for example, in inborn errors of metabolism. Even in genetic early infantile developmental and epileptic encephalopathies, tonic seizures are initially focal or asymmetric in the neonatal period and subsequently may become generalized in infancy.

Descriptors are determined by the predominant clinical feature and divided into motor, non-motor, sequential and unclassified. Pragmatically, it appears best to classify seizures according to the predominant clinical manifestation, as this is more likely to have clinical implications for etiology than determination of the seizure-onset zone. This may or may not be the first clinical manifestation. For example, a neonate may present with focal tonic posturing, and in addition have some ocular myoclonus—this can still be classified as a tonic seizure.

Studies have shown that the most of clinical-only events are not of epileptic origin and that in epileptic seizures an electrographic ictal pattern will become apparent during more prolonged EEG monitoring. In neonates, video-EEG recording is the gold standard for diagnosis.

When cEEG / aEEG is not available, observation by an experienced personnel in case of focal clonic/ focal tonic seizures can be considered as seizures with "**probable certainty**" as per algorithm by Brighton collaboration group. Clinical observed events such as automatisms, autonomic seizures, and seizures with behavioral arrest can be deemed "possible seizure," only.

Answer 2. (C)

This is the classical presentation of metabolic encephalopathy, likely classic form of non-ketotic hyperglycinaemia in this case scenario. The classic form of nonketotic hyperglycinaemia presents in the newborn period with hypotonia, feeding difficulties, encephalopathy, seizures, and apneas. The presence of hiccups is an important clinical clue. Characteristically EEG recordings show a burst suppression pattern which later evolves to hypsarrhythmia and multifocal epilepsy. On magnetic resonance imaging (MRI), with a classic newborn presentation, infants show increased signal on diffusion weighted images in the areas that are myelinated at birth, most often in the posterior limb of the internal capsule (figure 1A in the question 2) and dorsal pons (figure 1B in the question 2). Hypoplasia or agenesis of the corpus callosum has also been reported. Magnetic resonance spectroscopy demonstrates a glycine peak at 3.5 ppm. CSF and plasma glycine measurements are essential for the diagnosis of NKH with a ratio CSF and plasma glycine characteristically being >0.08.

Answer 3. (B)

Amplitude-integrated electroencephalography (aEEG) is a widely used bedside tool to identify potential candidates for therapeutic hypothermia after a perinatal asphyxia insult, for identifying seizures and for guiding limitation of life-sustaining therapy in severely encephalopathic infants. The aEEG acquired within the first 6 h of age was considered one of the best predictors of neurological outcome at 18 months in non-cooled neonatal encephalopathy (NE) infants (Hellstrom Westas L et al, 1995). However, since the widespread use of cooling therapy, the predictive value of early aEEG has changed and NE infants have been shown to have a normal neurological outcome if the aEEG background voltage activity recovers by 48 h (Thoresen M et al 2010, Hallberg B et al 2010, Azzopardi D, TOBY Study Group, et al 2014).

The positive predictive value of a persistently abnormal aEEG increased from 66% at 24h, to 85% at 48h and 89% at 72h, for predicting adverse outcomes. A persistently abnormal aEEG between 6 and 24 h of age has been associated with adverse outcomes in the pre-cooling era. Currently therapeutic hypothermia has shifted this time window and adverse outcome were seen only if a severely abnormal aEEG was persistent for at least 48 h. This shift in the prognostic accuracy could be explained, at least partly by the neuroprotective effects of therapeutic hypothermia (M Chandrasekaran et al, 2017).

Answer 4. (D)

Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association, 2019

- Magnetic resonance imaging (MRI) should be performed to diagnose the stroke. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) also should be performed, especially when venous thrombosis is

suspected.

- Thrombophilia evaluation in the neonate has limited clinical utility because levels of protein C, protein S, antithrombin, and factor XI are normally decreased to 30% of adults levels, and these levels only approach adult levels at various time points during childhood. Thrombophilia testing for the mentioned proteins in the neonatal period may be misleading and requires repeat testing for a confirmatory diagnosis. A recent prospective case-control study on neonates with AIS has suggested that routine thrombophilia testing is not indicated.
- **Antiplatelet therapy such as aspirin and anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is rarely indicated** because of the low risk of recurrent stroke after ne- onatal AIS; however, it must be considered in those exceptional neonates with high risk of recurrent AIS resulting from documented thrombophilia or complex congenital heart disease (not including patent foramen ovale [PFO]).

Answer 5. (D)

MRI Brain (SWI) showed extensive cerebral edema and fan shaped shaped hemorrhages in the deep white matter of bilateral frontal and parietal lobes. The radiating fan shaped haemorrhages are unique to deep medullary vein thrombosis with secondary haemorrhagic infarction. The common causes of neonatal ICH are sepsis, bleeding diathesis, trauma, vascular malformations, congenital thrombophilias, genetic causes (COL4A1, COL4A2), etc.

Answer 6. (C)

TOBY Children study: The study evaluated the neurocognitive function of cooled vs. control newborns at 6 to 7 years of age **(middle childhood).** The primary outcome of this analysis was the frequency of survival with an IQ score of 85 or higher. A total of 75 of 145 children (52%) in the hypothermia group versus 52 of 132 (39%) in the control group survived with an IQ score of 85 or more (relative risk, 1.31; P=0.04). More children in the hypothermia group than in the control group survived without neurologic abnormalities (65 of 145 [45%] vs. 37 of 132 [28%]; relative risk, 1.60; 95% confidence interval, 1.15 to 2.22). Among survivors, children in the hypothermia group, as compared with those in the control group, had significant reductions in the risk of cerebral palsy (21% vs. 36%, P=0.03) and the risk of moderate or severe disability (22% vs. 37%, P=0.03); they also had significantly better motor-function scores.

Answer 7. (C)

A possibility of transient neonatal myasthenia can be considered based on symptomatology and mother's clinical background. The symptoms manifest usually within a few hours of birth (upto third day) and generally last for 2 to 6 weeks. Feeding difficulties (poor suck/swallow) and generalized hypotonia are the most common clinical findings. Other manifestations include generalized weakness, weak cry, facial diparesis with an expressionless face and mild respiratory distress. Ptosis and opthalmoparesis are less common findings.

Serum AChR & anti-MuSK antibodies are elevated in both symptomatic newborn as well as the mother. Asymptomatic newborns will also have elevated antibody levels.

A positive response to anticholinesterase medications leading to transient improvement of feeding difficulties & respiratory functions aids in arriving at a final diagnosis. Neostigmine methylsulphate is the most commonly used drug for this diagnostic challenge.

Repetitive nerve stimulation test is rarely needed for diagnosis except in false negative pharmacologic test in newborns with prematurity/ hypoxic ischemic encephalopathy.

Answer 8. (B)

Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures (Ronit M. Pressler et al, 2023)

- Phenobarbital should be the first- line ASM (evidence-based recommendation) regardless of etiology (expert agreement), unless channelopathy is likely the cause for seizures (e.g., due to family history), in which case phenytoin or carbamazepine should be used.
- Among neonates with seizures not responding to first-line ASM, phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line ASM (expert agreement). In neonates with cardiac disorders, levetiracetam may be the preferred second-line ASM (expert agreement).
- Following cessation of acute provoked seizures without evidence for neonatal-onset epilepsy, ASMs **should be discontinued before discharge home, regardless of magnetic resonance imaging or electroencephalographic findings (expert agreement).**
- Therapeutic hypothermia may reduce seizure burden in neonates with hypoxic–ischemic encephalopathy (evidence-based recommendation).
- Treating neonatal seizures (including electrographic-only seizures) to achieve a lower seizure burden may

be associated with improved outcome (expert agreement).

- A trial of pyridoxine may be attempted in neonates presenting with clinical features of vitamin B6-dependent epilepsy and seizures unresponsive to second-line ASM (expert agreement).

Answer 9. (B)

Physiological discontinuous record i.e. trace alternant (TA) can be seen in the quiet sleep stage till 46 weeks of post menstrual age.

Beyond 37 weeks, an interburst interval of maximum 6 secs during TA in quiet sleep is normal. In the EEG epoch as depicted, an IBI of 9 secs is seen during quiet sleep suggesting dysmaturity with respect to a term neonate. Burst suppression consists of invariant, abnormally composed EEG bursts separated by prolonged and abnormally low voltage IBIs periods, strictly defined as IBI voltages < 5 uV. In all cases, the EEG should be invariant, with no spontaneous discontinuity changes because of internally mediated lability and no EEG change of reactivity because of external noxious stimulation of the infant. Burst suppression has no normal features or gestation specific graphoelements within the bursts. The above depicted EEG epoch is not suggestive of burst suppression as IBI interval amplitude is more than 5uV with presence of normal features within the bursts.

Answer 10. : (D)

Melatonin plays an important role in normal glial development and has anti-apoptotic, anti-inflammatory, and anti-oxidant effects. Magnesium sulphate is an NMDA receptor antagonist believed to reduce excitotoxic damage after a hypoxic ischemic insult. Topiramate blocks the voltage-dependent sodium and calcium channels and also inhibits the excitatory glutamate pathway while enhancing the inhibitory effects of gamma-aminobutyric acid (GABA). All these effects would work favourably in the pathophysiology of HIE.

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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