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DR. MAMTA JAJOO

President NNF Delhi

Dear NNF Delhi Members

It's a feeling of pride that we are coming with the 13th issue of NeoClips. On 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 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 add 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 ensure 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. Mamta Jajoo

President, NNF Delhi

From Secretary's Pen

DR NAVEEN PARKASH GUPTA

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 for bringing out the 13th edition.

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 neonatal galactosemia, situs inversus totalis and neonate with CHARGE association.

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 Naveen Parkash Gupta
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 (13th issue) and previous issues.

We have covered some interesting topics in the present issue.

The case report covers an interesting case of neonatal acute liver failure as a result of galactosemia.

Point-of-care sonography has evolved in a big way in neonatology. It helps neonatologists to make decisions in the care of sick neonates. Dr. Anup Thakur and Dr. Anurag have written a review article on lung ultrasound (LUS) highlighting the basics of LUS and various patterns seen in lung diseases.

An interesting case of the CHARGE association has been covered in the picture of the month.

The image section describes an interesting X-ray of situs inversus totalis.
OSCE is covering a few interesting questions on fluid and electrolyte balance.

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

Neonatal Acute Liver Failure: A Case Report

Dr Madhuri Jhanwar, Dr Anup Thakur, Dr Pankaj Garg and Dr Neelam KLer
Department of Neonatology,
Sir Ganga Ram Hospital, New Delhi

We report a case of preterm infant of 33 weeks gestation, born to a primigravida mother via caesarean section with history of preterm rupture of membranes. History of 3rd degree consanguinity was present. Antenatal period was otherwise uneventful. The infant cried immediately after birth, weighed 2450g and was accepting breastfeed well. On day 3 of life, he developed jaundice, received phototherapy and was discharged on day 7. Subsequently, the infant was admitted again, in the same hospital on day 9 of life with jaundice. Direct bilirubin was found to be raised. He was given phototherapy and discharged. On day 17 of life, the infant was re-admitted with jaundice. He deteriorated and developed abdominal distension, lethargy and feed intolerance. He was made nil per oral (NPO) and antibiotics were started after taking sepsis workup, which was negative. Laboratory investigations revealed anemia (Hb-7.7 g/dl), conjugate hyperbilirubinemia (4.2 mg/dl), hypoalbuminemia (1.8g/dl), raised liver enzymes (SGOT 237 IU/L, SGPT 102 IU/L) and deranged coagulation profile (INR 3). He was given injection vitamin K, antibiotics, packed red cell and fresh frozen plasma transfusions. He was referred to our institute on day 30 of life.

On admission, the infant was lethargic and deeply icteric. He had tachypnoea with mild subcostal retractions, gross ascites and hepatosplenomegaly. Neurological examination was normal. No bleeding manifestations or rash was noted. Blood glucose level was 23 mg/dl. He was supported on high flow nasal cannula, kept NPO and hypoglycemia was managed with 2 ml/kg dextrose 10% bolus followed by institution of parenteral nutrition with appropriate glucose infusion rate. Injection vitamin K was given and empirical antibiotics were started after sending sepsis workup including blood, urine and CSF culture. Blood investigations revealed leucopenia (TLC 3120/mm^3), thrombocytopenia (platelet 89000/mm^3), direct bilirubin 3.38 mg/dl, INR 2.3, albumin 2.3 g/dl, SGOT/SGPT was 91 and 67 IU/L respectively. Blood, urine and CSF culture were sterile. Serum ammonia was 103 umol/L. Urine reducing substances, urine glucose and urine CMV was negative.

DIFFERENTIAL DIAGNOSIS

Based on the clinical presentation and laboratory features, following differentials were considered:

No.	Suspected disease	Points in favour	Points against
1	HSV hepatitis	Early onset ALF, lethargy, poor feeding	No maternal history, no skin vesicles, AST and ALT only mildly raised
2	Galactosemia	Consanguinity, deterioration after feeds, lethargy, sick, hypoglycemia, ALF, Hepatosplenomegaly	Urine glucose negative, no documented hypoglycemia in previous hospital, no vomiting
3	Tyrosinemia	Lethargic, sick, hypoglycemia, early onset ALF	No history of renal tubular acidosis
4	Sepsis	Prematurity, PPROM, prolonged hospital stay	Blood culture sterile, no improvement after antibiotics
5	Biliary atresia	Neonatal cholestasis	No h/o pale stools, early onset ALF, sick baby
6	Gestational alloimmune liver disease	Early presentation with ALF, minimally raised AST/ALT	No h/o fetal losses, IUGR, oligohydramnios

ALF – Acute liver failure, **PPROM** – Preterm pre-labor rupture of membranes

On further evaluation by ophthalmologist, bilateral oil drop cataract was found. Galactosemia was suspected and other diagnostic investigations were withheld. Genetic analysis for GALT gene mutation was sent, while enzyme level assessment was postponed as the infant had received blood transfusion. Lactose free formula was started. Vitamin A, D, E and K supplementation were added. Tablet spironolactone (3 mg/kg/day) and IV albumin (1 g/kg/day) were given for management of ascites. He improved subsequently, ascites and respiratory distress decreased. Monitoring of liver function showed improvement in serum albumin (3.1 gm/dl) and repeat INR was 2. GALT gene mutation analysis result was homozygous for Duarte variant of Galactosemia. The infant was discharged on day 45 of life and lactose free formula was continued. On follow up after 15 days, he was active, feeding well, gained weight. Repeat eye examination showed reduction in the size of cataract.

At 3 months follow up, the infant is thriving well with a weight of 4200 g, length 55 cm and head circumference 38 cm. He is developmentally normal, social smile is present and he can track objects.

DISCUSSION

Galactosemia is an autosomal recessive disorder of galactose metabolism caused by a deficiency of the galactose-1-phosphate uridyl transferase (GALT) enzyme. There are 3 enzymes involved in this process which are galactokinase (GALK), GALT, and uridine diphosphate galactose 4-epimerase (GALE). Classic galactosemia or type I disease, refers to the disease caused by complete absence of GALT. Partial GALT activity is present in several variants, most common of which is the Duarte variant that was identified in our patient. The severity of symptoms in the Duarte variant depends on the quantity of GALT activity. Deficiency of either GALK, also called type II disease, or GALE, referred to as type III disease, is described as clinical variant galactosemia.[1]

Most affected cases with galactosemia present within one week of life with jaundice, vomiting and hepatomegaly. About a quarter of infants will have feeding problems and failure to gain weight. Hepatic damage occurs from toxic galactose metabolites, especially galactitol and this may cause only mild elevations of liver enzymes or lead to more severe hepatic insufficiency with coagulopathy and occasionally ascites. Jaundice associated with galactosemia is typically related to an indirect hyperbilirubinemia in the first week but typically progresses to cholestasis within another week. In our patient, conjugated hyperbilirubinemia was present by day 9 of life which was missed. Baby presented to us in acute liver failure in decompensated stage with ascites, hepato-splenomegaly and coagulopathy.

Our patient was started on lactose free formula and showed remarkable improvement over two weeks. There was resolution of ascites, improvement in liver function tests and coagulation profile. Baby started to gain weight and repeat eye examination at discharge showed reduction in size of oil drop cataract. At discharge, the infant was continued on lactose free formula. Patients with galactosemia should be treated with lifelong restriction of galactose in diet.

Our case is under regular follow up. Repeat Galactose-1-phosphate levels are normal. Growth and developmental parameters are satisfactory. Eye examination shows resolution of cataract. Timely follow up of these patients should be ensured. Galactose-1-phosphate levels should be repeated every 3 months and as and when needed, Growth parameters and developmental milestones should be documented at every visit. Ophthalmologic evaluation should be done at 1 year, 5 years and during adolescence. Females should be evaluated for premature ovarian insufficiency by measuring estradiol and follicle stimulating hormone (FSH) levels at 12 years of age. Calcium, phosphorous and vitamin D levels should be checked annually or as clinically indicated.[2]

Galactosemic is a life-threatening disorder. Newborn screening plays an important role in early identification and prevention of associated complications. A high index of suspicion should be kept in infants with prolonged jaundice or conjugate hyperbilirubinemia. It can be diagnosed by enzyme assay and treated by lactose free diet.

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Lung Ultrasound in Neonates–Part 1

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2. Dr Anurag Fursule, DNB (Pediatrics), DNB (Neonatology) #

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Introduction

Lung ultrasound (USG) is relatively a new tool for the neonatal intensivist. Given its simplicity, real-time and point of care nature, high sensitivity/specificity and superior or at par results with the so-called standard diagnostic tools such as chest X-ray and computed tomography scan, its use has been rapidly increasing in neonatal intensive care. In this article (Part 1), we describe the basic concepts of lung USG and four classical patterns i.e. interstitial syndrome, consolidation, pneumothorax and pleural effusion. Advanced lung profiles, conditions specific to neonates and related evidence will be discussed in the next section (Part 2).

Seven Basic Principles of Lung Ultrasound

Lung USG in critically ill (LUCI) is based on seven principles. First, lung USG is based on simplicity. It requires a simple machine. Filters of modern machines should be avoided as they suppress artefacts.While the classical signs have been described by using a 5MHZ micro-convex probe, a linear high frequency probe 8-13 MHz frequency can be used in neonates. The second principle states that lung USG images are generated from mixture of air and fluid in the thorax, which gives rise to relevant artefacts. The ratio of an air-fluid mixture (ranging from pure air to pure fluid) allows for unique findings in different pathologies. The third principle identifies six standardized points of analysis of lung by USG, such as two anterior and one semi-posterior point on each side of chest wall called BLUE points (figure 1).

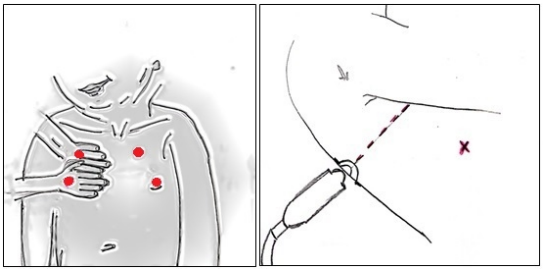

Fig.1. : Blue Points

In neonates, authors have modified these points of analysis into zones/areas. Three chest areas can be investigated -anterior, lateral and posterior. Anterior area is the area between sternum and anterior axillary line, lateral area between anterior and posterior axillary line and posterior area between posterior axillary line and the spine as shown in figure 2 and 3. Some authors have divided anterior area into upper and lower. USG probe can be kept at midclavicular line for anterior area, anterior axillary line for lateral area and at posterolateral alveolar and pleural syndrome (PLAPS) point[2] (as posterior as possible to the posterior axillary line) for posterior area.

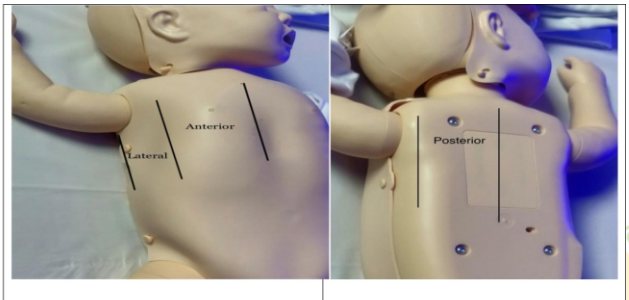

Figure 2 (Anterior and lateral lung area) | Figure 3 (Posterior lung area)

The fourth principle states that all signs of lung USG arise from pleural line. We use only a longitudinal view in LUCI, to generate a standardised sign called "Bat Sign", a signature of a normal lung (figure 4). The bony ribs do not allow the USG beam to pass through and

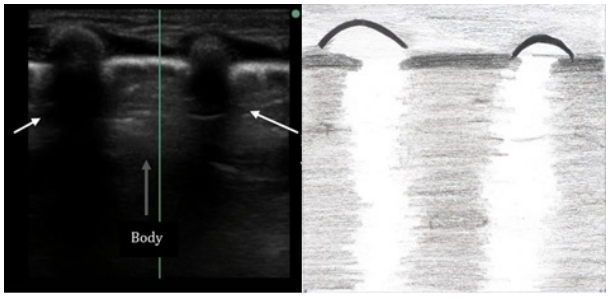

Fig.4: Bat sign

are seen as arciform hyperechoic structures that generate posterior acoustic shadows. Below the ribs, lies the pleural line that appears as a hyperechoic and almost horizontal linear structure. The fifth principle states that USG of lung is based on artefacts. Artefacts are undesired structures that are traditionally avoided and discarded in USG. The most basic normal artefact is called the A-line. A line is a horizontal line parallel to pleural line (figure 5).

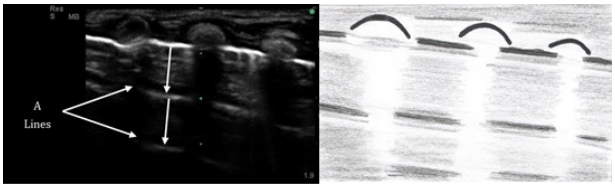

Fig.5: A lines

A-lines are produced due to reverberation artefact of the pleura and are demonstration of air. A-lines indicate air, either quasi-pure (normal lung surface) or pure (pneumothorax). The sixth principle emphasizes that dynamic permanent motion of lung generates the cardinal sign of lung called lung sliding. It is a kind of twinkling/sparkling/ glittering/ shimmering etc that begins exactly at the pleural line and spreads homogeneously below it. The space above the pleural line is called Keye's space and the one below it is called Merlin's space. On application of M mode, a standardized pattern called the seashore sign is seen due to sandy appearance below the pleural line and wavy appearance of the pleural line (figure 6 Sea shore sign, Merlin's space and Keye's space). The seventh principle states that all acute disorders that require immediate care abutt the pleura, are extensive and therefore can be readily accessed by USG at the standardized points.i

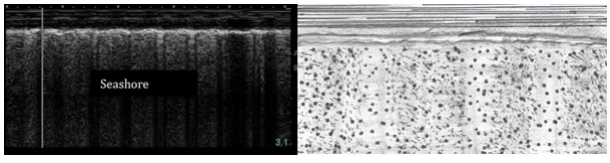

Fig.6: Seasshore sign

The terminologies used in lung USG are interesting. Cardinal signatures of normal lung such as pleural line, A-line, bat sign, lung sliding and seashore sign have been described above. We should refrain from commenting on an image or video of lung USG unless we see the shadow of the ribs and pleural line. The artefacts found in lung USG have been named from A to Z. In this article, we would introduce the basic artefacts only and the most important of them are B lines (figure 7). These are hydro-aeric artefacts generated due to major acoustic gradients and denote mingling of air and fluid. B lines almost always have seven characteristics. B line is a comet-tail artefact, arises from pleural line, moves with lung sliding, is well defined (laser-like), long spreading out without fading to the edge of the screen, obliterates the A-lines and is almost always hyperechoic. If a beginner applies all these criteria before labelling any artefact as B line, he/she would more often be correct and avoid mislabelling certain other artefacts as B line. B line indicates diseased interlobular septa due to fluid (transudate or exudate). However, an anterior B line may be normally present at the lower blue point and is an expression of minor fissure. A few physiological B lines may be present in the last two intercostal spaces above the liver and spleen. Lastly, a few B lines may be present posteriorly in a patient lying supine.

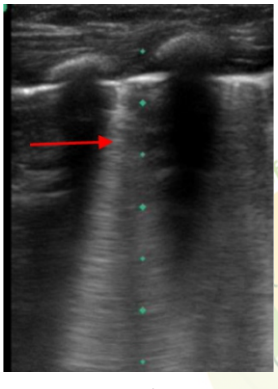

Fig.7: B line

Lung Pathology Patterns

Most lung pathologies across all age groups including

neonates can be reliably diagnosed by using principles of LUCI and its ten signs as outlined in Table 1. Classically, in adults four patterns of lung USG has been described (Table 2). Other disorders in neonates are extension of these patterns.

1. Interstitial Syndrome

Three or more B-lines simultaneously visible between two ribs in a longitudinal scan are called lung rockets. They can be septal rockets or ground glass rockets (number of B lines is almost double in ground glass variant compared to septal variant). The most severe variant is called birolleau variant, in which the B-lines are so closely packed that there is hardly any anechoic space between the two, resulting in homogeneous hyperechoic Merlin's space. Lung rockets in a dyspnoeic patient over the anterior lung fields indicate interstitial syndrome. This can be found in acute respiratory distress syndrome (eg Hyaline Membrane Disease), hemodynamic pulmonary oedema or permeability induced pulmonary oedema (secondary to inflammation eg Pneumonia).

2. Pneumothorax

For detection of a suspected pneumothorax, a sequential analysis is recommended. At first, one should detect abolished lung sliding. This translates into the standardized Stratosphere sign (figure 8) in the M mode, which is a pattern of exclusive horizontal lines in contrast to seashore sign of normal lung. Some authors call this a bar-code sign, which may not be appropriate as modern barcodes can be vertical, horizontal, oblique or crisscross. Stratospheric phenomenon are created by flying of fighter jets. The term was coined to denote a sense of emergency. Once this is accomplished, the next step is to seek for the A-line sign and a negative search for B lines in the field. We emphasize here that the presence of even a single B-line will rule out pneumothorax in the field of interrogation. The diagnosis in the next step is established if the next sign called lung point which is pathognomonic for a pneumothorax is demonstrated (figure 9). This is the junction between pneumothorax and the lung, when the sudden transition from abolished lung sliding to the presence of lung sliding appears. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of lung USG in diagnosing pneumothorax were reported to be 100%.

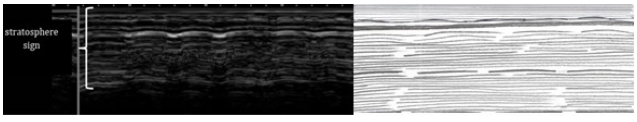

Fig.8: Stratosphere sign

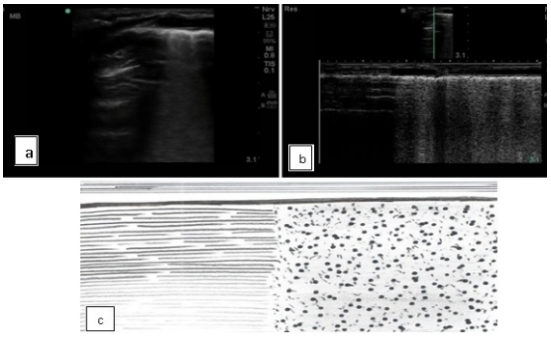

Fig.9: Lung point

3. Pleural Effusion

Pleural effusion, even if minute can be detected by interrogating the PLAPS point (posterolateral alveolar and/or pleural syndrome point i.e. intersection between longitudinal posterior axillary line and posterior transverse continuation of lower blue point). Two unique signs used to diagnose pleural effusion are the Quad sign and the Sinusoid sign. A quad is essentially a quadrangular area due to accumulation of fluid, limited by a pleural line and ribs above and a regular smooth deep border of visceral pleura below that represents the lung line (figure 10). The sinusoid sign is formed due to the movement of lung line (figure 11 grey arrow) towards pleural line (white arrow) with respiration. It can help to detect even small effusions but may be absent in septate or viscous effusions. The sensitivity and specificity of lung USG to detect pleural effusion with CT as the gold standard in adults is 93% and 97% i respectively, however studies in neonates are lacking.

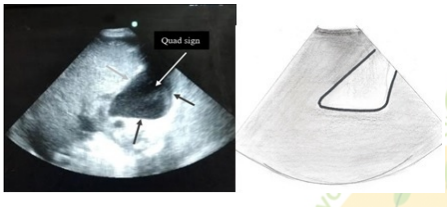

Fig.10: Quad Sign

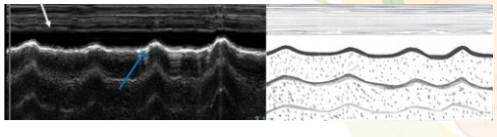

Fig.11: Sinusoid Sign

4. Consolidation

Lung consolidation implies that the alveoli are filled with fluid. This fluid may be a transudate, exudate, pus

or blood. Lung consolidation may be caused by various conditions. These include but are not limited to pneumonia, hemodynamic pulmonary oedema, hyaline membrane disease, meconium aspiration syndrome, broncho-pulmonary dysplasia or any lung mass. In most cases (>98%), consolidation is sub-pleural and can be easily diagnosed with lung USG. Although lung consolidation can be randomly situated anywhere, it should be sought for at PLAPS point, where it is likely to be found 90% of time. We use a simple approach to diagnose consolidation with two signs-shred (or fractal sign) and tissue-like sign. A Shred sign is a structural image that arises from pleural line and has a tissue-like pattern. It has an irregular, shredded border mimicking an impression as if crumbs of bread are lying below an irregular pleural line (figure 12). In translobar consolidation, a large number of alveoli are involved. On USG, the beam reflects through these diseased alveoli and multiple reflections on interlobular septa make the image look like a tissue. It is therefore called the tissue-like sign. The alveolar-interstitial pattern is similar to liver. Another sign described by Linchenstein et al is presence of punctiform or linear hyperechoic artefacts that represents air within the consolidation. These artefacts found in consolidation are centrifugal, move with inspiration and are called dynamic air bronchogram. They are indicative of pneumonia and help to distinguish consolidation from atelectasis. The authors reported specificity, sensitivity, PPV and NPV values of this sign to diagnose consolidation to be of 94%, 61%, 97% and 43% respectively. Other findings in consolidation may be abnormalities of pleural line such as irregularity, thickening or its absence and presence of B lines that do not move.

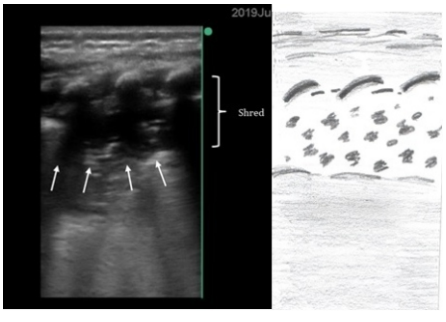

Fig.12: Shred Sign

Key points

- Lung USG is a relatively new, real-time, non-invasive and safe tool to evaluate neonatal lung disorders.
- The basic principles of lung USG must be understood. Lung USG is based on study of artefacts.
- Neonatologists should learn to interpret the basic signs of lung USG and complement it with other radiological investigations and clinical findings.
- All intensivist should understand the four basic patterns in lung USG i.e. interstitial syndrome, consolidation, pneumothorax and pleural effusion.

Acknowledgement

We acknowledge Dr Daniel Lichtenstein, who trained the first author in critical ultrasound in Hospital Ambrosie-Pare, Paris and certified him as a CEURFer (Cercle des echographistes d'urgence et de reanimation francophones).We acknowledge Dr Gunjan Sachdeva for drawing the schematic figures.

Signatures and terminologies in lung ultrasound

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Legends – Figure/images

Figure number	Caption	Description
Figure 1	*Blue Points*	(a) The upper hand is paced in such a way that the little finger touches the lower border of clavicle with finger tips being in the midline. The lower hand is placed below, with the thumb excluded as shown in the figure.The upper BLUE-point corresponds approximately to the mid-point between the base of middle and ring fingers. The lower BLUE-point corresponds to middle of the palm of the lower hand. (b) PLAPS-point is indicated by the probe. It is a point corresponding to intersection of horizontal continuation with the lower BLUE-point (dotted red line), as posterior as possible to the posterior axillary line with the patient remaining supine. (Modified from *Lichtenstein DA, Mezière GA. The BLUE points: Three standardized points used in the BLUE protocol for ultrasound assessment of the lung in acute respiratory failure. Crit Ultrasound J. 2011;3:109–10)*
Figure 2 and 3	*Areas of Lung*	Areas of lung USG scan suggested in neonates. Anterior area is the area between sternum and anterior axillary line, lateral area between anterior and posterior axillary line and posterior area between posterior axillary line and the spine
Figure 4	*Bat sign*	Lung USG demonstrating the Bat sign with its components. The white arrows indicate the shadow of the upper and lower ribs. The grey arrows indicate the body of the bat i.e., pleural reflection.
Figure 5	*A-lines*	Lung USG demonstrating A-lines. A-lines are reflections of pleural lines. They are equidistant. A-lines are the expression of air.
Figure 6	*Seashore sign*	A standardized pattern is seen called the *seashore sign,* due to the sandy appearance below the pleural line and the wavy appearance of the pleural line in the M mode.
Figure 7	*B line*	B line- a comet-tail artefact, arises from pleural line, moves with lung sliding, is well defined (laser-like), long spreading out without fading to the edge of the screen, obliterates the A-lines and is almost always hyperechoic
Figure 8	*Stratosphere sign*	*Stratosphere sign* in M mode, a pattern of exclusive horizontal lines is suggestive of abolished lung sliding. One should suspect pneumothorax and seek for lung point.
Figure 9	*Lung Point*	(a) Lung USG image on left shows interface between a normal lung and lung with pneumothorax. (b) When M mode is used at such interface, the stratosphere sign and seashore sign can be seen in one image. This is a lung point which is junction between pneumothorax and the lung when the sudden transition from abolished lung sliding to the presence of lung sliding appears.
Figure 10	*Quad sign*	This real-time lung USG image shows a quad sign having borders: lung line denoted by a grey arrow and pleural line denoted by black arrows.
Figure 11	*Sinusoid sign*	Wavy appearance of the pleural line due to fluid (blue arrow).
Figure 12	*Shred sign*	Shadow is acoustically anechoic (mimicking a pleural effusion according to the traditional definitions) but the deep limit (arrows) is shredded.

A Neonate with Charge Association

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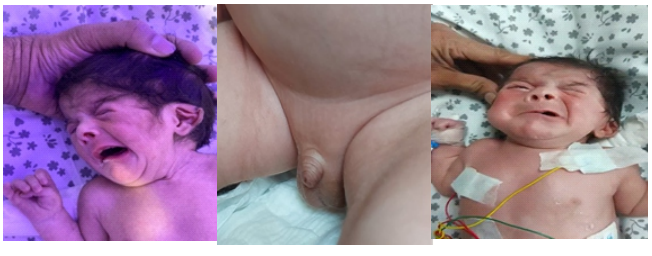
Case:

Late preterm, outborn male baby, born at 36 weeks appropriate for gestational age, with a birth weight of 2650 grams, born through emergency caesarean section in view of fetal distress with prolonged premature rupture of membranes. The baby had poor respiratory efforts at birth for which the baby was intubated. In the delivery room, the paediatrician was unable to pass the nasogastric tube and a diagnosis of bilateral choanal atresia was made. The baby was shifted to our hospital for further management. Antenatally, the mother underwent amniocentesis at 18 weeks in view of hypoplastic nasal bone and it was normal for trisomy.

The baby was admitted to our hospital on day 2 of life. Features of dysmorphism were present in the form of bilaterally deformed pinnae, deviation of the face towards the left side with absent nasolabial folds on the right side suggestive of right-sided facial nerve palsy, underdeveloped scrotum with bilateral descended testes and micropenis with a stretched penile length of 1.9 cm (Figure 1). On systemic examination, the baby had minimal pressure requirements on a mechanical ventilator, and a loud pan-systolic murmur was heard on auscultation.

Suspicion: CHARGE association with right LMN facial nerve palsy.

Course: Baby was continued on a mechanical ventilator with minimal pressure requirements. Non contrast CT paranasal sinuses were suggestive of bilateral complete posterior choanal atresia for which trans nasal choanal atresia repair was done on day 4 of life and the nasopharyngeal airway was placed. The baby was extubated to room air on day 8 of life and was on full paladay feeds by day 9 of life. Further, the 2D echo was suggestive of a common AV canal defect, and USG KUB was normal. In view of micropenis with a poorly



developed scrotum, the hormonal assay was sent which showed low testosterone levels and elevated FSH and LH levels suggestive of hypogonadism. Eye examination was normal.

In whole exome sequencing a heterozygous nonsense variation in exon 8 of the **CHD7** gene **(chr8: g.61729019C>T; Depth: 38x)** that results in a stop codon and premature truncation of the protein at codon 858 **(p.Arg858Ter; ENST00000423902.2)** was detected. The observed variation has previously been reported in patients affected with CHARGE syndrome and it lies in the Chromo (CHRromatin Organisation MOdifier) domain of the CHD7 protein.

Condition:

Most cases of CHARGE syndrome arise from de novo mutations. Rarely it is transmitted as autosomal dominant. It arises during early fetal development and affects multiple organ systems. The features of

CHARGE syndrome were first described independently by Hall and Hittner, and hence, it was initially called Hall-Hittner syndrome. Mutations in the CHD7 gene are the most common cause of CHARGE syndrome. The CHD7 gene controls the protein that regulates developmental pathways through chromatin organisation. Mutations in the CHD7 gene lead to abnormal, nonfunctional, short CHD7 protein, which interrupts the regulation of gene expression and disordered neural crest development. If these changes occur during the embryonic period, it leads to CHARGE syndrome. The incidence is 1 in 10,000 births and it does not have sex predilection.

Diagnosis: The major criteria are the 4 C's: coloboma, cranial nerve abnormalities, choanal atresia, and typical CHARGE ear. The minor criteria are heart defects, cleft lip or palate, genital abnormalities, hypotonia, kidney abnormalities, oesophageal atresia, poor growth, typical CHARGE face, and typical CHARGE hand.

Outline of baseline investigations:

Clinical	Combination of major and minor characteristics having three primary features or 4 major and 3 minor criteria.
Laboratory	Complete blood count (CBC), serum electrolytes, renal function test, luteinising hormone-releasing hormone, Human chorionic gonadotropin (hCG), blood urea nitrogen (BUN), creatinine, growth hormone levels, and immunologic studies
Genetic	Prenatal screening for CHD7 variants can be done by amniocentesis or chorionic villus sampling at 10–12 and 18–20 weeks gestation.
Imaging	Abdominal ultrasound, barium swallow, echocardiography, chest x-ray, cranial ultrasound in neonates, and head computed tomography (CT) scan and magnetic resonance imaging (MRI).

Differential diagnosis: Digeorge syndrome, Joubert spectrum, Kabuki syndrome, Holoprosencephaly spectrum disorders, Renal coloboma syndrome.

Neonates with CHARGE syndrome have multiple life-threatening medical conditions like small for gestational age, unable to pass nasogastric tube due to choanal atresia, dysmorphic features, and respiratory distress. Feeding difficulties are a significant cause of morbidity in all age groups.

Management:

Management involves multidisciplinary care and approach involving various speciality teams. The most common neonatal emergencies in CHARGE syndrome include cyanosis due to congenital heart defects, or bilateral posterior choanal atresia. Therefore a systematic management plan involving a cardiologist is ensured.

In babies with complex airway malformations, severe gastroesophageal reflux and recurrent aspiration, tracheostomy may be required.

Babies with feeding difficulty may require jejunostomy or gastrostomy feeding tubes.

In facial palsy, corneal scarring can be prevented by using artificial tears.

Supportive management should be continued along with regular follow-up visit in order to recognise any further complications and to ensure early initiation of treatment.

Prognosis: Infants in the first year of life are at high risk, specifically those who have severe congenital disabilities, increased risk of infections resulting in frequent hospitalisation and poor outcomes and, thus, a high morbidity and mortality rate.

In late childhood and in adults, more common causes of death include infection, aspiration, and obstructive sleep apnea.

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Situs inversus totalis with Hirschsprung disease

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Case- A late preterm (34 weeks) appropriate for gestational age male baby born in outside hospital through emergency LSCS in view of fetal bradycardia. The baby cried immediately after birth but started having respiratory distress which was managed with CPAP. The baby was taken off CPAP on day 4 of life. There was a history of delayed passage of meconium. Baby passed first meconium on day 3 of life after stimulation. X-rays and ultrasound were done in outside hospital to rule out malrotation. They were normal. X-ray chest and abdomen was suggestive of situs inversus totalis. Echocardiography was normal.

The baby was referred to us on day 8 of life with complaints of intermittent abdominal distension, infrequent passage of stools and situs inversus totalis. In view of the infrequent passage of stools associated with abdominal distension, a gastrograffin enema was planned to rule out colonic aganglionosis. On examination, the apex beat was displaced to the right side and chest X-ray showed situs inversus totalis (Figure 1). Gatrograffin study showed dilatation of the distal colon with narrowing of the rectum (transition point) with a rectosigmoid ratio < 1 suggesting Hirschsprung disease (Figure 2). Rectal stimulation was done regularly. Baby started passing stools post that. Baby tolerated feeds and was discharged home with a plan to do a rectal biopsy on follow-up (Parents wanted to wait for some time). At home, baby needed rectal stimulation regularly with periods of intermittent abdominal distension. So rectal biopsy was done on day 21 of life. Immunohistochemistry staining of the distal rectum showed an absence of calretinin and a paucity of ganglion cells at the distal rectum. Whole exome sequencing was planned to send to rule out primary ciliary dyskinesia (Hasn't been done yet).

Child is 2 months old and is growing well. Milestones are normal for age.

Diagnosis- Hirschsprung disease in a case of situs inversus totalis

Review of literature - Situs inversus totalis (SIT) is a rare condition defined by the complete positional inversion of cardiac and abdominal viscera. The incidence is approximately 1 in 8,000 to 1 in 25,000 live births.(1) SIT is inherited in an autosomal recessive pattern and is associated with multiple gene mutations (DNAH11 most common ZIC 3, ACVR2B and Pitxz genes), commonly seen in primary ciliary dyskinesia.(2) Situs inversus is associated with multiple associations like cardiac defects in form of a single atrium, abnormal atrioventricular connection and transposition of great arteries, renal anomalies and gastrointestinal problems like Hirschsprung disease, and malrotation.(3) Relevant investigations should be done to rule out associated disorders in babies with SIT.

Outcome- Outcomes of these babies depends upon associated anomalies like PID (primary immunodeficiency), cardiac, GIT and renal anomalies. These babies and very prone to recurrent infections, bronchiectasis, failure to thrive and gut obstruction and may need repeated hospital visits due to these issues.

Management- These babies should be evaluated for genetic association and inheritance by whole exome sequencing so that parents should be counselled regarding recurrence in further pregnancy. Baby should receive pneumococcal and meningococcal vaccines apart from routine vaccination and should be nursed in healthy environment to prevent repeated infections.

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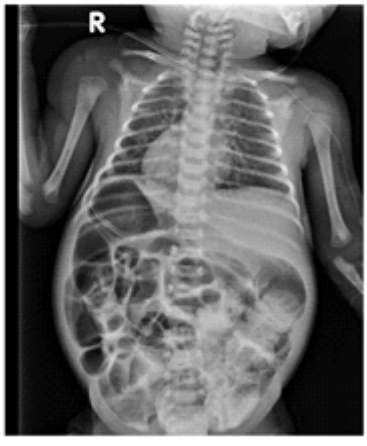

Fig.1.: Shows dextro-positioned heart with gastric bubble on right side and liver shadow on left-Situs inversus totalis.

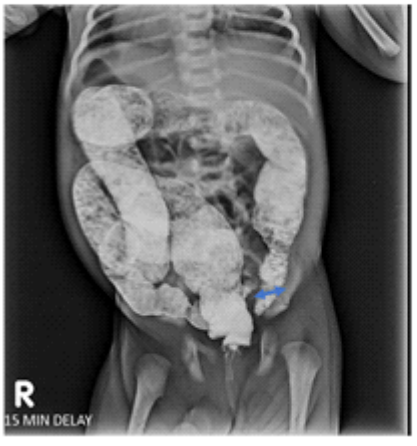

Fig.2.: Gastrograffin image (15min after dye) shows narrowing of rectum, arrow mark shows inverse rectosigmoid ratio (<1) suggestive of small distal segment Hirschsprung disease.

Journal Scan

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Early Human Milk Fortification in Infants Born Extremely Preterm: A Randomized Trial

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Research question

Does early supplementation of human milk with human milk fortifier improves fat free mass at 36 weeks post menstrual age?

Hypothesis

Population	Extremely low birth weight babies (≤ 28 weeks)
Intervention	Diet fortified with human milk based fortifier starting on feeding day 2
Control	Unfortified diet. This practice continued in both groups until the feeding day when a standard bovine-based fortifier was ordered.
Outcome	Fat-free mass (FFM) for age z score at 36 weeks of postmenstrual age (PMA)

Methods

Design: Masked, Randomized controlled trial. Caregivers were masked.

Settings: Single centre trial conducted at Birmingham Hospital, University of Alabama during August 2020 and October 2022.

Inclusion criteria

- Gestational age of 28 weeks or less

Exclusion criteria

- Major congenital anomalies
- Terminal illness in whom the decision to withhold life support has been made

Extreme preterm infants fed human milk were randomised to receive either a fortified human milk diet (intervention group) or a usual unfortified human milk diet (control group) within the first 96 hours after birth. Infants in the intervention group received unfortified maternal or donor milk on feeding day 1. On feeding day 2, a human milk-based fortifier was added. This was continued until the day when a standard bovine-based human milk fortifier was added. Infants in the control group received maternal or donor milk from feeding day 1 until the feeding day on which the standard bovine based human milk fortifier was added.

Feeds were administered as bolus feeds every three hours and they were initiated by using either maternal or donor human milk. 20 to 25 ml/kg/day feeds were started with daily increments of 20 to 25 ml/kg/day on feeding day 2 until full enteral nutrition was established(>120 ml/kg/day). Bovine-based fortifiers were added at approximately postnatal day 14 after

full enteral nutrition was established. If the maternal milk supply was insufficient, infants received donor milk until 32 or 33 weeks of PMA and later formula.

Outcome:

Primary- FFM for age z score at 36 weeks PMA or hospital discharge whichever occurred first using ADP(Air displacement plethysmography)

Secondary-

- Significant weight loss during the first 14 days after birth (Decline in weight for age z score from birth to 14 days >0.8)
- Weight gain velocity in grams per kilogram per day from birth to 36 weeks PMA calculated using the exponential method
- Post natal growth failure (weight < 10th centile at 36 weeks PMA)
- Moderate to severe malnutrition (decline in weight for age z score from birth to 36 weeks PMA >1.2)
- FFM in kilograms and percentage at 36 weeks PMA
- Fat mass in kilograms and percentage at 36 weeks PMA
- Anthropometric measures at 36 weeks PMA

Sample size /Statistical analysis- To detect a 0.5 difference in FFM for age z scores between the groups with SD 1, 0.05 level of significance and 80% power 126 patients were needed.

Accounting for a 20% loss to follow up at 36 weeks 150 patients, 75 in each group were required.

Fisher exact or chi-square was used for the categorical variable. T test was done for continuous variables. For analysis of the primary outcome, an unadjusted t-test comparison of the mean FFM for age z score between the control and intervention groups was performed.

Results:

Of eligible 230 neonates 150 were randomised and 105 were analysed for the primary outcome. The mean birth weight was 795 grams (SD 250) and the median gestational age was 26 weeks (IQR 24-27). More than 80% of infants achieved full enteral nutrition within the first two weeks after birth. FFM for age z scores did not differ between the groups. The decline in weight for age z score from birth to postnatal day 14 of life was higher in the control group (-0.8 vs – 1.1). Length gain velocities from birth to 36 weeks PMA were higher in the intervention group (0.9 vs. 0.8 cm/week). Declines in head circumference z scores were less in the intervention group.

The risk of postnatal growth failure and the risk of moderate to severe malnutrition at 36 weeks PMA were not significantly lower in the intervention group. The risk of SIP, NEC, death and the combined outcome of SIP, NEC and death was similar.

Reviewers comments:

Human milk fortification is recommended for all very low birth weight infants to fulfil their nutritional requirements. The ideal time point for initiating fortification i.e. early or late is controversial. Most of the current guidelines advocate the use of fortifiers at enteral milk intake of 40 to 60 ml per kg per day though the evidence supporting it is sparse. This randomised control trial evaluated the effects of early human milk fortification in extremely preterm infants and showed that initiating human milk fortifier as early as 20 to 25 ml per kg per day is feasible and possibly safe in this vulnerable population. Investigators also showed that early human milk fortification reduced post-natal weight loss on day 14 of life, improved length gain velocity at 36 weeks PMA and also had a lesser decline in head circumference z scores.

The study's biggest strength is it being conducted in the most vulnerable population with nearly 20% of neonates born at 23 weeks or less. They also showed that 75% of extremely pre-terms were able to reach enteral feeds of 120ml per kg per day in the first 12 days of life. They also utilised the Pea pod technology to estimate FFM a parameter rarely used in the feeding studies.

One of the limitations of the study is that the feeding strategy used in the control arm is quite conservative. The median age of reaching enteral feeds of 120 ml per kg per day was day eight of life but bovine milk fortifier was added only a week later that is on day 15 of life. Most of our current NICUs would have started fortification in such babies when they reach feeds of 60 to 100 ml/kg/day. Hence it is possible that starting bovine milk fortifiers in the control group might have resulted in less postnatal weight loss and better

anthropometric parameters. The required sample size to detect significant differences in FFM for age was 126 however the analysis for this outcome could be done in only 105 patients which is nearly 80% of the desired population.

The study should be continued further and the impact of early human milk fortification on neurodevelopmental outcome should be studied.

The trial concluded that human milk diets fortified soon after birth in infants who are extremely preterm do not increase FFM accretion at term equivalent age but may increase length gain velocity and reduce decline in head circumference z scores at 36 weeks.

Strengths

This is the largest RCT of early human milk fortification in extreme pre term infants . The trial was also masked hence avoiding differential noncompliance and reduced surveillance and ascertainment biases. The sample size had sufficient power to detect 0 .5 mean difference in Z scores ,a clinically significant growth outcome. The analysis was done as intention to treat which increases generalizability of the results.

Limitations

The power of the study was insufficient to identify the potential harms of early human milk fortification and study was also single centric.

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Question 1

A Preterm Neonate born at 28 weeks gestation weighs 900 grams. At 47 hours of life serum electrolytes were: Na 158 meq/l, K 4.9 meq/l, Cl 126 meq/l. What further course of action would you recommend to correct the electrolyte abnormality.

a. Give N/2 or N/3 fluid as we give for hypernatremia correction in term babies
b. Nurse baby in radiant warmer
c. Nurse baby in incubator with humidity 60%
d. Nurse baby in incubator with humidity 95%

Question 2

Match the Body fluid with its correct electrolyte concentration

Body Fluid	Electrolytes Na, K, Cl in mmol/l
a. Gastric	1. 120–140, 5–15, 80–120
b. Small Intestine	2. 45–135, 3–15, 20–115
c. Bile	3. 20–80, 5–20, 100–150
d. Ileostomy	4. 10–90, 10–80, 10–110
e. Diarrhoea	5. 100–140, 5–15, 90–130

Question 3

A term neonate is seen by pediatrician on 8th day of life. Baby is born with a birth weight of 3 kg, has been exclusively breast fed. There is history of decreased passage of urine in last few days. His current weight is 2.4 kg (20% weight loss from birth). His serum sodium is 170 meq/l. He is admitted in NICU for hypernatremic dehydration. You plan to give fluids. Which fluid (type and volume) will you chose and how?

Question 4

41 weeks 3.0 kg baby was born with MSL, developed severe distress and was intubated soon after birth. Chest x Ray and clinical findings have confirmed MAS with severe PPHN, shock and metabolic Acidosis. Serum potassium levels are 7.5 meq/L. Below is a list of Hyperkalemia measures and their mechanisms of action. Match the correct ones.

Medication	Mechanism of Action
a. Calcium gluconate	1. By capturing H +, increases pH without increasing CO 2 and thus shifts potassium intracellularly; no effect on total body potassium
b. Sodium bicarbonate	2. Increases renal excretion of potassium
c. Tromethamine (THAM)	3. Removes potassium from gut in exchange for sodium
d. Insulin plus dextrose	4. Shifts potassium intracellularly; no effect on total body potassium
e. Sodium polystyrene	5. By stimulating the Na +,K +-ATPase enzyme, it shifts potassium intracellularly; no effect on total body potassium
f. Furosemide	6. Protects the myocardium from toxic effects of potassium; no effect on total body potassium

Question 5

A. 3.2 kg Neonate born to a diabetic mother at term gestation, is found to be hypoglycaemic at 6 hours of

life with pre-feed RBS 35 mg/dL on routine screening.

a. What is the next plan of action?

The baby continues to be hypoglycemic. Fluids were started D 10% at 100 ml/kg/day.

b. Calculate the GIR of this fluid infusion.

c. What could be the possible cause of this hypoglycemia? Write other causes of hypoglycaemia

d. What is the treatment of choice in hyperinsulinemic hypoglycemia and its mechanism of action?

Question 6

A 4-day-old male neonate presented with a history of multiple episodes of clonic convulsions since the second day of life. The child was born to a 25-years-old primigravida at term, cried soon after birth, with a birth weight of 2.8 kg and was on exclusive breast feeds. The parents were healthy with normal stature and without any history of consanguinity. Anterior fontanelle was at level and there were no dysmorphic facies or gross congenital malformations. Urine output was 1 ml/kg/h. Rest of the systemic examination was normal. Blood glucose was within normal limits. The baby was loaded with Injecttion phenobarbitone in view of persistent seizures. A provisional diagnosis of metabolic seizure was made, and the initial screen revealed Serum Calcium- 5.9 mg/dl.

1. What is the initial approach to management?
   a) Repeat sepsis screening along with blood culture (Bactec), Viral Markers & start second-line antibiotics, continue iv calcium for 2 more days.
   b) b.To start on IV calcium gluconate correction and plan to repeat serum calcium, and metabolic screening (serum ammonia and extended newborn screening test) after 24 hours.
   c) c.To send Serum Calcium levels along with ionised calcium, Serum phosphorus, Serum magnesium, PTH, Vit D levels and alkaline phosphatase and to start on IV calcium gluconate correction.
   d) d.To start on Pyridoxine along with IV calcium Gluconate correction and plan for EEG and MRI brain to evaluate seizures.

Further investigations revealed serum phosphorus – 8.5 mg/dL (normal: 3.8-6.5 mg/ dL) and alkaline phosphatase of 926 IU/l (normal 150-400 IU/l). Serum magnesium was within normal limits. Serum PTH levels were 98 pg/ml (normal- 14.0–72.0 pg/mL). 25-hydroxyvitamin D was 48.1 ng/mL (normal, 31.0–100.0 ng/mL), calcitonin was <3.0 pg/mL (normal, <10 pg/mL). Blood urea was 32 mg/dl, serum creatinine- 0.8 mg/dL and blood glucose was 87 mg/dl. The sepsis screen along with CSF analysis was negative. Ultrasound skull and abdomen did not reveal any abnormality. In view of hypocalcemia, the child was started on i.v. calcium gluconate. Persistence of seizure led to metabolic screening which revealed normal serum ammonia and blood gas analysis.

2. What would be the provisional diagnosis of the current condition?
   a) a.Viral Meningitis
   b) b.Organic Acidemia with hypocalcemia
   c) c.Pyridoxine dependent seizures
   d) Early onset hypocalcemia secondary to? Neonatal pseudo hypoparathyroidism
3. What would be the appropriate treatment in the current scenario
   a) Continue Calcium supplementation with Calcitriol.
   b) Continue antibiotics along with IV Calcium Gluconate and other supportive medications.
   c) Continue IV Calcium Gluconate and IV Fluids with GIR of 8 to 10 mg/kg/min.
   d) Continue Oral Pyridoxal Phosphate 30mg/kg/day in 3 divided doses.

Question 7

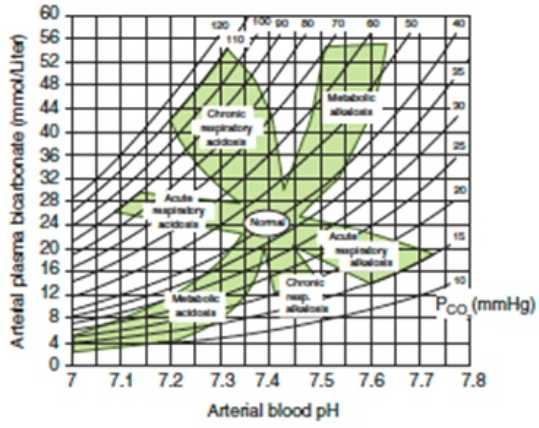
a. Calculate TPN requirements of a 5-day old neonate with birthweight of 1.3 kg suffering from NEC. Baby is nil by mouth.

b. What is Calorie Nitrogen Ratio. What is the formula for calculation and ideal values to be maintained while designing TPN?

Question 8

a. Interpret this ABG - pH 7.12, pCO2 54, HCO3 10, BE -17, PaO2 60

b. Identify this equation/graph



c. Calculate the Oxygenation index for the baby with ABG values as mentioned above. The neonate is on ventilatory support with settings of PIP 19/PEEP 6/FIO2 50%/RR60/Ti 0.4 sec

d. What are the various Buffer systems available in the body for compensation?

Question 9.

Write the composition of the following IV fluids per 100 ml

a. NS

b. 1/2 NS

c. N/2 D10 % Saline

d. RL

e. 3% NaCl

Question 10

a. Calculate anion gap.

Na 148, K 5, Cl 120, pH 7.10, pCO2 28, HCO3 10

b. Enlist 3 causes each of the normal Anion Gap and high anion gap Metabolic acidosis

c. Urine Sodium (Na+): 20 mEq/L, Urine Potassium (K+): 15 mEq/L;Urine Chloride (Cl-): 40 mEq/L, Urine Ammonium (NH4+): 5 mEq/L

Calculate the urine anion gap for this patient and interpret the result in the context of their acid-base status.

Answer 1 d

The high serum sodium level in extremely low birth weight (ELBW) babies is most likely due to free water loss. 2/3rd of this loss occurs trans-epidermally while the remaining 1/3rd is lost via respiratory tract and polyuria leading to extracellular fluid (ECF) contraction. Usually it occurs after 24–48 h after birth, corresponding to the diuretic phase as RDS improves. Clinical clues to this phase include weight loss, high serum sodium, blood urea nitrogen (BUN).

Management plan for ELBW with hypernatremia :

1. Increase humidity in incubator to 95% and then titrate it as per unit protocol (this is to minimize transepidermal water loss)
2. Increase amount of fluids by 20-30 ml/kg/day depending upon urine output, weight pattern and electrolytes. This fluid is extra from the parenteral nutrition which baby is receiving . It can be either plain 5% dextrose or 0.45% DNS depending upon serum sodium and day of life.
3. Its important to take into account the heparin saline solution which is usually running in these babies for umbilical arterial line. If we are making it in 0.9% NS, we are providing roughly 3 meq/l/day of sodium.
4. Monitor RBS values and avoid hyperglycemia as it can contribute to osmotic dieresis and may worsen dehydration.
5. Monitor KFT/Blood gas for rising urea/creatinine levels and blood gas for metabolic acidosis. Try and avoid multiple sodium bicarbonate boluses to treat metabolic acidosis.

   Ref: - Hypernatremia in newborns. A practical approach to management - Biomed Hub 2022;7:55–69

Answer 2

Body Fluid	Electrolytes (Na, K, Cl in mmol/l)
a. Gastric	3.20–80, 5–20, 100–150
b. Small Intestine	5.100–140, 5–15, 90–130
c. Bile	1.120–140, 5–15, 80–120
d. Ileostomy	2.45–135, 3–15, 20–115
e. Diarrhoea	4.10–90, 10–80, 10–110

Answer 3

Requirments	**Formula**	**Calculation**
Total fluid deficit	10 ml * WT * % Dehydration	10 * 3 * 20 = 600 ml
Maintenance fluid requirement	On day 8- 150 ml/kg	150 X 3 = 450 ml
Free water deficit	4 ml * birth weight * (S.Na- desired Na)	4 * 3 * (170-150) = 240 ml
Solute fluid deficit	Total fluid deficit- free water deficit	600-240 = 360 ml
Solute sodium deficit	Solute water deficit in litre * Distribution Factor * Normal ECF Na concentration	0.36 * 0.75 * 145 = 39.1 meq
Maintenance sodium requirement	4 X Body weight	4 X 3 =12 meq
Total sodium required	Solute Na deficit+ Maintenance Na requirement	39.1+12 = 51.1 meq

Reference – Harriet Lane 22nd edition 2021. Page no 361.

	Plan	Calculation	Water	Sodium
First 24 hrs	½ of free water	240/2 = 120	120	0
	Full solute replacement		360	39
	Full 24 hr Maintenance		450	12
		Total	930	51
Next 24 hrs	½ of free water	240/2 = 120	120	0
	Full 24 hr Maintenance		450	12
		Total	570	12

Fluid Order

First 24 hrs

Volume of normal saline (0.9% NS) = 51 X 6.5 = 331 ml
(1 meq of 0.9% NS is equal to 6.5 ml)

Volume of 5% Dextrose = 930 ml -331 = 599 ml

Fluid = 5%D 599 ml+ 0.9%NS 331 ml @38.7 ml/hour

Next 24 hrs

Volume of 0.9% NS = 12 X 6.5 = 78 ml

Volume of 5% Dextrose = 570- 78 ml =492 ml

Fluid = 5%D 492 ml+ NS 78 ml @23.7 ml/hour

Answer 4

a-6, b-4, c-1, d-5, e-3, f-2

Medication	Mechanism of Action
a. Calcium gluconate	6. Protects the myocardium from toxic effects of potassium; no effect on total body potassium
b. Sodium bicarbonate	4. Shifts potassium intracellularly; no effect on total body potassium
c. Tromethamine (THAM)	1.By capturing H +, increases pH without increasing CO 2 and thus shifts potassium intracellularly; no effect on total body potassium
d. Insulin plus dextrose	5. By stimulating the Na +,K +-ATPase enzyme, it shifts potassium intracellularly; no effect on total body potassium
e. Sodium polystyrene	3. Removes potassium from gut in exchange for sodium
f. Furosemide	2. Increases renal excretion of potassium

Medication	Dosage	Route	Onset	Duration of Effects	Mechanism of Action	Comments and Cautions
Calcium gluconate	100 mg/kg	Intravenously over 2-5 min	Immediate	30 min	Protects the myocardium from toxic effects of potassium; no effect on total body potassium	• Risk of precipitation when administered with sodium bicarbonate • Administer with caution when using peripheral venous access due to the risk of tissue injury with extravasation
Sodium bicarbonate	1-2 mEq/kg	Intravenously over 2-5 min	Immediate	Variable	By increasing pH, $NaHCO_3$ shifts potassium intracellularly; no effect on total body potassium	• Consider lower dose and infusion rate for very preterm infants in the first postnatal days • Risk of precipitation when administered with calcium gluconate
Tromethamine (THAM)	3-5 mL/kg	Intravenously over 1 hr	Immediate	Variable	By capturing H^+, THAM increases pH without increasing CO_2 and thus shifts potassium intracellularly; no effect on total body potassium	—
Insulin plus dextrose	*Insulin:* 0.1-0.15 U/kg *Dextrose:* 0.5 g/kg	Intravenously over 30 min	15-30 min	2-6 hr	By stimulating the Na^+,K $^+$-ATPase enzyme, it shifts potassium intracellularly; no effect on total body potassium	Monitor for hypoglycemia
Albuterol	0.4 mg (in 2 mL of NS)	Inhalation, up to every 2 hr	15-30 min	2-3 hr	By stimulating the Na^+,K $^+$-ATPase enzyme, it shifts potassium intracellularly; no effect on total body potassium	Should not be used as sole agent
Furosemide	1-4 mg/kg per dose Intravenously: 1-2 mg/kg per dose	Orally Intravenously	15 min to 1 hr (sooner with IV admin)	4 hr	Increases renal excretion of potassium	—
Sodium polystyrene	1 g/kg every 6 hr	Rectally or orally	1-2 hr (sooner with rectal admin)	4-6 hr	Removes potassium from gut in exchange for sodium	• Use with extreme caution in neonates, especially preterm neonates • Contains sorbitol • May be associated with bowel necrosis and sodium retention

Reference: Avery's diseases of newborn- 11th edition, page no 243

Answer 5

a. Give Measured Feeds and recheck RBS after the next feed

b. GIR 7 mg/kg/min

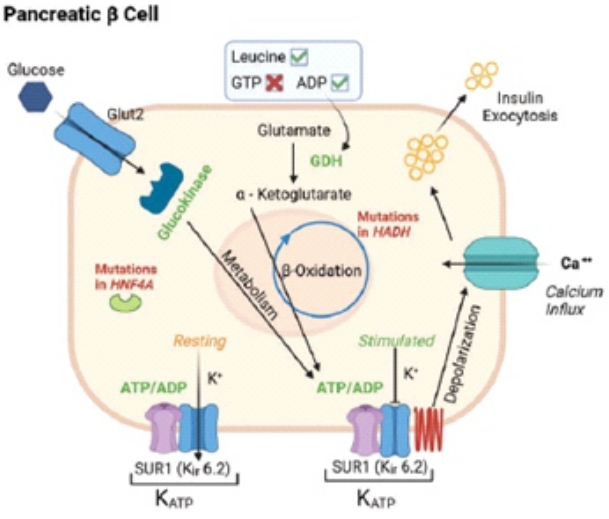
GIR = % dextrose *Fluid volume in ml/kg/day*0.007

c. Hyperinsulinemic Hypoglycaemia is the cause of this type of hypoglycaemia

Causes of hypoglycemia	
Hyperinsulinemic - Transient	Infant of diabetic mothers Intrapartum dextrose infusion to mother Stress in peripartum/ postnatal period: asphyxia, hypothermia Small for gestational age
Hyperinsulinemic – Permanent	KATP channel defects Glutamate dehydrogenase (GLUD1)-activating mutation Short-chain 3-hydroxyacyl-coenzyme A dehydrogenase (HADH or SCHAD) mutation Glucokinase (GCK) activating mutation HNF1A and HNF4A pathogenic variants Uncoupling protein-2 (UCP2) pathogenic variants Hexokinase-1 (HK1) pathogenic variants Beckwith-Wiedemann syndrome (BWS) Postfundoplication (dumping syndrome) Hyperinsulinism in congenital disorders of glycosylation β-cell adenoma—MEN1
Normoinsulinemic - Transient	Developmental immaturity in adaptation to fasting: prematurity, SGA Increased metabolic expenditure: sepsis, erythroblastosis fetalis, polycythemia Maternal conditions: toxemia, administration of tocolytics (β sympathomimetics)
Normoinsulinemic - Permanent	Hypopituitarism Primary adrenal insufficiency **Inborn errors of metabolism** Glycogen storage disease Disorders of gluconeogenesis Defects in fatty acid catabolism and ketogenesis Organic acidurias Galactosemia Hereditary fructose intolerance

Reference: Avery's disesases of the newborn- 11th edition, page no: 1258
d.Diazoxide is the drug of Choice. It binds to SUR1 Subunit, opens KATP Channel

Reference: Avery's diseases of newborn- 11th edition, page no1262



Mechanism of insulin secretion: Glucose transported into the β cell by the insulin-dependent glucose transporter, GLUT 2, undergoes phosphorylation by glucokinase and subsequent metabolism, resulting in an increase in the intracellular ATP: ADP ratio which closes the KATP channel and initiates an increase in intracellular potassium concentration, membrane depolarization, calcium influx, and release of insulin from storage granules. Leucine also increases insulin secretion by activating glutamate dehydrogenase (GDH) and the oxidation of glutamate, further increasing the ATP: ADP ratio and closure of the KATP channel.

(Modified from Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia, Pediatr Clin North Am. 2004;51:703–723.)

Table – Drugs used in the management of hyperinsulinemic hypoglycemia

Drug	Dose/Route	Mechanism of Action	Adverse Effects
Diazoxide	5-15 mg/kg/day in three divided doses orally	Binds to SUR1 subunit, opens K_{ATP} channel	Fluid retention, hypertrichosis, rarely eosinophilia, leukopenia, hypotension
Chlorothiazide (in conjunction with diazoxide to decrease fluid retention)	10-20 mg/kg/day in two divided doses orally	Synergistic response to diazoxide	Hyponatremia, hypokalemia
Octreotide	5–25 µg/kg/day 6–8 hourly SC injection or IV infusion	Inhibits insulin secretion by binding to somatostatin receptors and inducing hyperpolarization of β-cells, direct inhibition of voltage-dependent calcium channels	Anorexia, nausea, abdominal pain, diarrhea, tachyphylaxis Risk of NEC in young infants, thus lower doses are recommended
Glucagon	1–20 µg/kg/h, SC or IV infusion	Increases glycogenolysis and gluconeogenesis	Nausea, vomiting, paradoxical insulin secretion at high dose

Reference: Avery's disesases of the newborn- 11th edition, page no: 1265

Answer 6

1. c
2. d
3. a

Neonatal Pseudohypoparathyroidism can be type 1 or type 2. Type I is characterized by low or absent renal cyclic adenosine monophosphate (CAMP) production in response to parathormone (PTH). In type 1A, there is a genetic defect of the stimulator guanine nucleotide binding protein (GSα), with distinct morphological abnormalities called Albright's hereditary osteodystrophy which rarely develops before 3 years of age. Type IB is characterized with normal levels of G protein activity with defect in PTH receptor expression or subunit of adenyl cyclase. Type II responds to PTH with a normal increase in urinary CAMP but shows absent or subnormal phosphaturic response.

In the present case, the baby presented in the early neonatal period with hypocalcemic convulsions which were resistant to i.v. calcium gluconate. Hypomagnesemia, septicemia, and renal failure were ruled out. Elevated levels of serum parathormone levels further ruled out hypoparathyroidism. Few case reports of transient PHP that presented as late-onset hypocalcemia are available in the literature but to the best of our knowledge there is only one case report in literature of pseudohypoparathyrisdism presenting as early onset hypocalcaemia. At 3 months of age, the child was on oral calcium supplementation and calcitriol and

was seizure-free.

All patients with severe symptomatic hypocalcemia should be initially treated with intravenous calcium. Administration of oral calcium and 1 alpha- hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment and should be initiated in every patient with a diagnosis of PHP. The goals of therapy are to maintain serum total and ionized calcium levels within the reference range to avoid hypercalciuria and to suppress PTH levels to normal. This is important because elevated PTH levels in patients with PHP could cause increased bone remodelling and can lead to hyperparathyroid bone disease.

In the present case, in view of persistent hypocalcemia, hyperphosphatemia and high serum parathormone levels, a diagnosis of PHP was made, and the child was treated with calcium supplementation and calcitriol 0.25 µg/day. Serum calcium and phosphorus became normal within 15 days of starting calcitriol. On follow-up at 3 months, the child was asymptomatic on calcitriol and calcium supplementation.

ANSWER 7

a.

Step I

Calculate Fluid intake

a) Total fluid intake (TFI) 150 ml / kg / day = 150* 1.3 =195 ml

b) TPN volume = TFI – Feed Volume = 195 - 0 = 195 ml

c) Lipid volume (SMOF or Intralipid 20%) = 2 gm / kg / day = 2*1.3*5 = 13 ml (Rate of starting IV lipids may vary across units. Some units start it at 2 gm/kg/day on Day 1 of starting and then increase to maximum of 3 gm/kg/day)

d) Hyperalimentation volume (HAV) = TPN volume - Lipid volume = 195 – 13 = 182 ml

Step II

Make provision for overfill factor

You always need to make additional volume of solution to compensate for wastage in bottles & IV set This additional volume is generally is 10 to 20%.

Hyperalimentation volume (HAV) = 182 ml

Prepared Volume (PV) = 218.4 ml

Overfill factor = 1.2

Step III

Calculate additive volume

	Dose	Concentration	Volume (ml)
Amino acid (10% solution)	3 gm/kg/day	10%	3*1.3*10*1.2= 46.8
3% NS	3 meq/kg/day	1 ml = 0.5 meq	3*1.3*2*1.2 = 9.4
KCl	2 meq/kg/day	1 ml = 2 meq	2*1.3*0.5*1.2 = 1.5
Calcium Gluconate (10%)	4 ml/kg/day	1 ml = 9.3 mg	4*1.3*1.2 = 6.2
MVI (Adult)	1 ml/kg/day		1*1.3*1.2 = 1.6
Sum of additive volume (AV)			65.5 ml

Step IV

Calculate Dextrose volume

The hyperalimentation volume comprises of dextrose & additives. The additives have consumed 65.5 ml of the total HAV. The remaining volume is left for dextrose. Glucose infusion rate (GIR) should be 6 mg/kg/min on first day of PN and then increased depending on blood sugars (Aim is to keep Random blood sugars between 150-200 mg/dl).

Volume of dextrose = Prepared volume – Additive volume

= 218.4-65.5 = 152.9 or 153 ml

(118 mg/kg/day)

Step V

Calculate Dextrose concentration

If we have to give GIR of 6 mg/kg/min and volume is 153 ml, how much will be conc of glucose

Formula

GIR = ml/kg/day *0.007*% Dextrose

% Dextrose = 6/ (118*0.007) = 7.3%

Lets prepare it from 5% and 50% dextrose

Formula for volume of lower concentration is

= (High conc – Desired conc)*Volume of dextrose/ High conc – Low conc

Volume of D5 = (50-7.3)*153/(50-5) = 145 ml

Volume of D50 = 153 – 145 = 8 ml

Step VI

Write final composition

5% dextrose	: 145 ml
50% dextrose	: 8 ml
10% aminoacid solution	: 46.8 ml
3% NS	: 9.4 ml
KCl	: 1.5 ml
Calcium gluconate	: 6.2 ml
MVI	: 1.6 ml

Step VII

Final Orders

IV hyperalimentation solution (182 ml) to be infused over 24 hrs (@ 7.6 ml / hr)

IV 20% Fat emulsion (13 ml) to be infused by separate IV set over 24 hrs (@ 0.5 ml / hr)

b.

Calorie Nitrogen ratio

[(Fat calories + carbohydrate calories)*6.25/ Aminoacid (gms)]

Normal value : 100 – 200 Calories/ gram

Reference – Indian Pediatrics 2006;43: 953-964

Answer 8

a. Mixed metabolic and respiratory acidosis

How should one read the blood gas – Steps

1. Look at the pH- Acidosis (pH < 7.35), Alkalosis (pH > 7.45)

   In our case its 7.12, which means acidosis

2. Whether its respiratory or metabolic

   In metabolic acidosis (HCO3 is less than 20), In metabolic alkalosis (HCO3 is more than 28)

   In respiratory acidosis (PaCO2 should be more than 45 mm Hg), in respiratory alkalosis (PaCO2 should be less than 45 mm Hg)

   In our case HCO3 is 10 (metabolic acidosis), pCO2 is 54 (increased, respiratory acidosis).

3. Look for compensation

To calculate whether it is a compensated disorder- apply formula for compensation, in metabolic acidosis compensation for decrease HCO3 is by decrease PCO2.

pCO2 = (1.5 x HCO3) + 8 ± 2 = 21-25.

Here is a quick reference for other compensations which may occur in several other type of disorders.

Acid base disorder	Compensation	How much
Metabolic acidosis	↓ PCO2	PCO2= (1.5X HCO3) +8 ±2
Metabolic alkalosis	↑ PCO2	PCO2 increases by 7 for every 10 ↑ in HCO3

Acid base disorder	Compensation	How much
Respiratoryy acidosis	↑ HCO3	Acute: Increase by 1 for every 10 mmHg ↑ in PCO2 beyond 40 mmHg Chronic: Increase by 3.5 for every 10 mmHg ↑ in PCO2 beyond 40 mmHg
Respiratory alkalosis	↓ HCO3	Acute: Falls by 2 for every 10 mmHg ↓ in PCO2 below 35 mmHg Chronic: Falls by 4 for every 10 mmHg ↓ in PCO2

Interpretation – In our case its acidosis. Since HCO3 is 10 and PaCO2 is 54, it is a MIXED DISORDER ie METABOLIC ACIDOSIS WITH RESPIRATORY ACIDOSIS.

b. Siggaard Anderson Normogram

ABG Machine measures pH, pCO2 and pO2 (Measured parameters). All other parameters are derived parameters obtained using this normogram.

c. $OI = \frac{FiO2 \times MAP}{PaO2} \times 100$

To Calculate MAP (cm H20)

$MAP = \frac{(Ti \times PIP) + (Te \times PEEP)}{Ti+Te}$

OR

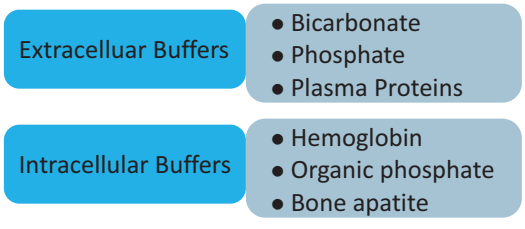
MAP = (PIP-PEEP) x (Ti/Ti+Te) + PEEP

MAP as per formulae = 10.5

OI = 8.7

d. Buffer system

Buffers are the substances that keep pH in place.



First-line buffers- These are chemical buffers eg. Bicarbonate, phosphate and proteins.

Second line buffers- Physiological buffers eg. Respiratory mechanism for compensation (CO2 excretion), the renal mechanism (H+ excretion)

Answer 9

All values are per 100 ml

a. NS = 0.9% NaCl, Na = 15.4 meq, Cl = 15.4 meq

b. 1/2 NS = 0.45% NaCl, Na = 7.7meq/L, Cl = 7.7 meq/L

c. N/2D10% Saline = 0.45% NaCl + D10% = Na= 7.7 meq, Cl = 7.7 meq, Dextrose 10 gm

d. RL= Ringer's Lactate = Na 13meq, K 0.4meq, Cl 10.9 meq, Lactate 3

e. 3% NaCL= Na 51.3 meq, Cl 51.3 meq

Answer 10

a. 23

Formula for Anion gap = (Sodium+Potassium)-(Chloride+Bicarbonate)

(148+5) - (120+10) =23

Normal anion gap is 8 – 16 meq/l

b.

Causes of high anion gap metabolic acidosis

Anion gap is the difference between unmeasured anions and unmeasured cations. It is affected by changes in unmeasured ions.

Causes of high anion gap metabolic acidosis (HAGMA):

1. Lactic acidosis
2. Ketoacidosis
3. Diabetic ketoacidosis
4. Hazardous alcohol use
5. Toxins: Methanol, Ethylene glycol, Propylene glycol, Lactic acid, Uremia, Aspirin, Phenformin, Iron, Isoniazid, Cyanide.
6. Kidney failure- causes high anion gap acidosis by decreased acid excretion and decreased HCO−3 reabsorption and accumulation of sulfates, phosphates, urate, and hippurate accounts for the high anion gap.

Normal anion gap

In patients with a normal anion gap, the loss of HCO_3 from body is the primary pathology. Since there is only one other major buffering anion, it must be compensated for almost completely by an increase in Cl−. This is therefore also known as hyperchloremic acidosis. The HCO_3 lost is replaced by a chloride anion, and thus there is a normal anion gap.

Causes of Normal anion gap metabolic acidosis

1. Gastrointestinal loss of HCO−3 (i.e., diarrhea and small bowel drainage: ileostomy, intestinal fistula) (note: vomiting causes hypochloraemic alkalosis)
2. Kidney loss of HCO−3 (i.e., proximal renal tubular acidosis (RTA) also known as type 2 RTA)
3. Kidney dysfunction (i.e., distal renal tubular acidosis also known as type 1 RTA)
4. Renal hypoaldosteronism (i.e., renal tubular acidosis also known as type IV RTA) is characterized by elevated serum potassium.

Renal hypoaldosteronism can be due to:

1. **Low Renin**- Hyporeninemic hypoaldosteronism (↓ aldosterone - Decrease renin):

Causes

Combined with cortisol insufficiency		Isolated hypoaldosteronism
· Genetic disorders	1. Salt-wasting forms of CAH 2. Adrenal hypoplasia congenita	Aldosterone synthase deficiency
· Metabolic disorders	1. Adrenoleukodystrophy/Adrenomyeloneuropathy 2. Wolman's disease	
· Acquired disorders	1. Autoimmune adrenalitis 2. Infections 3. Intra-adrenal hemorrhage	Drugs: Heparin, ACE inhibitors, ARBs

2. **Low aldosterone-** Defective stimulation by renin: Hyporeninemic hypoaldosteronism (↓ aldosterone-↓renin):

   lupus nephritis, post-infectious glomerulonephritis or mild-to-moderate chronic renal insufficiency Drugs: NSAIDs, COX-2 inhibitors, beta-blockers.

3. **Low response to aldosterone**- Aldosterone resistance: Pseudohypoaldosteronism (↑aldosterone - ↑renin)

   Primary, due to an inherited receptor defect Secondary (UTI, urinary malformation, drugs)

Reference- Vlachopapadopoulou EA, Bonataki M. Diagnosis of Hypoaldosteronism in Infancy. Renin-Angiotensin Aldosterone System. 2021 Jul 23.

c. -5 meq/l

Formula for the urine anion gap:

Urine Anion Gap = (Urine Na^+ + Urine K^+) - Urine Cl^-

Urine anion gap in our case:

Urine Anion Gap = (20 mEq/L + 15 mEq/L) - 40 mEq/L

Urine Anion Gap = 35 mEq/L - 40 mEq/L

Urine Anion Gap = -5 mEq/L

Urine anion gap (UAG)

Calculation of the urine anion gap is an indirect method to estimate urinary ammonium

($NH4^+$) excretion. UAG is only useful (and valid) for the differential diagnosis of patients with normal anion gap hyperchloremic metabolic acidosis (NAGMA).

It is determined by subtracting the sum of easily measurable anions from the sum of cations in the urine. The formula resembles the determination of the plasma anion gap.

UAG = $Na^+ + K^+ - Cl^-$

Note: In relatively acidic urine (pH < 6.5), the urine bicarbonate concentration (U [$HCO3^-$]) is essentially zero and its effect on the UAG is, therefore, negligible.

Unmeasured, and generally negligible are the urine anions sulfate and phosphate and the cations calcium and magnesium. $NH4^+$ constitutes the major urine cation, and its excretion is accompanied by chloride as $NH4^+Cl^-$.

Systemic metabolic acidosis leads physiologically to large urinary ammonium excretion, which serves to trap secreted protons. It is identified by a negative UAG owing to the increased Cl^- excretion that accompanies the unmeasured cation $NH4^+$. This scenario is commonly seen in neonates/ children with severe diarrhoea and NAGMA or after acid or $NH4^+Cl^-$ loading.

A small or positive UAG in a patient with NAGMA indicates failure to acidify the urine

(which happens in Distal RTA)

The UAG helps to diagnose patients with proximal renal tubular acidosis when the plasma bicarbonate level is below the bicarbonate threshold. The UAG is negative because the distal acidification mechanism (proton secretion by type A intercalated cells) is intact.

Interpretation – In diarrhoea and proximal RTA (where there is bicarbonate loss and the distal acidification mechanism is intact, urine anion gap is negative)

In Distal RTA, the urine anion gap is positive.

In our case, the urine anion gap is negative (-5 mEq/L), which suggests that the patient's metabolic acidosis may be due to diarrhoea or proximal RTA.

Reference – Pediatrics Clinics of North America 66 (2019) 135–157

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.**

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

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