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DR ASHISH JAIN
President, AON Delhi

DR NAVEEN PARKASH GUPTA
Secretary, AON Delhi

DR ANUP THAKUR
Chief Editor, Neo Clips

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From the President's Pen

DR. ASHISH JAIN

President AON Delhi

Warm greetings to all our members and esteemed readers!

It gives me great pleasure to present the latest issue of NeoClips (Neonatal Clinical Practice), the official journal of Delhi NNF. Over the past editions, NeoClips has steadily gained recognition and appreciation across the country, reflecting its growing role as an inclusive and versatile academic platform for the neonatal community. It has been heartening to witness how the journal continues to bring together diverse perspectives while remaining focused on issues most relevant to our practice.

I take this opportunity to place on record my sincere congratulations to the editorial team for their dedication and perseverance in producing this issue. I wish them continued success in carrying this important work forward.

As an organization, Delhi NNF/AON remains steadfast in its mission to train, support, and empower the neonatal community—be it students, nurses, pediatricians, or neonatologists. The recurring sections on ventilation, statistics, and OSCEs have been particularly well-received by postgraduate students and fellows, becoming trusted resources for both academic growth and examination preparation. The present issue stands out for the breadth of its coverage, addressing two important yet contrasting areas of neonatal medicine—inotropes and neonatal neurology. Alongside these, the case reports, clinical images, and pictorial features provide valuable real-world insights that will undoubtedly benefit clinicians in their day-to-day practice.

On behalf of Delhi NNF, I extend my heartfelt gratitude to all contributors, readers, and members who continue to support this initiative. Your engagement and encouragement remain the driving force behind the growth of NeoClips.

Looking to the future, we aspire to expand the journal into newer domains of neonatal practice, encourage broader participation from across the country, and strengthen its role as a dynamic, reliable, and forward-looking academic resource for all professionals dedicated to newborn care.

Together, let us strive for healthier beginnings for every newborn.
Thank you so much

Warm regards,
Dr. Ashish Jain
President, Association of Neonatologists

From Secretary's desk

DR NAVEEN PARKASH GUPTA

Secretary, NNF Delhi

Dear Friends,

Warm greetings from the Association of Neonatologists.

It gives me immense pleasure to present to you the third quarterly edition of NeoClips for the year 2025. Over the past issues, NeoClips has steadily grown into a trusted academic companion for practicing pediatricians, neonatologists, postgraduate students, and fellows. Its purpose has always been to provide concise, practical, and high-quality content that bridges the gap between clinical experience and academic learning.

This issue continues that tradition with a rich blend of contributions. Readers will find review articles, case reports, clinical images, and illustrations that highlight both common and challenging aspects of neonatal practice. The OSCE section in this edition is dedicated to scenarios in neonatal neurology, a topic that often poses difficulties during training and examinations. I am delighted to note that the OSCE series, since its inception, has been among the most widely appreciated features by postgraduate students, who have found it particularly useful for structured exam preparation.

Equally noteworthy are the seventh installments of both the statistics series and the ventilation series. Each of these continues to add depth to the understanding of subjects that are essential to modern neonatal practice. Together, these recurring sections have become hallmarks of NeoClips, steadily building knowledge step by step for our readers. I appreciate my gratitude to Dr Anup Thakur and his team for these innovative series.

I also extend my gratitude to all contributing authors, whose willingness to share their expertise and experiences have enriched the journal. Each contribution is a valuable step toward strengthening our collective knowledge and shaping the next generation of pediatricians and neonatologists. I warmly encourage all our members to continue submitting their scholarly work, unique case experiences, and innovative ideas to NeoClips..

For access to all previous editions of NeoClips, please visit our website: https://nnfdelhi.org

Warm regards,
Dr. Naveen Parkash Gupta
Secretary, Association of Neonatologists

From the Editor's Desk

DR. ANUP THAKUR

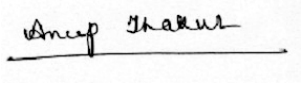
Editor

Warm greetings from the Association of Neonatologists.

It is with great satisfaction that I present the third quarterly issue of NeoClips for the year 2025. Since its inception, the journal has aimed to serve as a dependable academic platform for pediatricians, neonatologists, postgraduate trainees, and fellows. As Editor, I am mindful that it is both a privilege and a responsibility to curate issues that remain academically robust while catering to the diverse needs of our readership. The challenge lies in balancing comprehensive scientific discourse with practical insights that are of immediate relevance to clinicians, educators, and trainees. It is our constant endeavor to ensure that each issue reflects this balance and upholds the values of clarity, quality, and accessibility.

This issue exemplifies that vision through a diverse collection of scholarly contributions. The featured journal review discusses the MOCHA trial by Dr. Priyanka Gupta, while the review article in neurology has been authored by Dr. Nidhi. The topic of inotropes in shock is addressed comprehensively by Dr. Pradeep. The Picture of the Month is presented by Dr. Jaikrishan Mittal, Dr. Gunjana, and team, and the Image of the Issue is contributed by Dr. Yusuf and Dr. Swati. In addition, the OSCE section in neonatal neurology, a highly relevant area has been prepared by Dr. Pratima Anand. Continuing the popular academic series, the ventilation module is authored by Dr. Anita Singh, while the statistics section, focusing on the ROC curve, is presented by Dr. Gunjan. This issue also includes a valuable case report by Dr. Rajesh and team.

I extend my deep appreciation to each of the contributors for their efforts and commitment to knowledge-sharing. On behalf of the editorial board, I also take this opportunity to encourage our members and readers to contribute their original research, case experiences, and innovative perspectives to NeoClips.



Warm regards,
Dr. Anup Thakur
Editor-in-Chief
NeoClips – Neonatal Clinical Practice

MOLECULAR EMBRACE

All hail to you, my mother!
There is none like you 'Mother.
My very being intertwined to honor you,
Entire creation fashioned for the same; very true.

I lie all the day between your breast,
Where it has become my eternal nest.
The smell of your bosom, they comfort me,
I am always dancing in this glee.
The nectar from your nipples is sweet to my taste,
Let this; my banqueting house, be always embraced.

Allowing me to hear thy precious voice,
Letting my enriching heart always rejoice.
I long for the honey which flows from your bosom,
Making me to relish and lavish: truesome.
To rely on your breast, is to conquer the whole world,
and is to become the best.

Says the mother,
" O thou my Beloved, my soul waiteth and longeth for thee,
To set our journey ablaze and free.
Even through the turmoil,
I let you recoil.
The trickle from my breasts, will nurture you with the utmost;
To the generations to come, you can boast.
To crown thee with honor and valor,
I have woven thee, the wreath of garner and calor."

Jubilant James
EB Member, Delhi AON
Nursing Officer,
NICU, AIIMS, Delhi

Inotropes in Neonatal Shock: Current Perspectives and Clinical Applications

Authors
Dr Pradeep Sharma, DM (AIIMS)
Senior Consultant
Department of Neonatology,
Deep Hospital Ludhiana

ABSTRACT

Neonatal shock represents a critical state of circulatory failure with inadequate tissue perfusion and oxygenation. Inotropes form the cornerstone of pharmacological support in managing shock across a spectrum of neonatal pathologies. This review highlights the pathophysiology of neonatal shock, mechanisms of action of inotropes, and evidence-based guidance on their choice in distinct clinical contexts including septic shock, transitional circulation, pulmonary hypertension, extremely low birth weight (ELBW) neonates, and neonates with congenital heart disease (CHD).

INTRODUCTION

Shock in the neonatal period is a life-threatening condition, demanding timely diagnosis and therapeutic intervention. The etiology is multifactorial and includes sepsis, perinatal asphyxia, cardiac malformations, pulmonary hypertension, and transitional maladaptation. The selection of inotropic agents depends on the underlying pathophysiology, myocardial function, vascular tone, and the neonate's gestational age.

CLASSIFICATION AND PATHOPHYSIOLOGY OF NEONATAL SHOCK

Neonatal shock is traditionally classified into:

- Hypovolemic shock
- Cardiogenic shock
- Distributive shock (septic)
- Obstructive shock

Each type can overlap, especially in critically ill neonates. the immature myocardium and unique neonatal hemodynamics necessitate specialized approaches in pharmacologic management. An overview of commonly use inotropes is given in table 1.

Table 1. Overview of Commonly Used Inotropes

Drug	*Mechanism of Action*	*Hemodynamic Effect*
Dopamine	Dose-dependent α and β agonist	↑ HR, ↑ SVR, ↑ CO
Dobutamine	β1 agonist, mild β2 effect	↑ Contractility, mild vasodilation
Epinephrine	Potent α and β agonist	↑ HR, ↑ CO, ↑ SVR
Norepinephrine	Strong α and some β1 agonist	↑ SVR, ↑ MAP
Milrinone	PDE-3 inhibitor	↑ Contractility, ↓ PVR and SVR
Vasopressin	V1 receptor agonist	↑ SVR, ↑ MAP (vasoconstriction)
Levosimendan	Calcium sensitizer, PDE inhibition	↑ Contractility, vasodilation

INOTROPE CHOICE IN SPECIFIC CLINICAL CONTEXTS

1. Septic Shock

Neonatal sepsis is associated with myocardial dysfunction, vasodilation, and capillary leak.

- Early phase (warm shock): Vasodilation predominates. Dopamine is traditionally first-line but norepinephrine may be superior due to more potent vasoconstriction.
- Cold shock: With myocardial depression, epinephrine or dobutamine are preferred. Milrinone may be useful to improve diastolic function and reduce afterload.
- Combination therapy is often required to balance inotropy and vasoconstriction.

2. Shock during Transition

In the immediate postnatal period, inadequate fall in pulmonary vascular resistance (PVR) or maladaptation of systemic vascular resistance (SVR) can result in shock.

- Dobutamine is preferred to support myocardial contractility.
- Milrinone aids in reducing PVR while supporting cardiac output.
- Careful monitoring is necessary due to fluctuating vascular resistances.

3. Shock in Pulmonary Hypertension (PPHN)

High PVR leads to right ventricular failure and left-sided underfilling.

- Milrinone is beneficial due to its selective pulmonary vasodilation and inotropy without increasing myocardial oxygen demand.
- Dobutamine supports contractility, while Norepinephrine and vasopressin may help increase SVR and reduce right-to-left shunting.
- Avoid dopamine at high doses due to potential increase in PVR.

4. ELBW Neonates

Inotropes must be used cautiously due to fragile vasculature, immature receptors, and variable pharmacokinetics.

- Dobutamine is better tolerated and improves left ventricular output.
- Dopamine increases blood pressure but may compromise organ perfusion at high doses.
- Early use of low-dose hydrocortisone may be beneficial in refractory hypotension with adrenal insufficiency.

5. Neonates with Congenital Heart Disease (CHD)

Management depends on the type of lesion:

- Obstructive lesions (e.g., coarctation, HLHS): Prostaglandin E1 to maintain ductal patency is essential. Inotropes like epinephrine may be required.
- Mixing lesions: Balance between systemic and pulmonary circulation is key. Milrinone can improve diastolic relaxation and reduce PVR.
- Volume-sensitive lesions: Use of inotropes that increase heart rate and contractility without significantly altering SVR is crucial.

Table 2 matches key functional echocardiography (fECHO) parameters with their clinical interpretations and the suggested inotropes based on the findings:

Table2: Functional Echocardiography Parameters and Corresponding Inotrope Choices in Neonatal Shock

fECHO Parameter	Clinical Interpretation	Suggested Inotropes	Comments
Low Left Ventricular Output (LVO)	Left ventricular systolic dysfunction	Dobutamine, Epinephrine	Dobutamine improves contractility without excessive vasoconstriction
Low Right Ventricular Output (RVO)	Right heart dysfunction (e.g., PPHN)	Milrinone, Dobutamine	Milrinone reduces PVR and improves RV function
Low Superior Vena Cava (SVC) Flow	Low systemic blood flow (esp. in preterms)	Dobutamine, Low-dose Dopamine	SVC flow <40 mL/kg/min suggests risk of IVH

fECHO Parameter	Clinical Interpretation	Suggested Inotropes	Comments
Low Fractional Shortening (FS)	Global systolic dysfunction	Dobutamine, Epinephrine	Use epinephrine if hypotension is severe
Increased E/A or E/E' Ratios	Diastolic dysfunction or impaired relaxation	Milrinone, Levosimendan	Both improve lusitropy; milrinone preferred in PPHN
Increased Pulmonary Artery Pressure (TR jet velocity >40 mmHg)	Pulmonary hypertension	Milrinone, Dobutamine, ± Vasopressin	Avoid dopamine at high doses due to increased PVR
Duct-dependent systemic circulation (e.g., HLHS)	Need to maintain ductal flow	Prostaglandin E1, ± Epinephrine	Avoid high SVR; balance systemic/ pulmonary circulation
Duct-dependent pulmonary circulation (e.g., pulmonary atresia)	Pulmonary blood flow depends on PDA	Prostaglandin E1, ± Milrinone	Milrinone may help lower PVR
Significant PDA with systemic steal	Volume overload with diastolic run-off	Vasopressors (e.g., Norepinephrine), ± PDA closure	Increase SVR to reduce left-to-right shunt
Normal contractility with low BP	Vasodilatory/distributive shock	Dopamine, Norepinephrine, Vasopressin	Use vasopressors to restore tone

Monitoring and Titration of Inotropes

Frequent monitoring of perfusion parameters is crucial:

- Heart rate, BP, lactate, capillary refill
- Functional echocardiography (e.g., LVO, SVC flow)
- Near-infrared spectroscopy (NIRS) to assess regional oxygenation
- Adjust dosing based on dynamic assessments rather than static thresholds.

CONCLUSIONS

Inotropes are indispensable in the management of neonatal shock but require a nuanced understanding of the pathophysiology, pharmacology, and clinical setting. A tailored, physiology-guided approach using bedside functional echocardiography and perfusion indices is essential to optimize outcomes.

Disclaimer:The authors used ChatGPT (OpenAI GPT5,2025) to assist with language refinement, formatting of tables, and generation of draft outlines. All content was reviewed, verified, and edited by the authors for accuracy and appropriateness.

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Neurological assessment of a Neonate

Author
Dr Nidhi Gupta
Senior Consultant
Department of Neonatalogy
Amrita Hospital, Faridabad

INTRODUCTION

The neurological examination of the newborn constitutes an indispensable component of neonatal clinical evaluation, offering critical information regarding the integrity, maturity, and functional status of the central and peripheral nervous systems. In contrast to older children and adults, the assessment in this age group necessitates a nuanced approach that accounts for gestational age, perinatal events, and the rapid, ongoing processes of neurodevelopment.

Systematic evaluation of posture, muscle tone, primitive reflexes, spontaneous activity, and responsiveness provides valuable insights for the early recognition of neurological dysfunction, facilitates prognostication, and informs the need for timely intervention. Furthermore, a structured neurological assessment enhances the overall quality of neonatal care by serving both diagnostic and longitudinal monitoring purposes within the clinical and developmental continuum.

NEUROLOGICAL EXAMINATION OF A NEONATE

Indications of neurological assessment in a neonate

- Evaluate cerebral function
- Prognostication: HIE, Neonatal enceph-alopathy
- At discharge, in a high risk neonate

1. When should it be done

- The examination should ideally be done two-thirds of way in-between feeds when the infant is more likely to be in an optimal state
- Serial examinations are a better guide
- Preferably in Prechtl state 3 or 4

2. Prerequisite

- Estimation of Gestational age: as presentation may vary with maturation
- Head in midline

3. Sequence of examination

- Observation
- Higher Mental functions- Level of Alertness
- Cranial Nerves
- Posture
- Tone assessment (Active and Passive)
- Reflexes (Superficial, Deep and Primitive)
- Head and Spine

1.1 Observation

Most important step in a neurological examination

- Best done in quiet alert state
- Ideal position: supine, unclothed in warm room with head in midline with no boundaries /rolls
- Adequate Lighting but not excess
- Points to observe
- Behavioural state
- Level of alertness
- Any Dysmorphism
- Any facial asymmetry /symmetry of eye movements
- Resting posture /symmetry of limb movements
- Any skin lesions

1.2 Higher Mental Function

1.2.1 Alertness

Most sensitive marker of the integrity of neonate's higher brain function.

Gestational age and time of last feed etc /recent procedure /environmental stimuli may influence it, for example in an extreme preterm/very preterm (28-32 weeks) tend to sleep most of the time and wakefulness increases with maturation. We can elicit arousal by gentle tactile stimulation **(Table I).**

Table I: Level of Alertness in the Neonatal Period

Level of alertness	Appearance of infant	Arousal response	Motor responses
Normal	Awake	Normal	Normal
Stupor			
Slight	"sleepy"	Slightly diminished	Slightly diminished
Moderate	asleep	Moderately diminished	Moderately diminished
Deep	Asleep	Absent	Markedly diminished
Coma	Asleep	Absent	absent
Source : Volpe's Neurology of the Newborn, 7th edition			

1.2.2 Behavioural state of a Newborn

This refers to the alertness state of baby. There are two different classification systems exist.

- Brazelton-(**Table II)**
- Prechtl states of assessment

Table II: Behavioural States of a newborn (Brazelton)

State	State	Eyes	Respiration	Movements
1	Deep sleep	closed	Regular	No gross movements, startles /sucking +-
2	Light sleep	Closed (Rapid eye movements +-)	Irregular	No gross movements Somebody/face movements +-
3	Drowsy (Transitional state)	Open and close	Regular	Gentle smooth movements No gross movements
4	Quiet alert	Open	Regular	Calm, minimal activity Visual and auditory can be tested best
5	Active alert	Open	Irregular	Some more movement, Fussing
6	Crying	Maybe closed	Irregular	Lot more movement /Grimace

- Prechtl states are similar just that there are 5 states

1.2.3 Habituation

Decremental response to incremental stimuli

- Auditory
- Visual

10 presentations maximum with 5 seconds interval from the end of first response

Visual: Soft light (at the frequency of approximately 1/sec): response maybe blinking, general motor activity and change in respiration

Blinking response /baseline response reduces after 3-5 presentations

Auditory: Soft sound similarly with an egg shaped rattle/bell

1.2.4 Consolability

Measured in an upset state after the infant has been crying for 15 seconds.

Consolability is demonstrated when baby quietens for atleast 5 seconds.

- Not consolable
- Pacifier/finger to suck alongwith dressing, holding and rocking
- Dressing, Holding in arms and rocking
- Holding and rocking

- Picking up and holding
- Hand on belly and restraining one or both arms
- Hand on belly
- Examiner's voice and face
- Examiner's face alone

It can be simplified as spontaneous, to voice, hand on abdomen, being picked up and not consolable

1.2.5 Cuddliness

Measure of infant's response to being held in a cuddled position against examiner's chest /up on his shoulder. Infant normally would mould into arms and clings to the examiner.

1.2.6 Cry

Strong/weak/irritable etc.

1.3 Cranial Nerve Examination in a Newborn (Table III)

Table III: Cranial Nerve Examination in a Newborn

Nerve	Type	Testing
I Olfactory	Sensory	rarely tested in neonates Maternal Colostrum maybe used Grimacing/startle maybe seen
II Optic	Sensory	Response to light Fixation (32-34 weeks) and following (30 cm away) Fundoscopy Visual acuity, Colour perception and visual discrimination
III Oculomotor	Mainly Motor	III, IV,VI Cranial Nerves together Extraocular movements /Doll's eye movement Pupillary size and reaction (III)
IV Trochlear	Motor	
V Trigeminal	Mixed	Rooting and sucking Facial sensation
VI Abducens	Motor	
VII Facial	Mixed	Facial symmetry nasolabial folds, angle of mouth, sucking
VIII Auditory	Sensory	Auditory Orientation and discrimination Startle/blink Later on: changes in RR/HR etc
IX Glosspharyngeal	Mixed	Pooling of secretions, swallowing
X Vagus		Gag reflex (during suction)
XI Spinal Accessory	Motor	Tautness of SCM- not really tested in neonates
XII Hypoglossal	Motor	Tongue Size/asymmetry/Fasciculations (can assess by infant's sucking on examiner's finger -stripping action)
Suck -5,7 and 12 Swallowing -9 and 10 Taste-7,9		

1.4 Motor Examination

- Quality, quantity and symmetry: see Prechtl movements
- Passive Tone
- Active Tone
- Reflexes
- Primitive reflexes

1.4.1 Posture and Tone (Table IV and Table V)

Resting posture of the baby is noted with respect to upper limbs/lower limbs/hips etc whether flexed/extended/abducted respectively. Any undue rotation/extension is noted.

Passive tone: It is resistance of the limbs to passive movements. Neonate remains at rest while movements are carried out.

Active tone: assesses resistance of axial muscles when neonate is in active state

A caudocephalic progression of Passive tone especially flexor tone with maturation has been described.

- 28 weeks: minimally flexed UL and LL
- 32 weeks: distinct flexor tone in lower limbs (LL) at knees and hips
- 36 weeks: flexor tone prominent LL and flexion at elbows (UL)
- Term: strong flexor tone all limbs (UL and LL)

When an infant grows, tone progression is in reverse direction to previously i.e. it progresses in a cephalocaudal (head to toe) and proximal to distal direction.

Table IV: Examination of active and passive tone in all limbs and head & neck

Upper Limbs	
Passive tone	Scarf sign, Arm recoil, Square window, Arm traction
Lower Limbs	
Passive tone	Leg recoil, All Angles-Popliteal etc., Leg traction
Axial	
Active tone	Pull to sit, flexor and extensor tone, Ventral suspension

Table V: Gestation -wise progression of Passive tone

Gestation -wise progression of Passive tone (based on Amiel Tison)				
	Popliteal angle	Adductor angle	Ankle Dorsiflexion	Scarf sign
28 weeks	150 degrees	130-140	60-70	Elbow reaches opposite axilla (till <34 weeks)
30 weeks	110-120			
32 -34 weeks	100-110		40-50	
36-40 weeks	80-100	40-80	20-30	Elbow just crosses midline 36-38 weeks 40 weeks-does not cross midline
Square window- decreases from around 90 degrees in extreme preterm to around 0 degrees at term Heel to ear: reaches ear in extreme preterm, then umbilicus around 30-32 weeks and then just the femoral crease by term				

1.4.2 Reflexes

Deep tendon Reflexes

Knee jerk is the easiest to elicit. Any tendon reflex is best elicited by tapping examiner's finger placed over the tendon. In a neonate, it's usually associated with a crossed adductor response (adduction of the opposite thigh).

Ankle clonus of 5-10 beats in the first few months (<3 months) is considered normal in a neonate provided its symmetrical.

Primitive reflexes –(Table VI)

- Moro's
- Palmar
- Tonic Neck Response

Placing and Stepping

Table VI: Progression of primitive reflexes

Neonatal Reflex	Onset	Well established	Disappears
Moro's	28-32 weeks	37 weeks	6 months
Palmar	28 weeks	32 weeks	2-3 months
Tonic neck response	35 weeks	1 month	6 months
Source : Volpe's Neurology of the Newborn, 7th edition			

1.5 Head and Spine

- Size
- Shape
- Sutures
- Fontanelle
- Spine
- Transillumination

2 Different structured neurological examinations for a neonate

- Hammersmith Neonatal Neurological Examination (HNNE)
- Amiel Tison Neurological assessment at term (ATNAT)
- Neurobehavioural assessment of a Preterm Infant (NAPI)
- Prechtl's assessment of GM
- Newborn behavioural observation (NBO)
- Newborn behavioural assessement Scale (NBAS)
- Test of Infant Motor Performance (TIMP)
- Assessment of a preterm infant's behaviour (APIB)

The Dubowitz exam now revised as Hammersmith Neonatal Neurological examination (HNNE) consists of 34 items organised into six groups: tone, tone patterns, reflexes, movements, abnormal signs and behaviours. These are illustrated on a standardised proforma and responses are accordingly given a raw score, sum of which is added up to generate an Optimality score.

Items

- Tone and Posture
- Tone pattern
- Reflex items
- Movements
- Abnormal signs
- Behavioural Signs, Vision and hearing

3. Prechtl assessment of General Movements

What are General movements?

These movements are named after Professor Heinz Prechtl who first described them.

Whilst Normal neurological examination entails assessment of tone, reflexes in response to a stimuli in general, this assessment involves simply observation of spontaneously generated movements. These are said to be generated from Central Pattern Generators (CPGs) and occur without an external stimulus. These movements are present from fetal life as early as 9-10 weeks upto 5-6 months post term age. Movements presenting this early include startles, isolated limb

movements, twitches, yawns and breathing movements.

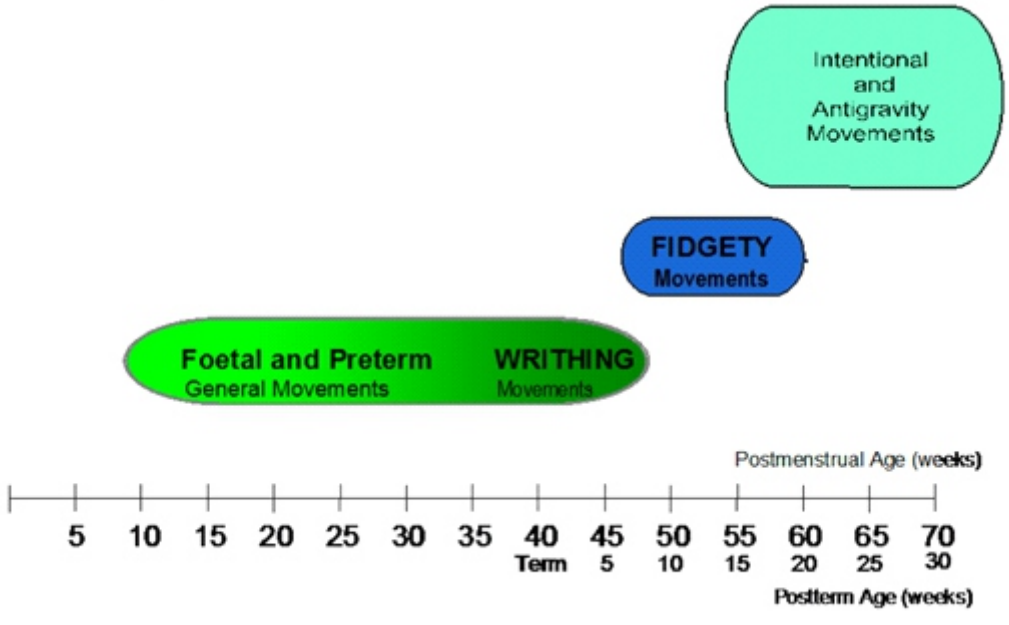
In general, they wax and wane in intensity, force and speed and involve a variable sequence of arm, leg, neck and trunk movements. Rotations along the axis of trunk and limbs gives them complexity and adds to variability.

Before 5 months of corrected age, Prechtl assessment is the most sensitive tool for detection of Cerebral Palsy (98% sensitivity) followed by Hammersmith Infant Neurological Examination (90% sensitivity) and term-age Magnetic resonance imaging (86-89%).

3.1 Types of General Movements [What is normal]- Table VII

Table VII: Age wise characteristic of GM

Type of GM	Time period in PMA	Characteristics
Preterm GM	+-28 to 36 -38 weeks	Similar to fetal movements, large amplitude and fast speed, pelvic tilt and trunk rotations
Writhing GM	36-38 to 46-52 weeks	Slower than Preterm GMs, elliptical, slow to moderate speed
Fidgety GM (FM)	46-52 to 54-58 weeks (till about 20 weeks post Term)	Small amplitude, moderate speed, variable acceleration of neck, trunk and limbs. These may be associated with other movements like manipulation of fingers, swipes, manipulation of clothes, lifting legs +- hand to knee.



Abnormal GMs include

- Poor Repertoire (PR): sequence is monotonous and repetitive, lacking complexity.

  These may be followed by normal, absent or abnormal Fidgety movements and have a low predictive value.

- Cramped Synchronized GMs (CS): Simultaneous contraction/relaxation of limbs. This pattern is highly predictive of Spastic CP. Persistent pattern of these movements is invariably associated with CP.
- Chaotic GMs: rare and as the name suggests

chaotic with no fluency or smoothness

- Absent Fidgety (F-): If usually occurring FMs are not observed during 9-20 weeks post term
- Abnormal Fidgety (AF): exaggerated FMs in amplitude, speed and jerkiness

4 Summary -evaluate

- Higher mental functions and Cranial Nerves
- Tone and Tone Pattern- Upper, lower limbs and Head & neck age appropriate
- Reflexes- DTR and Primitive mainly
- Movements- GM
- Abnormal signs
- Behaviour/auditory/vision

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High frequency ventilation in Neonates

Author
Dr Anita Singh
MD (Pediatrics), DNB (Neonatology)
Additional Professor
Department of Neonatology
Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow

INTRODUCTION

The basic concept of HFV lies in delivery of small tidal volume sometimes even smaller than anatomical dead space at very high rate (120-1200 breaths/minute). This may lead to advantage of reduced ventilation induced lung injury along with adequate gas exchange as compared to conventional ventilation. Results from clinical trials comparing HFV and conventional ventilation have shown mixed results. Despite this fact HFV is used by its proponents both as primary and rescue mode.

MECHANISM OF HIGH FREQUENCY VENTILATION

Several mechanisms have been proposed for mechanism of gas exchange in HFV. In conventional ventilation there occurs bulk convection that is during inspiration certain amount of as is delivered in the airways and comes out during expiration. Gas exchange occurs at alveolar level. Minute ventilation (MV) is product of tidal volume (TV) and number of ventilatory breaths (MV=TV x rate). Tidal volume during mechanical ventilation is usually 4-6 ml/kg. During mechanical ventilation amount of gas left in proximal airways do not contribute to gas exchange which is anatomical dead space and is usually 2 ml/kg.

During HFV tidal volume delivery per breath is very small (2-2.5 ml/kg) which are closer to anatomical dead space. So there occurs no bulk flow and little amount of gas is propelled in airways. Instead of bulk convection fresh gases are delivered in proximal airways and mixing of fresh and exhaled gases occurs by molecular diffusion. Following mechanism are responsible for gas exchange during HFV **(Figure 1)**.[1]

1. Molecular diffusion
2. Taylor dispersion
3. Deformation of gas flow profiles at bifurcations
4. Intraalveolar Pendelluft effect
5. Bulk convection
6. Cardiogenic mixing
7. Collateral ventilation

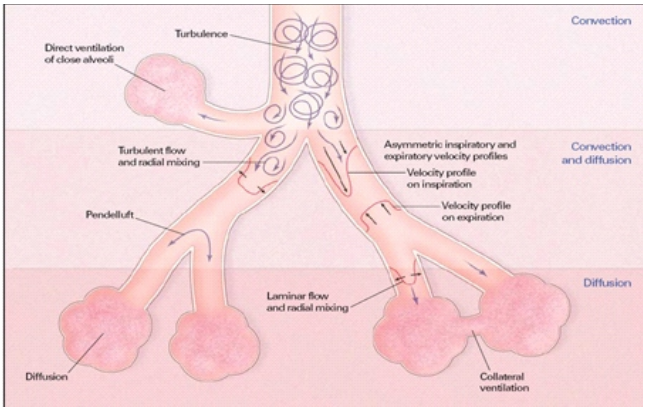

Fig.1 : Different mechanism of gas-transport during high-frequency oscillatory ventilation (HFOV).
N Engl J Med 2002;347:630–631.

- *Molecular diffusion:* This is the main mechanism of gas exchange during HFV. Diffusion of gases occurs in airways across osmotic gradient. Oxygen diffuses in and carbon dioxide diffuses out.
- *Taylor dispersion and turbulence:* During HFV gas flow occurs at rate of 20-30 liters/minute as opposed to flow rate of 6-8 liters/minute during conventional ventilation. At flow rate of 6-8 liters/minute during conventional ventilation gases move in airway with leading edge as plane in contrast to leading edge as bullet in HFV **(Figure 2).** Due to this along with faster longitudinal transport overall surface area for molecular diffusion increase.
- *Deformation of gas flow at bifurcations:* At the bifurcation of airways the high velocity gas profiles make secondary eddy currents in swirling motions. Though it impedes longitudinal transport but increases lateral mixing **(Figure 3).**
- *Intra-alveolar Pendelluft effect:* There are time constant (product of compliance and resistance)

inequalities and phase lag in between different lung regions. While some units are in filling phase while others are in emptying phase. Computational lung models have shown that in HFV interaction of flow between neighboring units results in distribution of fresh gases even to smallest units. This effect is known as pendelluft **(Figure 4).**

- *Bulk convection:* This mechanism is important in physiology of conventional ventilation where certain amount of gas is delivered in each breath in inspiration. Gas exchange occurs at alveolar level and during expiration gases are forced out by elastic recoil of lung. This mechanism does not contribute much to gas exchange during HFV but it contributes to gas exchange in proximal airway units.
- *Cardiogenic mixing:* Due to rhythmic contraction of heart, there occurs generation of flow within neighboring parenchymal regions. Cardiogenic mixing may account for up to half of oxygen uptake in totally apneic respiration.
- *Collateral ventilation:* Collateral ventilation occurring through non airway connection between neighboring airways is an additional method of gas transport both in conventional and HFV.

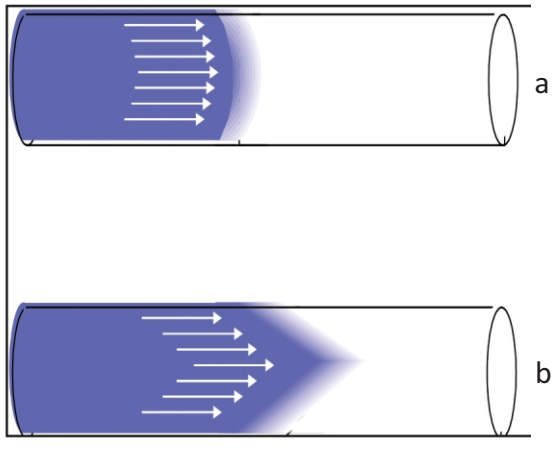

Fig. 2 a : Plane gas front of conventional ventilation at flow of 6-8 liters/minute
Fig. 2 b : Bullet shaped gas front of HFV at flow rate of 20-30 liters/minute

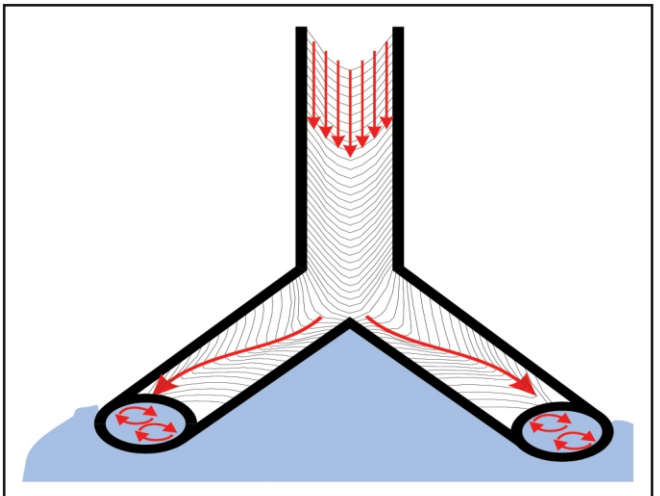

Fig.3 : Deformation of gas front at bifurcation and generation of secondary eddies.

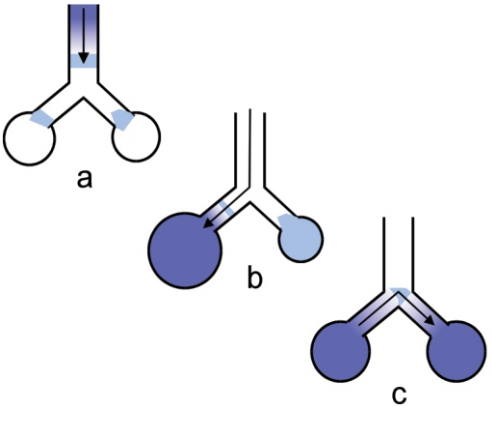

Fig. 4 : Intraalveolar pendelluft

The advantage of HFV over conventional ventilation is to use lower mean airway pressure, the ability to adequately and independently manage oxygenation and ventilation with tidal volume closer to dead space, and preservation of normal lung architecture even at high mean airway pressure.

CLASSIFICATION OF HIGH FREQUENCY VENTILATORS

Depending on mechanism of generation of high frequency breaths there are three types of high frequency ventilators.

1. ***High frequency oscillatory ventilators (HFOV):*** These ventilators produce vibration of gases in airways and lungs either via piston pumps (Dräeger Babylog 8000, Dräeger VN800, SLE 6000) or electromagnetically driven diaphragm

(SensorMedics 3100A). They usually operate at rates of 180 to 1500 breaths/minute (3-25 Hz). In HFOV inspiration and expiration both is active. Bulk flow is negligible while continuous flow of fresh gases rushes past the source and generates oscillations. Oscillations of airway gases provide tiny tidal volume. Frequency, percent inspiratory time, amplitude and mean airway pressure can be adjusted independently. Mean airway pressure is modulated by variation in bias flow rate and patient circuit outflow resistor control.

2. ***High frequency jet ventilators (HFJV):*** High frequency jet ventilators delivers short pulses of heated and humidified gases to upper airway through a separate narrow injector or directly into triple lumen endotracheal tube. In addition to gases delivered via jets the surrounding gases are pulled into airways by venture effect. Gases through injector jet generate servocontrolled peak inspiratory pressure. A conventional ventilator has to be used simultaneously with HFJV to generate peak end expiratory pressure. Exhalation is passive. HFJVs are efficient in carbon dioxide removal at low mean airway pressure like pulmonary interstitial emphysema. It is also safe and effective at the time of neonatal transport. They operate effectively at rates of 150-600 breaths/minute (2.5-10 Hz).

   Examples of HFJV is Bunnell Life Pulse jet ventilator.

3. ***High frequency flow interrupter (HFFI):*** These are also referred as high frequency flow interrupter. They are basically conventional ventilators adapted to work at very rapid rates. They are neither true oscillators nor true jets. These ventilators have microprocessor controlled pneumatic solenoid valves that alter inspiratory flow to achieve peak inspiratory pressure. These ventilators deliver inspiratory gases some distance away for trachea and endotracheal tube into ventilatory circuit, so are also referred as setback jets. Velocity of gas is also not as high as in HFJV. Exhalation is passive. These ventilators have been basically approved for air leaks. They mostly operate at ventilatory rate of 60-150 breaths/minute (1-2.5 Hz).

   Example of HFFI is Infant Star neonatal ventilator.

Table 1 gives information about different mechanism of HFV. The information about various high frequency ventilators is given in Table 2.

Table 1: Different types of high frequency ventilation

Feature	HFOV (High Frequency Oscillatory Ventilation)	HFJV (High Frequency Jet Ventilation)	HFFI (High Frequency Flow Interruption)
Mechanism	Oscillates gas around a set mean airway pressure using a piston, diaphragm, or vibrating membrane	Pulses of high-pressure gas jets delivered via injector catheter into Endotracheal tube	Rapidly interrupts continuous gas flow using valves/shutters
Exhalation	Active	Passive	Passive
Tidal Volume	Smaller than dead space; both inhalation & exhalation forced	Very small, injected jet volumes	Very small, delivered in interrupted bursts
Gas Exchange	Excellent CO_2 removal and oxygenation control via MAP	Good CO_2 elimination; oxygenation depends on MAP from conventional ventilator	Moderate gas exchange efficiency; less effective than HFOV/HFJV
Mean Airway Pressure (MAP) control	Directly set on ventilator	Provided by separate conventional ventilator	Can be modulated by duty cycle of flow interruption
Need for conventional Ventilation	No — HFOV can be stand-alone or integrated	Yes — requires conventional ventilator for PEEP and background breaths	Sometimes combined with conventional modes

CHARACTERISTIC PARAMETERS IN HIGH FREQUENCY VENTILATION

The main parameters to be set in high frequency ventilators are Mean airway pressure (MAP), Frequency and amplitude **(Figure 5)**.

1. *MAP*- Mean airway pressure is average pressure maintained in the airway throughout the respiratory cycle. MAP is set either through a committed knob or through PEEP knob in different high frequency ventilators. MAP is usually set as either same or 2-3 cm above to level on which baby was maintaining on conventional ventilation. Optimum MAP should recruit the lung by opening up atelectatic alveoli and should not result in overinflation. It is assessed by Chest X-ray (right dome of diaphragm at 8-9 posterior ribs) which has to be done within 30-45 minutes of putting the baby on ventilator. During HFV, in few IMV breaths of higher peak inspiratory pressure and longer inspiratory time can be added which are called as sigh breaths. They are mainly helpful in re-recruitment of lung post suction and during weaning.
2. *Frequency (f)*-The unit of frequency in HFV is hertz (1 hertz-1 cycle/second or 60 cycles/minute). The frequency also determines oscilla-

Table 2: Comparative Table of High Frequency Ventilators

Device / Model	Mechanism (HFV type)	Exhalation type	Conventional ventilation available?	Volume measurement details
SensorMedics 3100A/B (CareFusion / Vyaire)	HFOV with piston pump oscillator	Active	No (stand-alone HFOV only)	No
Dräger Babylog VN800	HFOV via diaphragm oscillator	Active	Yes	Yes
SLE6000 / SLE6000H	HFOV using valveless high-speed bidirectional jets	Active	Yes	Yes
Humming Vue (Metran, Japan)	HFOV with electromagnetic vibrating membrane oscillator	Active	Yes	Yes
Dragonfly (Inspira, USA — emerging)	Next-gen HFOV platform (digital, ultra-low tidal volume, advanced monitoring)	Active	Yes	Yes
Leoni Plus (Heinen + Löwenstein, Germany)	HFOV via membrane oscillator	Active	Yes	Yes
VDR-4 / Bronchotron (Percussionaire, USA)	High Frequency Percussive Ventilation (HFPV) using Phasitron device	Passive	Yes	No precise tidal volume monitoring; designed for portability rather than NICU precision
Bunnell LifePulse HFJV (USA)	High Frequency Jet Ventilation	Passive	Requires a separate conventional ventilator for PEEP and sigh breaths	No

tory volume and in HFV decrease in frequency results in increased removal of CO2. This paradoxical relationship can be explained by fact that minute ventilation in HFV is equal to $TV^{(1.5-2)} x f^{(0.5-1)}$. So once the frequency is lowered there is increase in inspiratory time and higher tidal volume is delivered resulting in higher elimination of carbon dioxide. Optimal frequency to be set usually varies between 5-15 Hz. A rough guide would be to start with 10-12 Hz in preterm babies and 8-10 Hz in term babies. Time constant is another parameter of lung mechanics which help in determining frequency. As respiratory distress syndrome is short time constant disease so frequency should be higher while meconium aspiration syndrome is long time constant disease so frequency should be lower.

3. *Amplitude/Power*- The amplitude of waveform oscillation in HFV is also an important determinant of tidal volume. It varies from 0-100%. It is clinically assessed with visible vibration of chest wall and should be set such that to achieve oscillations of chest wall and abdomen. It should be set approximately double of mean airway pressure. It is one of the major determinants of CO2 elimination. Final adjustment is to be done according to Pco2 in blood gas. In HFOV amplitude is set directly while in HFJV it is difference between independently adjusted PEEP and PIP.
4. *Inspiratory time*- Some HFV devices allow setting of percent inspiratory time to allow I: E ratio from 1:1 to 1:2.3 in HFOV, 1:6 in HFJV and 1:5 in HFFI.

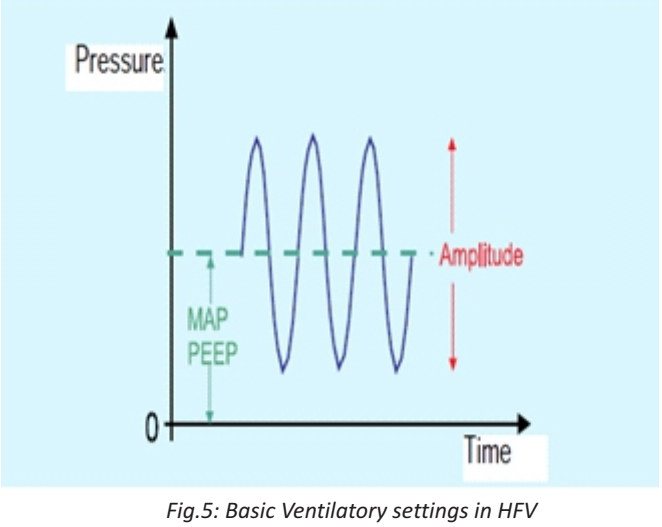

Fig.5: Basic Ventilatory settings in HFV

INDICATIONS OF HIGH FREQUENCY VENTILATION

Use of high frequency ventilation have been reported in virtually all the neonatal respiratory disorders varying from suboptimal lung recruitment (respiratory distress syndrome, meconium aspiration syndrome, pneumonia, air leaks, atelectasis) to pulmonary hypertension. Its use has also been reported in congenital diaphragmatic hernia, trachea-esophageal fistula, primary pulmonary hypertension and pulmonary hypoplasia syndromes.

In above mentioned disorders clinical trials have been done both as primary and rescue treatment. It is preferred mode of ventilation where there is restriction of chest movement due to abdominal distension as in necrotizing enterocolitis, pleural effusion (hydrops) and post-operated gastroschisis, omphalocele, or diaphragmatic hernia.

There is no objective evidence-based criteria to use high frequency ventilation as rescue treatment but most clinician will use once baby requires MAP of more than 25 cm of H2O and Fio2 of 0.4 to 0.6 to maintain oxygenation (Martin Keszler*, Neoreviews 2006)*.

INITIATION OF HIGH FREQUENCY VENTILATION

1. Assess the need of switching to HFV once baby meet above mentioned MAP and FiO_2 criteria to maintain oxygenation on conventional ventilation.
2. Switch to HFO mode when using ventilator having both conventional and HFO option, while in committed HFV baby has to be shifted.
3. Be familiar with controls of the ventilator to be used.
4. Assure proper heating and humidification of respiratory gases.
5. Set the flow to 20-30 liters/minute.
6. Set the MAP 2-3 cm above of that on conventional ventilation. Asses the adequacy of MAP by CXR which should be done within 30-45 minutes of starting of high frequency ventilation.
7. Set the amplitude and frequency and percent inspiratory time (not in all HFV).
8. Low rate IMV breaths (sigh breaths) can be added after suctioning or reintubation.

9. Adjust Fio2 to maintain SPo2 in target saturation range (90-94%).
10. A blood gas is to be done within 10-15 minutes of HFV initiation to adjust the settings and also to avoid sudden hypocapnia which can occur. If possible and available continuous Transcutaneous PCO2 monitoring should be done.
11. Sedation can be required and should be used intermittently and as needed.

VENTILATORY ADJUSTMENT DURING HIGH FREQUENCY VENTILATION

Once baby is put on HFV monitoring and further modulation of ventilatory settings is to be done to optimize recruitment, oxygenation and ventilation.

- *Hypoxemia with atelectasis/poor lung expansion on CXR*- Increase the mean airway pressure by 1-2 cm of H2O or add sigh breaths, the decrease after improvement.
- *Hypoxemia with lung overexpansion on CXR, ± hypercarbia*- Decrease MAP by 1-2 cm of H2O and then repeat CXR.
- *Hypercarbia with normal lung volumes on CXR*- Increase amplitude/power or decrease frequency
- *Hypocarbia*-Decrease amplitude/power or increase frequency
- *Hyperoxia*-Decrease FIO2 to 0.3- 0.4 or less, then MAP

WEANING FROM HFV

- Usually, babies are weaned to conventional ventilation from HFOV and then extubated, but they can also be extubated directly.
- Weaning should be attempted once babies are on FIO2 less than 0.6. Once oxygen requirement comes down to 0.6, MAP should be decreases slowly (1-2 cm at one time), while still maintaining optimal lung inflation and oxygenation.
- Simultaneously amplitude can be decreased by 30-50% in alternation with MAP if tolerated.
- Frequency is usually weaned at last.
- Monitoring of weaning needs to be done by frequent blood gas monitoring.
- Once baby is on MAP of 8-10 cm of H2O, Amplitude <50% and frequency of 10-12 Hz, a trial of switching to conventional ventilation can be given. Alternatively, IMV breaths can be added along with HFO and then gradually increased along with lowering of HFV settings before shifting to conventional ventilation.

USE OF HFV IN NEONATAL RESPIRATORY CONDITIONS

Several animal models had been done before 1980 which suggested efficacy of HFV in lowering ventilation induced lung injury and improving oxygenation. Human trials of HFV started in early 1980s and even after four decades the same results have not been reproduced consistently because of heterogeneity of studies due to variation in population, use of antenatal steroid/ surfactants, disease condition, type of HFV ventilation used, strategies of ventilation etc.

Respiratory distress syndrome

High frequency ventilation (HFV) has been widely studied in neonatal respiratory distress syndrome (RDS). Early trials in the pre-surfactant era showed no benefit and even increased risks such as intracranial hemorrhage, largely due to suboptimal ventilation strategies. With the introduction of surfactant therapy and lung-protective approaches, later studies demonstrated improved oxygenation and, in some cases, reduced chronic lung disease (CLD). However, large multicenter trials in the modern era using synchronized ventilation have produced mixed results, with some showing earlier extubation and modest pulmonary benefits, while others found no significant improvement compared to conventional ventilation. Recent systematic review concluded that Elective HFOV is superior to CMV in reducing the incidence of CLD or death in ventilated preterm infants administered surfactant, especially in the subgroup of >1 dose of surfactant. Optimal outcomes are more likely when HFV is used with appropriate lung recruitment and protective strategies.

Pulmonary Interstitial Emphysema

High Frequency Oscillatory Ventilation (HFOV) can be an effective rescue strategy in neonates with air leak syndromes (e.g., pulmonary interstitial emphysema, pneumothorax, bronchopleural fistula). The small tidal volumes and constant mean airway pressure in HFOV help minimize overdistension and reduce further air leak while maintaining adequate gas

exchange. Studies have shown that HFOV improves oxygenation and can reduce the progression of new air leaks, though it is less effective in resolving existing ones. HFOV is particularly useful for stabilizing gas exchange and preventing worsening of air leaks, but HFJV is often superior for treating established pulmonary interstitial emphysema. Mean airway and peak pressure should be low and it should be same as or lower to that on conventional ventilation.

Meconium aspiration syndrome

HFV can be useful rescue modality for meconium aspiration syndrome. Studies have shown have shown improved gas exchange and less damage in piglet and canine model in comparison to conventional ventilation respectively. Meconium aspiration syndrome is a heterogeneous disease and HFV may be effective, particularly in babies in whom the surfactant-inhibitory effect of meconium predominates and in the subsequent inflammatory stages of MAS.

Bronchopleural and Tracheoesophageal Fistula

As gas flow in HFV is more rapid, inspiratory gas tends to remain in the center of the airways, enabling it to penetrate more deeply into the lung and to bypass airway disruptions, such as bronchopleural or tracheoesophageal fistulas. Gonalzes et al, demonstrated reduced air leak through chest tubes in babies who have bronchopleural fistula when they were shifted from conventional to HFJV. Improved gas exchange and reduced flow through tracheoesophageal fistula was observed by Goldberg and Donn et al.

Abdominal Distention/Decreased Chest Wall Compliance

Improved gas exchange and better hemodynamic have been shown in animal models increased intra-abdominal pressure with HFJV. Fok and Keszler et al, have demonstrated improved ventilation and gas exchange in babies with conditions leading to increased intra-abdominal pressure who were failing on conventional ventilation.

Combined therapy

In a study by Kinsella et al, patients with severe lung disease and PPHN; combined treatment with HFV and inhaled nitric oxide was better than either therapy alone. It was probably due to better recruitment of lung leading to better delivery of nitric oxide.

Rescue of Babies needing Extracorporeal Membrane Oxygenation (ECMO)

In a multicenter RCT by Clark et al, babies who were potential candidate for ECMO were randomized to either best available conventional ventilation or HFOV. Fifty six percent of babies improved on HFOV in comparison to 40% on conventional ventilation. In a study by Paranka et al, 50% of the ECMO-eligible patients could be rescued with HFOV alone.

SAFETY OF HFV

1. *IVH/PVL*- Early trials, especially in the pre-surfactant era, reported increased risk of severe ICH and PVL, likely due to inexperience, low mean airway pressures, and suboptimal ventilation strategies. Modern protocols with lung-protective strategies, optimal mean airway pressure, and careful monitoring have not shown increased risk compared to conventional ventilation.
2. *Overinflation and air leaks*- Air leaks during HFV are generally linked to high frequencies or inappropriate I:E ratios. Overinflation and air trapping can create "choke points" in smaller airways during active exhalation, potentially leading to pulmonary interstitial emphysema (PIE). Early trials like the HiFi study and limited HFFI studies showed more frequent air leaks due to suboptimal lung-protective strategies. Modern HFOV and HFJV, when used appropriately, do not increase the risk of gross air leaks, and HFJV is particularly safe in this regard.
3. *Hemodynamics*- High mean airway pressures can reduce venous return, myocardial activity, and cardiac output. Intravascular volume should be optimized before and during HFV to maintain stability.
4. *Necrotizing tracheobronchitis*- A complication which was more frequently reported with initial use of HFV is now rare. was more common with HFJV due to high-velocity jets, poor humidification, and proximal airway trauma. Risk is influenced by ventilator settings, FiO_2, illness severity, ventilation duration, epithelial integrity, and infections.

KEY LEARNING POINTS

- High frequency ventilation is based on unique principles of very low tidal volume and high frequency

- High frequency oscillatory ventilation type is most widely studied in neonates.
- There are different types of high frequency ventilators are available.
- The ventilation parameters need to be optimized and one should be cautious about risk of hypocapnia.
- Rescue HFO is a reasonable option in babies with hypoxemic respiratory failure
- It is superior to conventional ventilation in case of air leaks
- At experienced centers, it may be beneficial than conventional ventilation in neonates with respiratory distress syndrome as primary modality.

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Understanding ROC Curves in Diagnostic Test Evaluation

Authors

1. Dr Kumari Gunjan

(DrNB Neonatology), Senior Consultant, Cloud-nine Hospital, Patparganj, New Delhi.

2. Dr Anup Thakur

(DrNB Neonatology), Asso. Prof and Senior Consultant, Sir Ganga Ram Hospital, New Delhi

INTRODUCTION

In the previous two editions, we delved into methods for assessing the validity of diagnostic tests, focusing on statistical metrics such as sensitivity, specificity, predictive values, and likelihood ratios. These measures are most appropriate for tests with binary outcomes, where both the test result and the gold standard are classified as either positive or negative. However, many diagnostic tools, including the measurement of C-reactive protein (CRP), generate continuous data—commonly expressed in units like mg/L. To interpret these results in clinical settings, a threshold value (e.g., 10 mg/L) is often set to categorize outcomes into “positive” or “negative.” The choice of this cut-off is crucial:

- A lower threshold increases sensitivity (detecting more true positives), but may also lead to a higher false positive rate, reducing specificity.
- A higher threshold enhances specificity (fewer false positives) but at the cost of decreased sensitivity, potentially missing true cases.

This interplay highlights the inherent trade-off between sensitivity and specificity—improving one often leads to a compromise in the other. To visualize and evaluate this trade-off across various thresholds, the Receiver Operating Characteristic (ROC) curve is employed. It plots sensitivity (true positive rate) against 1-specificity (false positive rate), providing a detailed view of a test's performance at multiple decision points. Clinicians and researchers rely on the ROC curve not only to determine the most appropriate threshold but also to compare the diagnostic accuracy of different tests. As such, ROC analysis serves as a critical tool in optimizing decision-making in diagnostic medicine.

COMPONENTS OF ROC CURVE

Figure 1 illustrates the fundamental components of an ROC curve. The horizontal axis (AD) represents the false-positive rate, calculated as 1 minus specificity, while the vertical axis (AB) indicates the true-positive rate, or sensitivity. Both axes span a range from 0 to 1. The diagonal line from point A to point C is commonly referred to as the "line of no discrimination" or the line of random chance. This line signifies that the diagnostic test performs no better than random guessing in distinguishing between individuals with and without the disease.

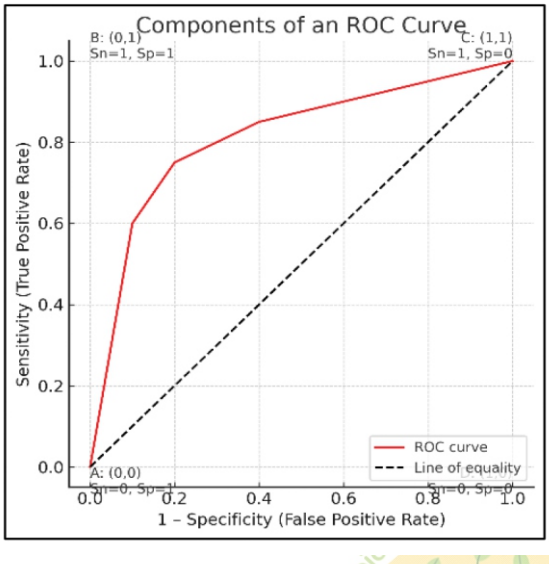

Fig. 1. Components of an ROC curve

Sn: Sensitivity Sp: Specificity

The specific coordinates corresponding to various points along the ROC curve are detailed in Table 1.

Table 1. Coordinates of different points of an ROC curve

	Sensitivity	Specificity
A	0	100
B	100	100
C	100	0
D	0	0

HOW TO DRAW AN ROC CURVE

An ROC curve is a graphical representation that plots the false-positive rate (1 – specificity) on the X-axis against the true-positive rate (sensitivity) on the Y-axis. To illustrate this concept, consider the use of C-reactive protein (CRP) as a diagnostic marker for culture-confirmed sepsis. In a study involving 200 individuals with suspected sepsis, quantitative CRP levels were measured. A CRP value exceeding 10 mg/L was categorized as a positive result. A summary of these findings is provided in a partial Excel dataset (see Fig. 2), and the corresponding cross-tabulation is presented in Table 2. From this 2×2 table, both sensitivity and specificity values can be computed.

Figure 2

Sno	CRP	Blood Culture
1.0	67.07	1.0
2.0	46.28	1.0
3.0	49.08	1.0
4.0	45.04	1.0
5.0	46.51	1.0
6.0	36.81	1.0
7.0	31.52	1.0
8.0	46.06	1.0
9.0	19.82	1.0
10.0	47.4	1.0
.	.	.
.	.	.
.	.	.
191.0	8.82	0.0
192.0	11.01	0.0
193.0	18.77	0.0
194.0	11.14	0.0
195.0	14.83	0.0
196.0	18.44	0.0
197.0	15.41	0.0
198.0	12.92	0.0
199.0	15.27	0.0
200.0	4.42	0.0

Table 2: Cross tabulation of data as shown in figure 2. The cut off used for CRP is 10 mg/dl

	Blood culture positive	Blood culture negative	Total
CRP POSITIVE	30	70	100
CRP NEGATIVE	10	90	100
Total	40	160	200

Table 3: Sensitivity, specificity and false-positive rate (1 – specificity) at each cut-off of CRP

Cut off value	Sensitivity	Specificity	1-specificity
10	0.75	0.56	0.44
20	0.65	0.76	0.24
30	0.50	0.90	0.10
40	0.30	0.97	0.03

By adjusting the CRP threshold to higher values such as 20, 30, or 40 mg/L, alternative sensitivity and specificity metrics can be derived (as outlined in Table 3). These sets of values corresponding to different cut-offs serve as the foundation for plotting the ROC curve (Fig. 3). Additionally, statistical software can be employed to generate this curve. For example, Fig. 4 displays the ROC curve produced using SPSS version 17.0 based on the dataset presented in Fig. 2.

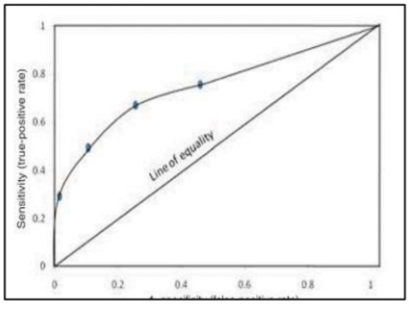

Fig. 3. ROC curve based on data in Table 3

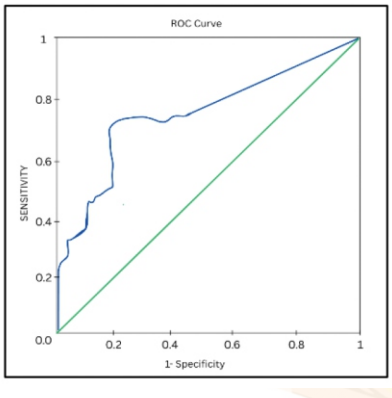

Fig. 4: ROC curve based on data in figure 2 as obtained from SPSS

INTERPRETING THE ROC CURVE

A Receiver Operating Characteristic (ROC) curve provides a comprehensive view of how a diagnostic test performs across all possible threshold values by plotting sensitivity against the false positive rate (1 – specificity). To evaluate the overall effectiveness of the test, the area under the ROC curve (AUC) is calculated. Statistical tools such as SPSS not only determine the AUC but also report its statistical significance (p-value) and the 95% confidence interval (CI).

For example, Table 4 presents the ROC analysis for CRP levels, yielding an AUC of 0.755 and a p-value of 0.000. This AUC value reflects the test's overall diagnostic capability.

Table 4: SPSS output for the ROC curve in figure 4

Area	Standard error	Asymptotic significance	Asymptotic 95% confidence interval
			Lower bound: 0.658
0.755	0.049	0.000	Upper bound: 0.852

An AUC of 1.0 indicates a flawless test with perfect sensitivity and specificity—graphically represented by a curve that touches the top-left corner of the ROC plot. However, such perfection is rarely seen in clinical settings.

The closer the AUC is to 1.0, the higher the test's accuracy. In contrast, an AUC nearing 0.5 suggests poor diagnostic ability, equivalent to random chance, and is represented by the diagonal line on the ROC graph. An AUC less than 0.5 may misleadingly imply that the test identifies healthy individuals better than diseased ones. In most cases, this indicates that the classification is reversed, with healthy subjects mistakenly identified as having the disease.

Optimal cut off threshold for a diagnostic test:

The optimal cut-off threshold for a diagnostic test from a ROC (Receiver Operating Characteristic) curve is the point that best balances sensitivity (true positive rate) and specificity (true negative rate). This threshold is used to distinguish between diseased and non-diseased individuals as accurately as possible.

Methods to Determine the Optimal Cut-off:

1. Youden's Index (J)

- **Formula:** $J = \text{Sensitivity} + \text{Specificity} - 1$
- The cut-off point that maximizes **Youden's index** is often considered the optimal threshold.
- **Why it's useful:** It identifies the point on the ROC curve farthest from the diagonal (line of equality), representing the best trade-off between sensitivity and specificity.

2. Closest Point to (0,1)

- This method selects the point on the ROC curve **closest to the top-left corner**, where sensitivity = 1 and 1-specificity = 0.
- **Distance formula:** $d = (1 - \text{Sensitivity})^2 + (1 - \text{Specificity})^2$
- The cut-off with the smallest distance (d) is considered optimal.

Let's determine the optimal cut-off value for CRP using the data provided in Table 3.

Table 5: Evaluation of diagnostic test performance at various cut off levels using sensitivity, specificity, Youden's Index, and Distance to the Optimal ROC Point (Optimal cut-off by Youden's Index and by Closest Point (0,1) is 20 mg/ l)

Cut off (mg/l)	Sensitivity (Sn)	Specificity (Sp)	Youden's index J= sensitivity + specificity -1	Closest distance to (0,1) $d = (1\text{-}Sn)^2 + (1\text{-}Sp)^2$
10	0.75	0.56	0.31	0.496
20	0.65	0.76	0.41 (maximum)	0.412 (minimum)
30	0.50	0.90	0.40	0.500
40	0.30	0.97	0.27	0.702

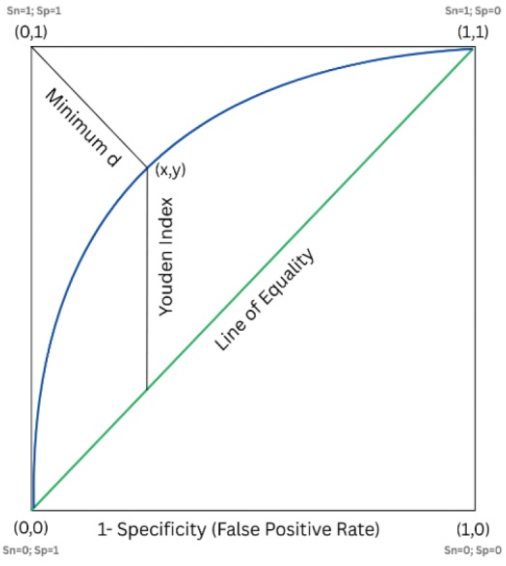

Fig. 5: A hypothetical ROC (Receiver Operating Characteristic) curve illustrating the calculation of the Youden Index (J) and the concept of the closest distance to the top-left corner of the graph, representing the optimal cut-off threshold for a diagnostic test.

Comparing performance of more than one diagnostic tests

We created a set of hypothetical data to compare the diagnostic accuracy of three different tests—A, B, and C—for detecting tuberculosis. After analyzing the data using ROC curve analysis, it was found that Test A had the highest area under the curve (AUC) of 0.955, indicating superior overall diagnostic performance.

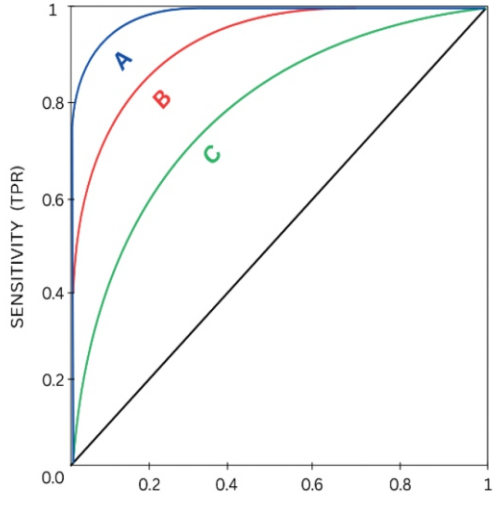

Fig. 6: ROC curves illustrating diagnostic accuracy of three tests (A, B, and C) with varying performance levels.

However, it's important to note that two diagnostic tests can have the same AUC and still differ in their effectiveness at various thresholds. For example, if Tests A and B have identical AUCs, their ROC curves might still cross each other, suggesting that while their overall accuracy is the same, each test may perform better in different sensitivity or specificity ranges.

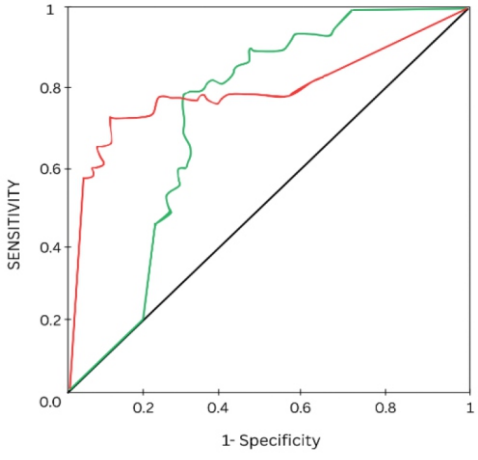

Fig. 7: Two ROC curve with same AUC

Test A might outperform Test B when a lower false positive rate is crucial—meaning it's more reliable when we need higher specificity. Conversely, Test Y could be more effective when higher sensitivity is needed, such as in situations where missing a diagnosis would have severe consequences. For instance, in the context of a contagious disease like tuberculosis, where early detection is critical to prevent outbreaks, a test like Y that has high sensitivity would be ideal for initial screening. However, if treatment involves potentially harmful medication, a more specific test like X should be used to confirm the diagnosis before initiating therapy. This approach ensures both efficient case detection and patient safety.

SUMMARY

To summarise, an ROC (Receiver Operating Characteristic) curve is a visual tool used to assess the performance of a diagnostic test that produces results on a continuous scale. The curve helps determine the most suitable threshold value depending on whether the test is intended for screening or confirmation. The area under the curve (AUC) reflects the test's overall accuracy—higher AUC values, closer to 1, indicate better diagnostic performance. Additionally, AUC can

be used to compare the effectiveness of two diagnostic tests.

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Bladder Exstrophy in a Newborn: Surgical and Postoperative Insights

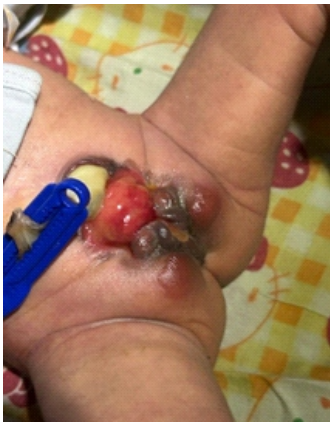
Authors

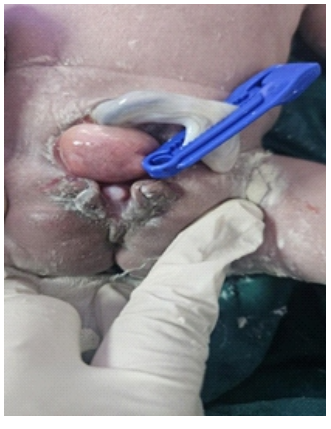
Dr Jai Krishan Mittal[1], Dr Gunjana Kumar[2], Dr Souradip Banik[3]

[1]Professor and HOD, Department of Neonatology, National Institute of Medical Science and Research Hospital, Nims University Rajasthan, Jaipur, India.

[2]Associate Professor, Department of Neonatology, National Institute of Medical Science and Research Hospital, Nims University Rajasthan, Jaipur, India.

[3] Second Year DM resident, Department of Neonatology, National Institute of Medical Science and Research Hospital, Nims University Rajasthan, Jaipur, India.





A female term neonate, born via vaginal delivery at 38 weeks' gestation with a birth weight of 2380 grams, was referred to our centre on day 2 of life with a diagnosis of classic bladder exstrophy. The baby had a typical low-set umbilicus, exposed bladder plate, and anteriorly placed anus. Antenatal scans had missed the anomaly. Initial stabilisation was done using a polythene wrap over the exposed bladder, with sterile precautions. Multidisciplinary counselling was provided. Surgical repair, including bladder neck reconstruction and genitoplasty, was performed on day 6 of life. Postoperatively, the baby required short-term ventilatory support and gradually transitioned to full enteral feeds. As the baby had a fever episode on post-operative day 2, urine culture was sent, which showed growth of multidrug-resistant *Klebsiella pneumoniae*, which was managed with colistin**,** guided by sensitivity. Kidney function test was monitored throughout the stay, and was normal; also, there were no issues related to urinary retention. The baby was discharged on day 36 of life with stable vitals, full feeds, and good weight gain. Follow-up includes growth and neurodevelopmental surveillance and urological review.

DISCUSSION:

Bladder exstrophy is a rare, complex congenital anomaly that affects the urinary bladder, abdominal wall, bony pelvis, external genitalia, and often the gastrointestinal and musculoskeletal systems, with an incidence of 3–5 per 100,000 live births. It arises due to a developmental defect in the closure of the lower abdominal wall and anterior bladder**,** typically due to failure of mesodermal migration and cloacal membrane disruption during the 4th to 6th week of gestation.

The classic features include:

- Low-set umbilicus
- Open bladder plate on abdominal wall
- Epispadias
- Anteriorly displaced anus
- Widened pubic symphysis

This condition has lifelong implications and necessitates a **structured, multidisciplinary approach** from birth through adulthood.

Initial Management

- Cover the exposed bladder with non-adherent material
- Avoid trauma and infection
- Early surgical planning within 72 hours is

preferred

Surgical Options

1. Complete Primary Repair (CPRBE): Single-stage repair of bladder and epispadias.
2. Modern Staged Repair (MSRBE): Involves staged bladder closure, epispadias repair, and bladder neck reconstruction.
3. Urinary Diversion: In rare, complex cases.

Long-Term Complications

Even with early surgical repair, children with bladder exstrophy are at risk for multiple long-term complications, including:

- Urinary Incontinence
- Recurrent UTIs: leading to renal scarring and dysfunction.
- Upper Tract Damage: Poor bladder compliance, high voiding pressures, or obstruction can lead to hydronephrosis and progressive kidney injury.
- Genital Dysfunction: Males often have shortened penis and chordee, while females may have bifid clitoris and short vaginal length.
- Orthopaedic Issues: Diastasis of pubic symphysis and pelvic malrotation can contribute to abnormal gait and hip dysplasia.
- Psychosocial Impact: Visible genital anomalies, urinary leakage, and repeated procedures can lead to emotional distress, anxiety, and low self-esteem, especially during adolescence.
- Need for Reconstructive Surgeries: Many children require multiple staged surgeries to achieve continence, genital cosmesis, and functional bladder capacity.
- Risk of Malignancy: Although rare, long-term exposure of the bladder mucosa to environmental irritants and chronic inflammation may increase the risk of bladder adenocarcinoma in adulthood.

Follow-Up and Longitudinal Care

Given these potential complications, lifelong surveillance is mandatory. The goals of follow-up include:

- Monitoring renal function (serum creatinine, eGFR)
- Screening and treating UTIs
- Assessing bladder capacity, compliance, and continence
- Evaluating growth and development, including sexual maturation
- Providing psychosocial support through adolescence and transition to adult care

Surveillance Imaging:

- Periodic renal ultrasound
- Urodynamic studies in older children to assess bladder function
- MRI pelvis, if needed for surgical planning or complex anatomy

Multidisciplinary Team Involvement

Management of bladder exstrophy should ideally occur at tertiary centers with expertise and a coordinated multidisciplinary team. The team typically includes:

- **Neonatologist:** For early stabilisation, feeding support, and coordination of initial care
- **Pediatric Urologist:** For surgical planning and long-term bladder management
- **Orthopedic Surgeon:** For management of pelvic osteotomies or gait abnormalities
- **Nephrologist:** For renal function surveillance and hypertension management
- **Pediatric Endocrinologist or Gynaecologist:** For assessment of pubertal development, sexual health, and fertility concerns
- **Clinical Psychologist/Counsellor:** To provide mental health support for body image, coping with chronic illness, and emotional resilience
- **Rehabilitation and Physical Therapy Team**
- **Social Worker/Child Life Specialist:** For supporting family

Family education and empowerment are vital. Parental training for wound care, understanding warning signs, and supporting the child's developmental needs can significantly improve long-term outcomes.

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Persistent life threatening hyperkalemia: A challenge for neonatologists!!!!

Authors
Dr Rajesh Kumar, Dr Nitish Kumar, Dr Sonali Kumari, Dr Shishir Sinha, Dr Raunak Raj, Dr Shriya Akanksha
Department of Neonatology, Rani Hospital, Ranchi

ABSTRACT

Neonatal hyperkalaemia and hyponatremia are medical conditions that require an emergent diagnosis and urgent treatment. Common causes of hyperkalaemia in infancy include acute haemolysis, kidney disorders, and hormonal disorders. Pseudohypoaldosteronism (PHA) though a rare entity, is a life threatening condition that can present as impressive hyperkalemia & severe salt wasting crisis requiring urgent medical attention, often misdiagnosed as CAH. Here, we report a 10-day-old female baby presenting with life-threatening hyperkalaemia, salt wasting crisis and metabolic acidosis diagnosed as autosomal recessive pseudo hypoaldosteronism type 1B (PHA 1B). This case emphasizes the importance of including PHA in the differential diagnosis of persistent neonatal hyperkalemia . We share our experience about difficulty faced in managing this case.

Keywords: hyperkalaemia, hyponatremia, neonate, metabolic acidosis, pseudo hypoaldosteronism.

INTRODUCTION

Pseudo hypoaldosteronism type (PHA) is a rare inherited disorder, resulting from end organ resistance to the action of aldosterone, leading to impaired sodium resorption and potassium excretion, resulting in salt-wasting, hyperkalemia and metabolic acidosis. There are 2 major forms of PHA: Type 1, which includes an autosomal dominant (renal limited PHA 1A) and autosomal recessive (systematic, PHA 1B) variant, and type 2 (Gorden syndrome), which typically presents later in life. PHA type 1B presents in infancy with severe systemic salt loss and hyperkalemia and is caused by mutations in genes encoding the epithelial sodium channel (ENaC). Prompt diagnosis is essential to initiate appropriate management and prevent fatal complications.

CASE REPORT

A 10-day female neonate, second order by birth, born out of consanguineous marriage, presented with lethargy, poor feeding, loose stool and breathing difficulty. The antenatal and perinatal period was uneventful; however there was a notable family history of sibling death at 15 days of life, with the cause remaining undetermined.

On examination, the neonate appeared lethargic and severely dehydrated. Vital signs revealed a heart rate of 178/min, respiratory rate -68/min, and mean arterial blood pressure 24mmHg (below 5th centile for age). Peripheral pulses were weak, capillary refilling time was prolonged at 4 seconds, and signs of dehydration including shrunken eyes, depressed anterior fontanel, decrease urine output and 22% weight loss was evident. No signs of virilization were observed.

Initial venous blood gas revealed severe metabolic acidosis (pH7.083, bicarbonate 10.3mmol/L), hyponatremia (91.9mmol/L), hyperkalemia (12.09mmol/L) and hypochloremia (76.5mmol/L). The baby was managed emergently for hyperkalemia with intravenous calcium gluconate, sodium bicarbonate and insulin- dextrose infusion. Respiratory support was initiated with non-invasive ventilation (NIMV), and broad spectrum antibiotics were started. Shock was managed with fluid resuscitation and vasopressor support. Later on a complete blood count, sepsis work up, renal and liver function tests, chest x ray and abdominal ultrasound were done and the results were unremarkable.

Given the electrolyte abnormalities, adrenal insufficiency was initially suspected. Serum 17-OH Progesterone and serum cortisol were sent. The level of 17-OH Progesterone was 15.9ng/ml (slightly raised) and serum cortisol was 45.59µgm/dL (within normal limit). Despite starting stress dose of hydrocortisone (100mg/m^2/day) and fludrocortisone (0.5mg/kg/day), the hyperkalemia (K^+ 7.8 mmol/L) and hyponatremia (Na^+ 110 mmol/L) persisted. A low trans-tubular potassium gradient (TTKG=2) suggested

aldosterone deficiency or resistance.

In the absence of androgen excess and due to lack of response to steroid therapy pseudohypoaldosteronism (PHA) was suspected. The neonate subsequently developed seborrheic dermatitis and worsening respiratory symptoms, requiring CPAP support for the next 10 days. Hormonal assay revealed markedly elevated serum renin (>500mIU/L) and aldosterone(>1000ng/dL) levels, strongly supporting a diagnosis of PHA.Whole exome sequencing confirmed autosomal recessive Pseudo hypoaldosteronism Type 1B with SCNN1B gene mutation, which was later confirmed with Sanger sequencing.

Fludrocortisone was gradually discontinued due to a lack of therapeutic response. Owing to persistent salt-wasting, oral sodium supplementation was initiated at admission at a dose of 10 mEq/kg/day. This was progressively titrated to a maximum of 25 mEq/kg/day, and the infant was eventually discharged on a maintenance dose of 15 mEq/kg/day.

In view of the high sodium requirement, persistent acidosis, and hyperkalemia, oral sodium bicarbonate (Syrup Nodosis) was introduced on day 16 at a dose of 1.5 mEq/kg/day and increased to 5 mEq/kg/day by the time of discharge. Life-threatening hyperkalemic episodes were managed with intravenous calcium gluconate and insulin-dextrose infusions, which were required intermittently until day 40 of life. Per rectal administration of potassium binding resin, calcium polystyrene sulfonate (K-bind) was initiated at 1 g/kg every 6 hours, subsequently increased to every 2 hours, and discontinued by day 32 of life. Concurrently, oral K-bind was started on day 16 at a dose of 1 g/kg every 6 hours, later increased to a 2-hourly schedule due to persistent hyperkalemia.

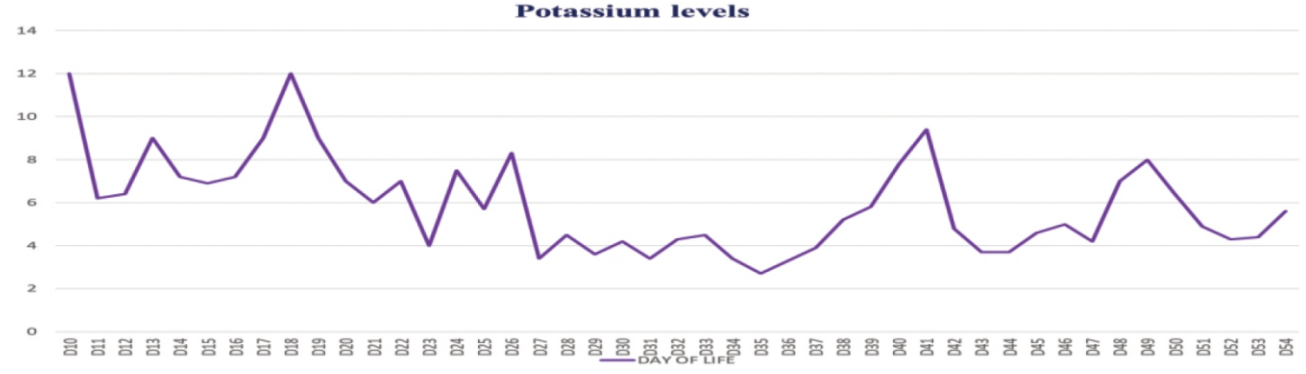
As hyperkalemia continued despite frequent oral and rectal K-bind, the decantation method was introduced on day 19, wherein expressed breast milk was mixed with K-bind to reduce potassium content before feeding. This method was continued beyond discharge.

The neonate showed clinical improvement over the next 15 days following initiation of sodium supplementation, with normalization of electrolytes maintained on oral sodium therapy and potassium-binding resins using the 2-hourly decantation method. At the time of discharge, the infant required 1 g of K-bind every 2 hours for decantation, along with oral 3% sodium chloride and sodium bicarbonate syrup for sodium supplementation.

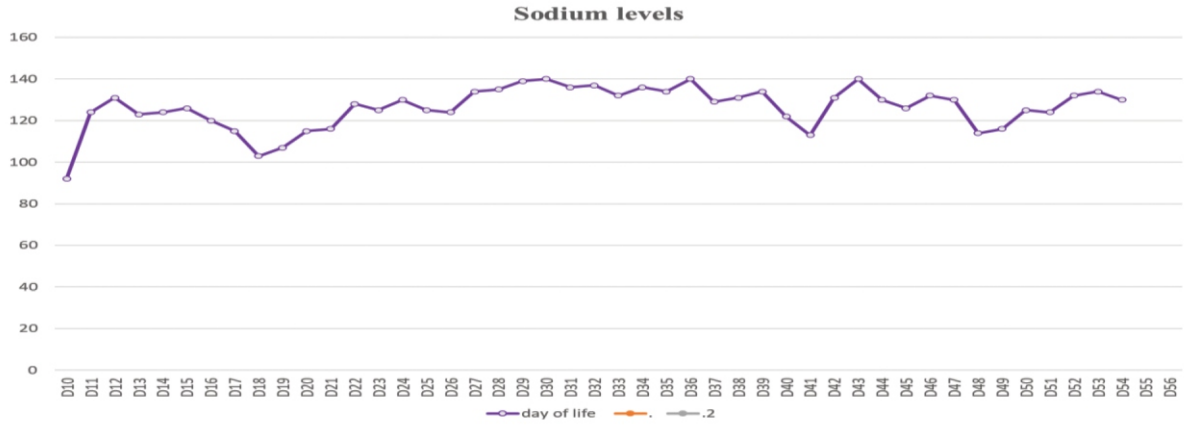
At 2 months of age, the child is thriving well, with normal growth and developmental mile

The trend of sodium, potassium and interventions is summarized in the graph below.

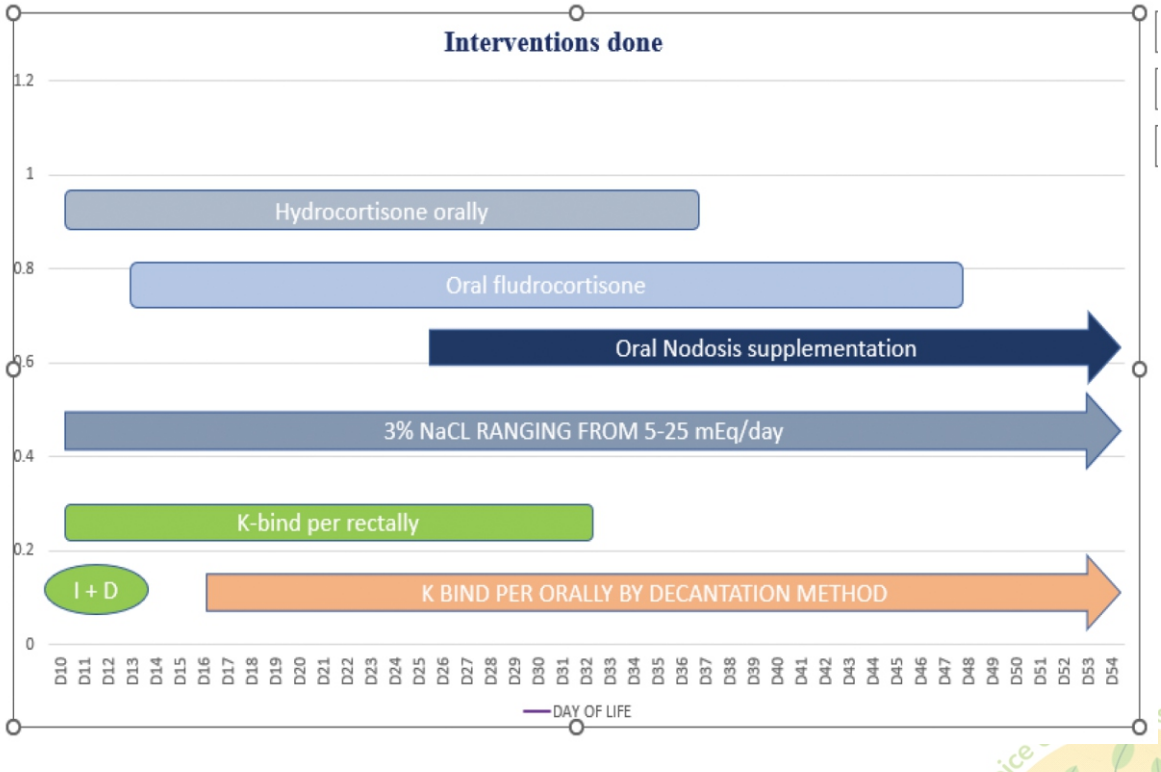
GRAPH 1



GRAPH 2



GRAPH 3



GRAPH 1: Denotes level of serum potassium

GRAPH 2: Denotes level of serum sodium

GRAPH 3: Denotes the interventions done

DISCUSSION

This case highlights the diagnostic and management challenges physician may face when encountering type 1B pseudo hypoaldosteronism (PHA), a rare but critical differential diagnosis in neonates presenting with salt wasting crisis. Clinically and biochemically,

PHA can closely mimics congenital adrenal hyperplasia (CAH) which is significantly more prevalent. As a result, PHA is often overlooked. However persistence of life threatening hyperkalaemia and severe salt wasting unresponsive to stress dose of hydrocortisone should prompt consideration of PHA and cast doubt on a CAH [1,2].

Diagnostically, a major limitation is the turn-around time for aldosterone level testing- the primary investigation that distinguishes PHA from CAH, which often requires 3 to 4 days. Additionally laboratory errors such as the "hook effect", where antigen levels interfere with antigen -antibody binding may yield falsely low aldosterone readings further complicating timely diagnosis.

Management of PHA requires careful titration of sodium supplementation alongside the use of potassium binding agents. Even after initial stabilisation and discharge, affected infants remain at risk of recurrent life threatening hyperkalemic episodes, necessitating close follow up and regular dose adjustments to ensure favourable outcomes.

PHA is an inherited salt- wasting disorder caused by resistance to mineralocorticoids at target organ level [1,3] .It is broadly classified into two types of PHA; type 1 and 2 PHA. PHA1 is further classified into renal (Autosomal dominant) and systemic (Autosomal recessive) forms [4]. The Renal form results from heterogeneous mutations in the gene encoding the aldosterone receptor [5], in which salt loss is restricted only to the kidney. In contrast, systemic PHA1 is due to autosomal recessive (AR) mutation in the SCNN 1B gene which encodes the epithelial sodium channel (ENaC) on which aldosterone acts to permit sodium absorption, thereby facilitating potassium and hydrogen excretion[6,7]; it is characterized by generalized salt loss from multiple organs, including the lung, kidney, colon, and sweat and salivary glands [8,9] .Systemic PHA1 typically presents in the neonatal period with hypovolemia, hyponatremia, hyperkalaemia, and metabolic acidosis [10]. Clinical features include severe salt wasting, hyperkalemia, metabolic acidosis, and complications such as pulmonary infections due to impaired mucociliary clearance (often resembling cystic fibrosis), recurrent diarrhea due to sodium loss and elevated sweat sodium concentration. Biochemically, it is characterized by elevated aldosterone and plasma renin activity, with normal or slightly increased cortisol and ACTH levels.

The clinical presentation of our patient was consistent with systemic PHA1, marked by severe, refractory hyperkalaemia requiring aggressive management and ongoing salt supplementation. Additional manifestations included skin involvement [11], recurrent pulmonary infections [9], diarrhoea, and a continued dependence on potassium binding resins. Systemic PHA1 may also be associated with polyhydramnios [12], and cholelithiasis [13] as described in literature. Our patient also developed skin disease, diarrhea, pulmonary infections and continues to require salt supplementation, k^+ bind resins to manage hyperkalaemia.

Treatment of PHA1 is a medical emergency. Acute management involves prompt rehydration, correction of electrolyte imbalance (particularly hyperkalaemia), and reversal of metabolic acidosis. Once stabilized, long term therapy includes sodium supplementation and potassium exchange resins. While other options such as indomethacin and thiazide diuretics have been explored, their effectiveness is variable. Importantly, mineralocorticoids like fludrocortisone are ineffective due to post receptor resistance, a hallmark of the condition.

CONCLUSION

Mutations in the SCNN1B gene can lead to systemic pseudohypoaldosteronism type 1B (PHA 1B), a severe form of aldosterone resistance affecting multiple organ systems. Early recognition of this rare but life-threatening condition is critical, especially in neonates presenting with persistent hyperkalemia and hyponatremia unresponsive to steroid therapy. Understanding the underlying role of epithelial sodium channels (ENaC) and their dysfunction is essential for accurate diagnosis and management. Genetic testing remains the cornerstone for confirming the diagnosis and differentiating PHA from other endocrine or renal disorders with similar presentations.

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Transverse facial cleft: An unusual cause of asymmetric crying facies

Authors
Dr Swati Upadhyay and Dr Yusuf
Deptl. of Neonatology, Max Super Speciality Hospital, Patparganj, Delhi

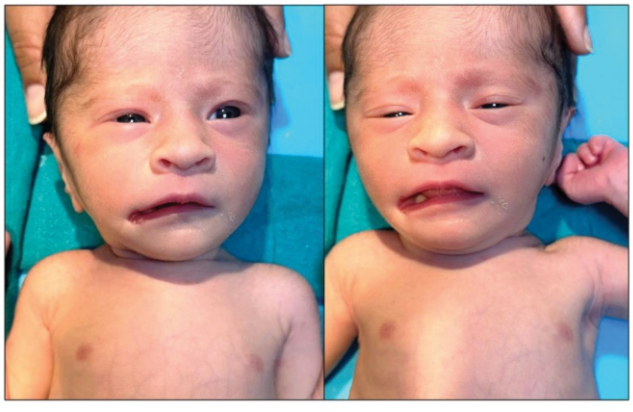

Image- Right-sided transverse facial cleft, measuring 15 mm in length. A) At rest, the cleft created an impression of right-sided deviation of angle of mouth
B) While crying, this deviation became more prominent, appearing as asymmetric crying facies

A term low-birth-weight female neonate was born to a primigravida mother via cesarian section. The neonate cried immediately after birth but had asymmetric crying facies. On examination, she was noted to have macrostomia with a transverse facial cleft on right side, giving an impression of right-sided deviation of angle of mouth, which became more prominent on crying (Image). Rest of the physical and systemic examination was normal. Echocardiography, hearing screen and ultrasound abdomen was normal. She had difficulty in breastfeeding with drooling of milk. However, she accepted expressed breastmilk well via katori and spoon. The mother was trained in oromotor exercises and non-nutritive sucking to aid in easier transition to breast feeding. She was discharged on day 4 with plan to follow up under plastic surgery and commisuroplasty at 3 month.

Transverse or lateral facial cleft (Tessier type 7 or mac rostomia) is a rare congenital anomaly, affecting 1 in 80000 newborns [1]. It arises due to failure of maxillary and man-dibular processes of the first branchial arch to fuse. It may be associated with other anomalies such as preauricular tags, microtia, additional first and second arch abnormalities, polydactyly, and syndromes like Goldenhar and Treacher Collins [2]. Functional issues secondary to dysfunction of orbicularis oris muscle include sialorrhea, compromised speech & chewing ability, difficulty sucking and increased frequency of ear infections. A multidisciplinary approach and an early surgical correction during the first year is recommended

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Journal Scan

Reviewed by
Dr Priyanka Gupta
MD, DrNB Neonatology
Consultant Neonatologist
Nutema Hospital, Meerut
drpriyanka23sep@gmail.com

Extended Caffeine for Apnea in Moderately Preterm Infants: The MoCHA Randomized Clinical Trial.
Carlo WA, Eichenwald EC, Carper BA, et al. *JAMA*. 2025;333(24):2154-2163. doi:10.1001/jama.2025.5791

RESEARCH QUESTION

- Can extended caffeine treatment reduce the duration of hospitalization while waiting for apnea of prematurity to resolve?

CLINICAL QUESTION (PICOT FORMAT)

- P: 29+0 to 33+6 weeks GA) at 33–35 weeks postmenstrual age (PMA), clinically stable, off respiratory support, and on full enteral feeds.
- I: Extended caffeine [10 mg/kg/day] to 28 days post-discharge
- C: Placebo (caffeine discontinued)
- O: Days to hospital discharge (primary); Physiological maturity apnea-free days, safety, adverse events, readmission (secondary)
- T: From randomization to 28 days post-discharge

STUDY DESIGN-

- **Type**: Multicenter, double-blind, placebo-controlled randomized clinical trial
- **Sites**: 29 hospitals' NICUs of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN)
- **Period**: February 2019 to December 2022 (follow-up through March 2023)

SELECTION CRITERIA-

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Being **33 0/7** to **35 6/7** weeks' PMA at the time of randomization	Receiving respiratory therapy (ie, supplemental oxygen [more than room air equivalent for high altitude sites], nasal cannula, CPAP, and/or MV;
2. Receiving caffeine with a plan to discontinue treatment	Being discharged from an apnea monitor due to underlying disease or family history, including history of a sibling with sudden infant death syndrome
3. Receiving oral and/or tube feedings at 120 mL/kg/d or more	Parents requesting an apnea monitor
4. Having the ability to start the study medication within 72 hours after stopping caffeine	Having congenital heart disease other than ASD, VSD, or PDA
	Having a neuromuscular condition affecting respiration
	Having a major congenital malformation and/or genetic disorder
	Planning to transfer to a non-NRN site before discharge

RANDOMIZATION

- **Randomization**: 1:1 randomization using a central web-based system; stratified by site and gestational age [29 0/7 to 30 6/7 weeks or 31 0/7 to 33 6/7 weeks]. Infants of multiple births were randomized separately. **Blinding:** Triple-blinded (investigators, clinicians, and families blinded to group assignment). **Allocation Concealment**: Adequately described and performed**. Sample Size**: 827 infants across 29 U.S. NICUs; powered for primary outcome with pre-planned futility stopping rule. **Baseline Comparability**: Baseline demographics and clinical characteristics are well balanced. **Follow-up completeness**: Minimal attrition or protocol violations reported.

INTERVENTION

- Intervention: Oral caffeine citrate 10 mg/kg/dose or 5mg/kg caffeine base, given throughout hospital stay and until 28 days post-discharge.
- Control: Placebo (same volume) that contained all excipients except the caffeine citrate (Exela Pharma Sciences).

Follow-up: Obtain post-discharge information regarding adherence and clinical status within 72 hours after discharge and on weeks 1, 2, 3, 4, 6, and 8 after discharge

OVERALL VALIDITY : HIGH

- The study design, execution, and reporting meet the standards of high-quality RCT methodology.

RESULTS AND INTERPRETATION

PRIMARY OUTCOME	*SECONDARY OUTCOME*
No significant difference in time to discharge: Caffeine: median 18.0 days Placebo: median 16.5 days Adjusted median difference: 0 days (95% CI, −1.7 to 1.7)	Apnea resolution was faster in the caffeine group: Median time: 6 days vs. 10 days (adjusted difference −2.7 days) Physiological maturity not significantly different: 14 vs 15 days Adverse events/readmissions: No significant difference

STATISTICAL ANALYSIS:

Appropriate methods used (Cox proportional hazards, adjusted models). However, outcomes were not powered for long-term developmental impact or rare adverse events.

RELEVANCE AND APPLICABILITY

Study population: The Population is relevant for moderately preterm infants in well-resourced NICUs; it may not generalize to extremely preterm or resource-limited settings like INDIA. **Intervention Feasibility:** Caffeine citrate is low-cost, widely available, and simple to administer. **Outcomes:** Clinically meaningful (hospital stay, apnea resolution), though discharge timing is often influenced more by feeding milestones. **External Validity:** Strong; 29 diverse U.S. NICUs increase generalizability in similar healthcare systems. **Clinical Significance**: Despite improved apnea resolution, no meaningful benefit in reducing hospital stay or advancing maturity, which limits routine adoption.

STRENGTHS

- Large sample size with adequate power
- Rigorous randomization and blinding
- Real-world applicability across multiple centers
- Pragmatic outcomes tied to discharge readiness
- Good safety profile confirmed for outpatient caffeine continuation

LIMITATIONS

- Dose (10 mg/kg/d) may be suboptimal
- Apnea assessment based on clinical judgment
- Analyses of secondary outcomes were only used for generating hypotheses and did not include adjustment for multiple comparisons
- COVID-19 affected recruitment and follow-up

- Infants born at less than 29 weeks' gestational age who are at high risk of apnea of prematurity were not the target of this trial.
- Short-term follow-up, long-term neurodevelopmental outcomes not reported.
- Effect of caffeine continuation may have been diluted due to natural apnea resolution in some infants.
- Variability in discharge practices, differences in institutional feeding or discharge protocols could mask minor benefits

CONCLUSIONS-

Extended caffeine did not reduce hospital stay

Earlier resolution of apnea is not sufficient to enable earlier discharge

FINAL JUDGMENT

The MoCHA trial is a methodologically sound, well-executed randomized trial that adds important nuance to the clinical use of caffeine in moderately preterm infants. While caffeine resolves apnea faster, it does not impact hospital discharge or overall physiologic maturity, challenging the assumption that prolonged therapy leads to earlier home readiness.

Given the absence of discharge benefit, routine use of home caffeine therapy in this population is not supported. Future research should focus on more immature infants, neurodevelopmental follow-up, and refining discharge criteria beyond apnea resolution.

WHY LENGTH OF STAY [LOS] IS A COMPLEX PRIMARY OUTCOME IN MoCHA TRIAL

Factor	Impact on LOS
Feeding readiness	Delays discharge even if apnea improves
Thermoregulation	Prolongs stay until baby can maintain temperature
Apnea/bradycardia resolution	Directly related to caffeine/apnea studies
Parent readiness & education	May delay discharge despite clinical stability
Social/family discharge issues	Non-medical factor affecting LOS
Medical stability (jaundice, infections, etc.)	Comorbidities may extend LOS

Each factor can independently shorten or prolong the length of stay

HOW MOCHA TRIAL FITS WITH CAP, ICAF, AND LATE PRETERM INTERMITTENT HYPOXAEMIA TRIALS

Feature (2023)	MoCHA (2025)	CAP (2006–2012)	ICAF (2014 pilot & ongoing)	Late-preterm IH Dose Trial
Population	29–33 wk GA, at 33–35 wk PMA; ready to stop caffeine	VLBW 500–1250 g (mostly very preterm) within the first 10 days	Preterm infants after routine caffeine cessation: focus on IH post-discontinuation	Late-preterm (34–36 wk)
Intervention	Continue 10 mg/kg/day until 28 days post-discharge	Caffeine vs placebo through early postnatal weeks (standard CAP regimen)	Extended caffeine to ~40 wk PMA vs placebo	5, 10, 20 mg/kg/day caffeine citrate vs placebo
Primary Outcome	Days to discharge	BPD, ventilatory outcomes; later NDI	Intermittent hypoxia (IH) burden	IH frequency at ~2 weeks
Main Effect	No reduction in LOS; earlier apnea-free status	↓BPD, earlier extubation; better survival without NDI; benefits persist to 5 yrs	Extended caffeine ↓IH after routine cessation	Dose-dependent ↓IH (20 mg/kg/day most effective)
Take-home	Treats physiology (apnea timing) but not discharge timing	Strong efficacy and long-term safety for very preterm/VLBW early treatment	Signals IH persists post-caffeine and is modifiable	Supports caffeine to reduce IH in late preterm

RECONCILING DIFFERENCES

Different babies, different questions. CAP tested early caffeine in very preterm/VLBW infants—where respiratory morbidity and neurodevelopmental risk are highest—and found broad neonatal and long-term benefits. MoCHA asked a late-course management question in moderate preterm infants nearing discharge; here, feeding and thermoregulation often drive the length of stay more than apnea, so improving apnea alone didn't impact the length of stay.

Outcome selection matters. When the primary endpoint is intermittent hypoxaemia [IH] (ICAF pilot; late-preterm trial), caffeine reduces IH. When the endpoint is length of stay, the signal can vanish because length of stay is multifactorial.

Dose/timing heterogeneity. CAP used standard dosing early; late-preterm data suggest higher maintenance (≈20 mg/kg/day) is most effective for IH reduction. MoCHA used 10 mg/kg/day; a higher dose could further reduce IH, but no evidence would translate to shorter LOS in moderate preterms.

PRACTICE IMPLICATIONS (MY TAKE)

1. Don't extend caffeine solely to shorten length of stay in 29–33 wk infants ready for discharge—MoCHA trial concluded that it doesn't.
2. If an infant has clinically significant desaturations after routine stopping, targeted extension of caffeine is reasonable (ICAF/late-preterm data), with careful dose selection and monitoring.
3. Continue early caffeine in very preterm/VLBW infants per CAP evidence; benefits extend to neurodevelopment at least to 5 years.

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Neonatal Neurology

Authors
Dr Pratima Anand
Department of Neonatology
Lady Hardinge Medical College and Associated Hospitals, New Delhi.

Question 1.

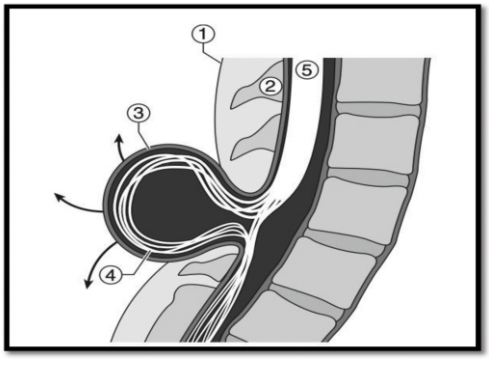
Peak time of occurrence for neuronal migration is

(i) 3 to 5 weeks of gestation
(ii) 2 to 4 months of gestation
(iii) 6 to 7 months of gestation
(iv) 3 to 5 months of gestation

Question 2.

Identify Number 3 and 4 in the figure of meningomyelocele below:

(i) Spinal cord and herniating neural tissue
(ii) Herniating neural tissue and spinal cord
(iii) Dysplastic meningeal tissue and herniating neural tissue
(iv) Herniating neural tissue and dysplastic meningeal tissue



Question 3.

The severity of fetal ventriculomegaly is based on the size of

(i) Third ventricle in axial view
(ii) Lateral ventricle in axial view
(iii) Lateral ventricle in coronal view
(iv) Third ventricle in coronal view

Question 4.

Which of the following is TRUE about visual acuity & other discriminations in a neonate

(i) Visual acuity in premature infants with birth weight of 1500 to 2500 g studied at approximately 38 weeks of gestation is similar to that of term infants.
(ii) Color vision can be demonstrated as early as 8 months of postnatal life
(iii) Binocular vision and depth perception appear by 10 months of postnatal life
(iv) Preference for novel patterns appears by 12 months of life

Question 5.

A neonate who is asleep, with moderately diminished arousal response is in which state of alertness?

(i) Coma
(ii) Moderate stupor
(iii) Slight stupor
(iv) Deep stupor

Question 6.

High quality of motor response in a neonate are characterized by

(i) Stereotypies, latency and non-habituating
(ii) Non stereotypic, latency and habituating
(iii) Stereotypic, no latency and habituating
(iv) Non stereotypic, no latency and habituating

Question 7.

Which of the following is not a standardized method for predominantly motor (tone) assessment

(i) HNNE
(ii) ATNAT
(iii) HINE
(iv) NBAS

Question 8.

In the Brainstem Auditory Evoked Responses, the CORRECT statement is:

(i) Wave I to V internal is prolonged in peripheral and brainstem lesions

(ii) Wave I latency is prolonged in peripheral and brainstem lesions

(iii) Wave V latency is prolonged in peripheral and brainstem lesions

(iv) The threshold for wave I is elevated in periphery and brainstem lesions

Question 9.

As per the latest ILAE (International League Against Epilepsy), "automatism seizures" is the new terminology for which class of seizures?

(i) Clonic seizures

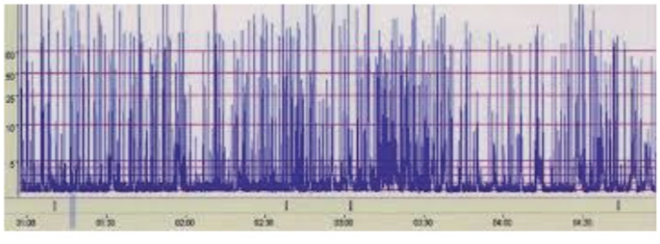
(ii) Tonic seizures

(iii) Subtle seizures

(iv) Myoclonic seizures

Question 10.

Identify the pattern on the Amplitude Integrated EEG



(I) Continuous normal voltage

(ii) Discontinuous normal voltage

(iii) Low voltage

(iv) Burst suppression

Question 11.

The preferred second line antiseizure medication used in neonates is

(i) Midazolam infusion

(ii) Phenytoin

(iii) Fosphenytoin or Levetiracetam

(iv) Phenobarbitone

Question 12.

The probable interval between passage of in utero meconium when fetal nails are meconium stained is

(i) More than 12 hours

(ii) More than 3 hours

(iii) More than 4 to 6 hours

(iv) More than 1 hour

Question 13.

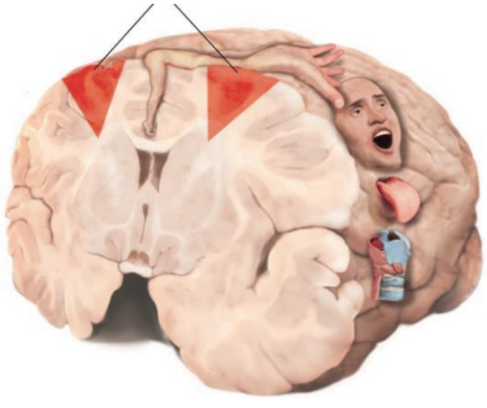
Identify the pattern of hypoxic injury given in the figure

(i) Periventricular

(ii) Frontal

(iii) Frontoparietal

(iv) Parasagittal



Question 14.

Which grade of intraventricular haemorrhage is this on cranial ultrasonography Intraventricular haemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)

(i) Grade III

(ii) Grade II

(iii) Grade I

(iv) Parenchymal bleed

Question 15.

Which of the following is NOT a criterion to consider therapeutic hypothermia in a neonate with perinatal asphyxia?

(i) Birth weight > 2000g and gestation >35 weeks

(ii) Presents to the neonatal unit at 8 hours of life from home

(iii) Cord pH < 7.0 and Apgar score < 5 at 10 minutes of life

(iv) Evidence of moderate to severe encephalopathy as per clinical examination on Modified Sarnath staging

Answer 1

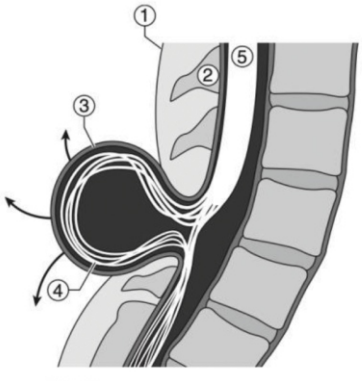
(iv) 3 to 5 months of gestation (Volpe textbook of neurology)

TABLE 1.1 Major Events in Human Brain Development and Peak Times of Occurrence

MAJOR DEVELOPMENTAL EVENT	PEAK TIME OF OCCURRENCE
Primary neurulation	3–4 weeks of gestation
Prosencephalic development	2–3 months of gestation
Neuronal proliferation	3–4 months of gestation
Neuronal migration	3–5 months of gestation
Organization	5 months of gestation to years postnatally
Myelination	Birth to years postnatally

Answer 2

(iii) Dysplastic meningeal tissue and herniating neural tissue



① Skin
② Bony spinal element
③ Dysplastic meningeal tissue
④ Herniating neural tissue
⑤ Spinal cord

Diagram of myelomeningocele. Note herniation of neural tissue through the bony spinous defect, dorsal displacement of the cord by ventral CSF collection, cyst covered by dysplastic meningeal tissue, leakage of CSF, and lack of skin coverage.

Answer 3 (ii)

Fetal ultrasound is the standard prenatal screening modality for identifying foetal VM and has become an important tool for monitoring ventricular size, configuration, and its progression over gestation. By convention, foetal ventricular size is measured by US as the diameter of the lateral ventricular atrium on an axial view at the level of the thalami or the glomus of the choroid plexus.

Fetal VM has been classified by a number of different criteria, including severity (mild, moderate, or severe), evolution (transient, stable, or progressive), laterality (unilateral or bilateral), symmetry (symmetrical or asymmetrical), and association with other findings (isolated or complex).

Classification by Ventricular Size. The severity of foetal VM is based on the size of the lateral ventricle measured at the conventional axial location discussed earlier. If VM is mild-moderate (≤15 mm) or severe (>15 mm), some authors further categorize the mild-moderate form into mild (10–12 mm) and moderate (13–15 mm) categories. Although not entirely satisfactory, this classification is the most widely accepted.

Another ultrasonographic indicator of VM is the "dangling choroid" sign (increased space between the choroid plexus and lateral ventricle)

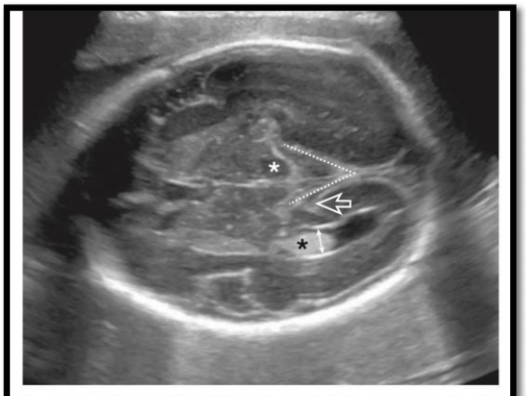


Fig. 3.4 Axial view of fetal US at the level of the cerebral peduncles *(white asterisk)*, the ambient cistern *(V-shaped dotted lines)*, cavum septi pellucidi, and the glomus of the choroid plexus *(black asterisk)*. The *double-headed white arrow* indicates the standard location for measurement of the lateral ventricular atrium diameter directly in line with the parieto-occipital sulcus *(open block arrow)*. (Image courtesy Dr. Dorothy Bulas.)

Answer 4 (i)

Visual Acuity, Colour, and Other Discriminations.

Using a visual fixation technique, Fantz showed that the newborn attended to stripes of 1/8-inch width.

Visual acuity in premature infants with birth weight of 1500 to 2500 g studied at approximately 38 weeks of gestation is similar to that of term infants. Although studies of color perception in the newborn period often have not rigorously distinguished brightness and color, newborn infants clearly will follow a colored object. Color vision is demonstrable by at least as early as 2 months of age. Contrast sensitivity increases dramatically between 4 to 9 postnatal weeks.

Discrimination of a rather complex degree has been demonstrated for newborn infants.

Infants as young as 35 weeks of gestation exhibit a distinct visual preference for patterns, particularly those with a greater number of and larger details. Curved contours are favoured over straight lines. Preference for novel patterns becomes apparent at 3 to 5 months.

Preference for patterns with facial resemblance develops between approximately 10 and 15 weeks of age, and promptly thereafter there is discrimination according to facial features.

The degree of contrast has a direct effect on preferences. Binocular vision and appreciation of depth also appear by approximately 3 to 4 postnatal months. Binocular visual acuity increases most rapidly during the same interval These higher-level visual abilities may reflect a change in the major anatomical substrate from subcortical to cortical structures.

Full-term infants in the first days of life also have been shown to imitate facial gestures.

Answer 5 (ii)

TABLE 12.10 Levels of Alertness in the Neonatal Period

LEVEL OF ALERTNESS	APPEARANCE OF INFANT	AROUSAL RESPONSE	MOTOR RESPONSES	
			QUANTITY	QUALITY
Normal	Awake	Normal	Normal	High level
Stupor				
Slight	"Sleepy"	Diminished (slight)	Diminished (slight)	High level
Moderate	Asleep	Diminished (moderate)	Diminished (moderate)	High level
Deep	Asleep	Absent	Diminished (marked)	High level
Coma	Asleep	Absent	Diminished (marked) or absent	Low level

Answer 6 (ii)

The distinction between deep stupor and coma is based primarily on the quality of the motor responses; that is, in deep stupor motor responses are high level in type (nonstereotyped, definite latency, and habituating), whereas in coma they are low level (stereotyped, rapid onset, nonhabituating), or totally absent.

Answer 7 (iv)

Various assessment methods are as below:

APIB, Assessment of Preterm Infants' Behaviour; ATNAT, Amiel-Tison Neurological Assessment at Term; GMA, General Movements Assessment; HNNE, Hammersmith Neonatal

Neurologic Examination; NAPI, Neurobehavioral Assessment of the Preterm Infant; NBAS, Neonatal Behavioural Assessment Scale; NBO, Newborn Behavioural Observations;

NNNS, Neonatal Intensive Care Unit Network Neurobehavioral Scale; TIMP, Test of Infant Motor performance.

NBAS is predominantly for neonatal behavioural assessment.

TABLE 12.18 Principal Characteristics of the Neonatal Standardized Neurological/Neurobehavioral Exams

TEST	OVERALL DESCRIPTION	POPULATION	CERTIFICATION/ TRAINING	EXAMINATION TIME	ONLINE RESOURCE
HNNE[426]	A general neurodevelopmental exam (Video 12.2)	34 weeks postmenstrual age—4 months corrected age	None	10–15 minutes	https://hammersmith-neuro-exam.com/
ATNAT[427]	A general neurodevelopmental exam with emphasis on both upper and lower motor control systems and the definitions of passive and active tone	Term equivalent age	None	5 minutes	–
NAPI[428]	A measure of the progression of neurobehavioral performance over time and differentiates performance within a 2-week age range	32 weeks postmenstrual age—term equivalent age	Limited training to achieve reliability in exam and scoring	30 minutes	–
Preemie Neuro[429]	A measure of alterations in early functions in the very immature or clinically unstable preterm infant	23–37 weeks postmenstrual age	Reading a manual available from the authors (unpublished) and by checking reliability with an experienced clinician	3–5 minutes	–
GMA[213]	An assessment that depends on visual observation of videotapes of nonstimulated infants to characterize their movement patterns	Preterm and term—6 months corrected age	Standardized basic and advanced training courses, lasting 4–5 days	30–60 minutes of videotaping, and 1–3 minutes to evaluate each general movement	https://general-movements-trust.info/
TIMP[430]	An assessment that uses clinical observation and responses to elicited stimuli to quantify motor performance and capture how infants are able to respond to movement demands in typical daily activities	34 weeks postmenstrual age—17 weeks corrected age	15 hours of instruction either in-person or via online modules	20–35 minutes to administer and score	https://www.thetimp.com/learn-the-tests
NBAS[431]	A comprehensive examination of neonatal behavior (Video 12.4)	36 weeks postmenstrual age—2 months corrected age	Requires a formal training program provided by the Brazelton Institute	No time limit (usually about 30 minutes)	https://www.childrenshospital.org/research/centers/brazelton-institute-research.

TABLE 12.18 Principal Characteristics of the Neonatal Standardized Neurological/Neurobehavioral Exams—cont'd

TEST	OVERALL DESCRIPTION	POPULATION	CERTIFICATION/ TRAINING	EXAMINATION TIME	ONLINE RESOURCE
NBO[432]	An infant-family centered tool designed to inform parents about the competencies and difficulties of their infant, aiming for providing a positive parent-infant relationship (Video 12.5)	From birth to 3 months of age	Requires a 2- to 3-day training course followed by a follow-up period of 3 months	15–30 minutes	https://www.childrenshospital.org/research/centers/brazelton-institute-research/training
NNNS[433]	A comprehensive neurobehavioral exam and stress assessment	34 weeks postmenstrual age—5 weeks corrected age	Formal 3–5 days of training and reliability testing are needed for certification	Less than 30 minutes. More time is needed for scoring	https://www.brown.edu/research/projects/children-at-risk/about
APIB[434]	An assessment of the mutually interacting behavioral subsystems in the newborn and simultaneous interaction with the environment	28 weeks postmenstrual age—1 month corrected age	Requires 1–2 years of training	No time limit (1 hour to perform, 30–45 minutes to score, 3 hours to write a report)	https://nidcap.org/apib-training-overview/

Answer 8 (iii)

TABLE 13.4 Two Basic Abnormal Patterns of Brainstem Auditory Evoked Responses in Neonatal Disease

	SITE OF DISORDER	
RESPONSE CHARACTERISTIC	**PERIPHERY**	**BRAINSTEM**
Threshold (wave I)	Elevated	Normal
Wave I latency	Prolonged	Normal
Wave V latency	Prolonged	Prolonged
I–V interval	Normal	Prolonged

Wave I represents activity of the eighth nerve, wave II the cochlear nucleus, wave III the superior olivary nucleus, wave IV the lateral lemniscus, and wave V the inferior colliculus. The precise origins of waves VI and VII remain to be established, but these waves probably are generated in the thalamus and thalamic radiations, respectively.

Answer 9 (iii)

The initial classification system by Volpe and the new classification system from the International League Against Epilepsy have slightly different terminology.

The new classification system uses "automatism seizures" in place of "subtle seizures" and classifies most motor seizures as "bilateral" in place of "generalized.

TABLE 15.7 Classification of Neonatal Seizures

	ELECTROENCEPHALOGRAPHIC CORRELATE	
MOTOR SEIZURE TYPE	**COMMON**	**UNCOMMON**
Automatism (subtle)	+	
Clonic		
Focal	+	
Multifocal	+	
Tonic		
Focal	+	
Bilateral (generalized)		+
Myoclonic		
Focal, multifocal		+
Bilateral (generalized)	+	

TABLE 15.10 Motor Seizure Types and Descriptors as Defined by the International League Against Epilepsy

MOTOR SEIZURE TYPES	DESCRIPTORS
Automatisms	Unilateral Bilateral asymmetrical Bilateral symmetrical
Clonic	Focal Multifocal Bilateral
Epileptic spasms	Unilateral Bilateral asymmetrical Bilateral symmetrical
Myoclonic	Focal Multifocal Bilateral asymmetrical Bilateral symmetrical
Tonic	Focal Bilateral asymmetrical Bilateral symmetrical

Answer 10

(iv) Burst suppression pattern

Two major classification systems used to interpret the patterns on aEEG are

Classification Based on Amplitude (Naqeeb et al)

For term infants

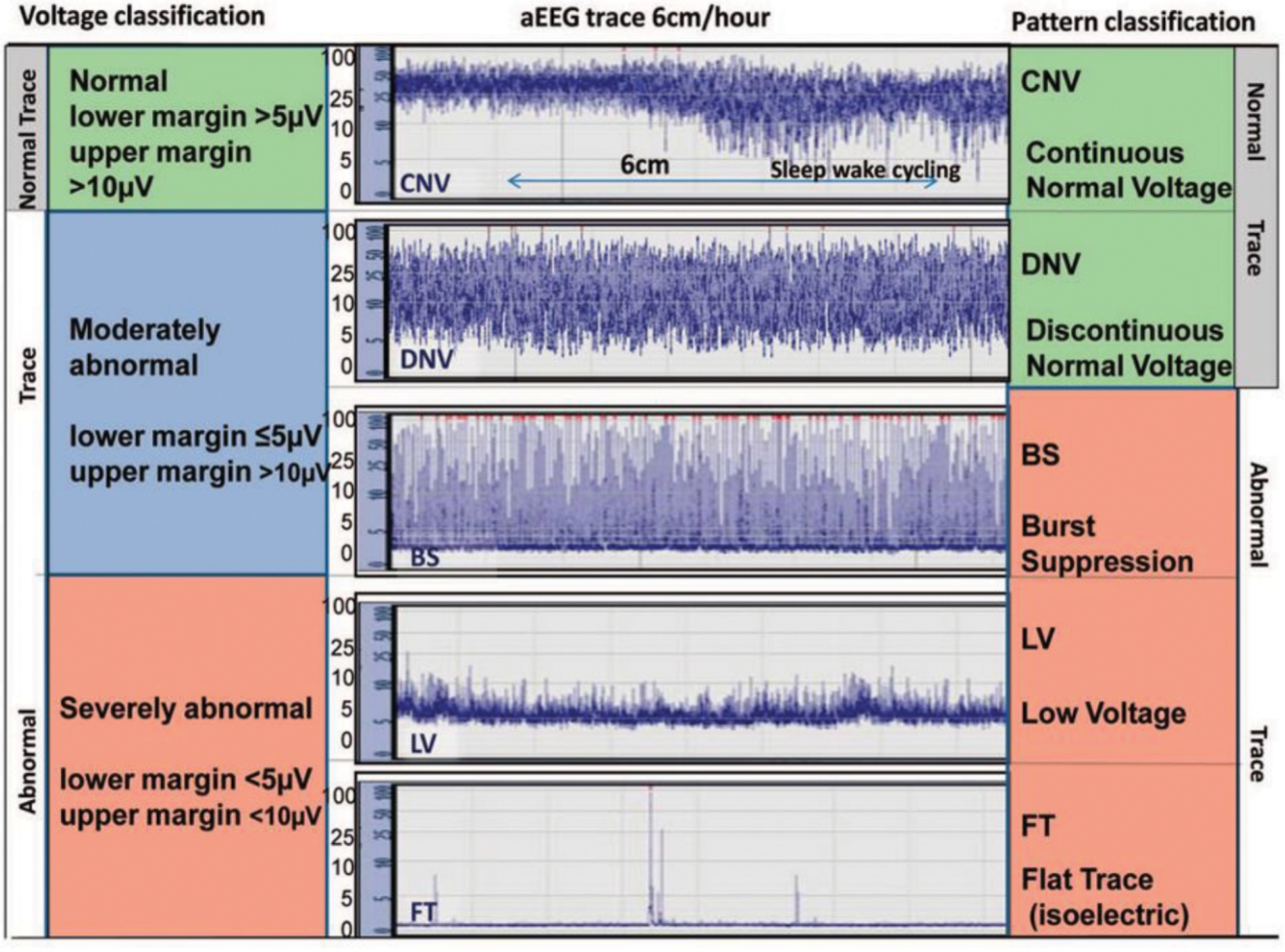
- Classified into 3 categories based on the height of the upper and lower margins
- Normal amplitude: lower limit > 5 mV and an upper limit > 10 mV
- Moderately abnormal amplitude: lower limit < 5 mV and an upper limit > 10 mV
- Severely abnormal amplitude: lower limit < 5 mV and an upper limit < 10 mV

Hellstrom-Westas Classification

Based on

- Background pattern
- An estimation of burst rate
- Sleep-wake cycling
- Presence of seizure patterns

Can be used for both term and preterm infants

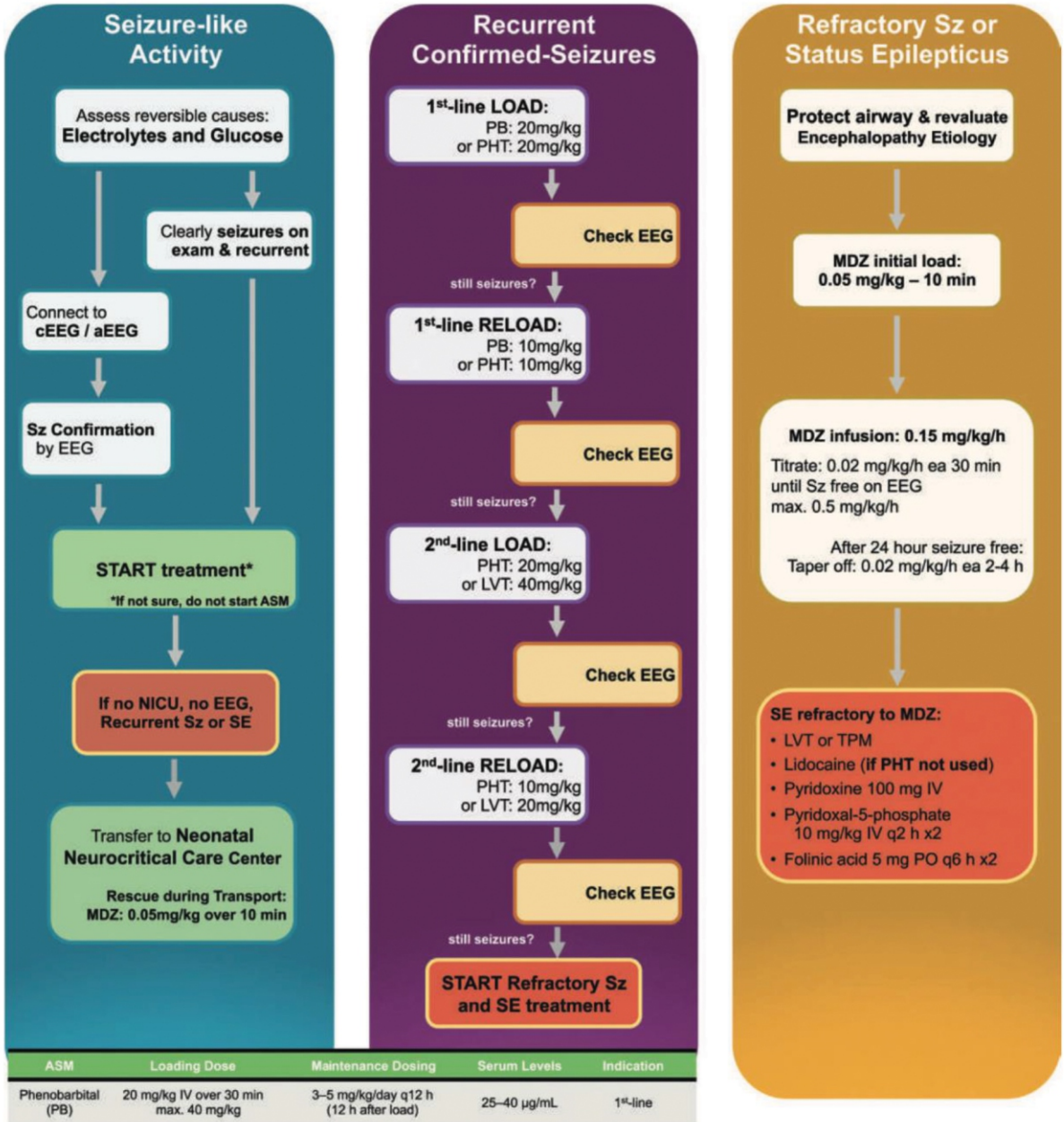

Voltage classification
aEEG trace 6cm/hour
Pattern classification
Normal Trace
Trace
Abnormal
Normal
lower margin >5μV
upper margin
>10μV
Moderately
abnormal
lower margin ≤5μV
upper margin >10μV
Severely abnormal
lower margin <5μV
upper margin <10μV
100
25
10
5
0
CNV
6cm
Sleep wake cycling
DNV
BS
LV
FT
CNV
Continuous
Normal Voltage
DNV
Discontinuous
Normal Voltage
BS
Burst
Suppression
LV
Low Voltage
FT
Flat Trace
(isoelectric)
Normal
Trace
Abnormal
Trace


Be the voice of voiceless. Save New Born!

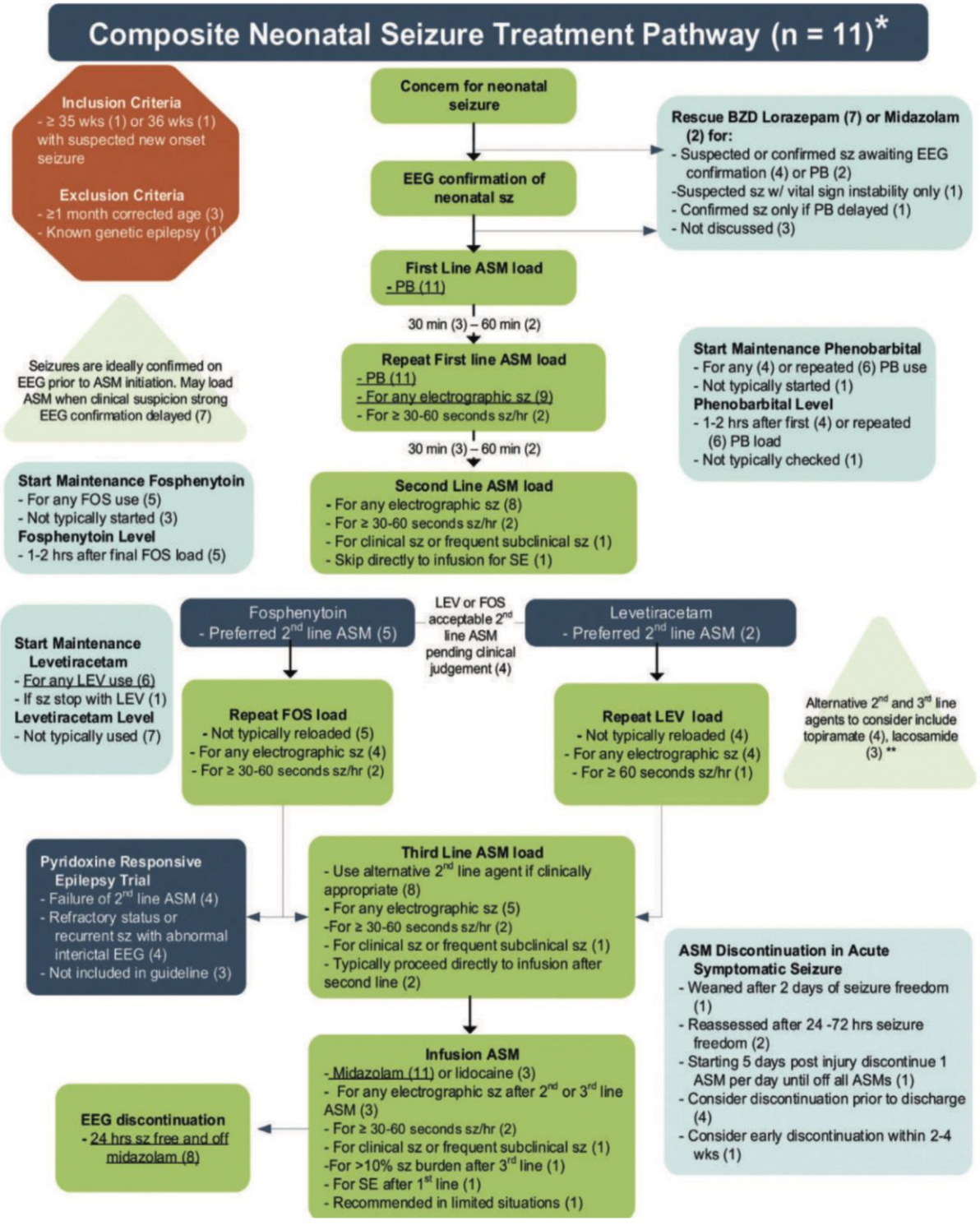
Answer 11

(iii) Fosphenytoin or Levetiracetam

Composite neonatal seizure treatment pathway from 11 centers



ASM	Loading Dose	Maintenance Dosing	Serum Levels	Indication
Phenobarbital (PB)	20 mg/kg IV over 30 min max. 40 mg/kg	3–5 mg/kg/day q12 h (12 h after load)	25–40 µg/mL	1st-line
Phenytoin (PHT)	20 mg/kg IV over 30 min max. 30 mg/kg	8–10 mg/kg/day q8 h (8 h after load)	15–25 µg/mL	1st-line or 2nd-line
Levetiracetam (LVT)	40 mg/kg IV over 15 min max. 60 mg/kg	40–60 mg/kg/day q8 h (8 h after load)	12–46 µg/mL	2nd-line
Midazolam (MDZ)	bolus 0.05 mg/kg IV over 10 min	infusion: 0.05 mg/kg/h max. 0.5 mg/kg/h	No serum level	Refractory Sz or SE
Lidocaine	bolus: 2mg/kg	infusion: 7 mg/kg/h x3.5 h then 3.5 mg/kg/h x12 h then 1.75 mg/kg/h x12 h	No serum level	Refractory Sz or SE


Composite Neonatal Seizure Treatment Pathway (n = 11)*
Inclusion Criteria
- ≥ 35 wks (1) or 36 wks (1) with suspected new onset seizure
Exclusion Criteria
- ≥1 month corrected age (3)
- Known genetic epilepsy (1)
Concern for neonatal seizure
EEG confirmation of neonatal sz
Rescue BZD Lorazepam (7) or Midazolam (2) for:
- Suspected or confirmed sz awaiting EEG confirmation (4) or PB (2)
-Suspected sz w/ vital sign instability only (1)
- Confirmed sz only if PB delayed (1)
- Not discussed (3)
First Line ASM load
- PB (11)
30 min (3) – 60 min (2)
Seizures are ideally confirmed on EEG prior to ASM initiation. May load ASM when clinical suspicion strong EEG confirmation delayed (7)
Repeat First line ASM load
- PB (11)
- For any electrographic sz (9)
- For ≥ 30-60 seconds sz/hr (2)
Start Maintenance Phenobarbital
- For any (4) or repeated (6) PB use
- Not typically started (1)
Phenobarbital Level
- 1-2 hrs after first (4) or repeated (6) PB load
- Not typically checked (1)
30 min (3) – 60 min (2)
Start Maintenance Fosphenytoin
- For any FOS use (5)
- Not typically started (3)
Fosphenytoin Level
- 1-2 hrs after final FOS load (5)
Second Line ASM load
- For any electrographic sz (8)
- For ≥ 30-60 seconds sz/hr (2)
- For clinical sz or frequent subclinical sz (1)
- Skip directly to infusion for SE (1)
Fosphenytoin
- Preferred 2nd line ASM (5)
LEV or FOS acceptable 2nd line ASM pending clinical judgement (4)
Levetiracetam
- Preferred 2nd line ASM (2)
Start Maintenance Levetiracetam
- For any LEV use (6)
- If sz stop with LEV (1)
Levetiracetam Level
- Not typically used (7)
Repeat FOS load
- Not typically reloaded (5)
- For any electrographic sz (4)
- For ≥ 30-60 seconds sz/hr (2)
Repeat LEV load
- Not typically reloaded (4)
- For any electrographic sz (4)
- For ≥ 60 seconds sz/hr (1)
Alternative 2nd and 3rd line agents to consider include topiramate (4), lacosamide (3) **
Pyridoxine Responsive Epilepsy Trial
- Failure of 2nd line ASM (4)
- Refractory status or recurrent sz with abnormal interictal EEG (4)
- Not included in guideline (3)
Third Line ASM load
- Use alternative 2nd line agent if clinically appropriate (8)
- For any electrographic sz (5)
-For ≥ 30-60 seconds sz/hr (2)
- For clinical sz or frequent subclinical sz (1)
- Typically proceed directly to infusion after second line (2)
ASM Discontinuation in Acute Symptomatic Seizure
- Weaned after 2 days of seizure freedom (1)
- Reassessed after 24 -72 hrs seizure freedom (2)
- Starting 5 days post injury discontinue 1 ASM per day until off all ASMs (1)
- Consider discontinuation prior to discharge (4)
- Consider early discontinuation within 2-4 wks (1)
Infusion ASM
- Midazolam (11) or lidocaine (3)
- For any electrographic sz after 2nd or 3rd line ASM (3)
- For ≥ 30-60 seconds sz/hr (2)
- For clinical sz or frequent subclinical sz (1)
-For >10% sz burden after 3rd line (1)
- For SE after 1st line (1)
- Recommended in limited situations (1)
EEG discontinuation
- 24 hrs sz free and off midazolam (8)

Answer 12 (iii)

TABLE 21.12 Timing of Meconium Passage Before Birth

CLINICAL-PATHOLOGICAL FEATURE	PROBABLE DURATION BEFORE BIRTH
Pigment-laden macrophages in amnion	>1 hr
Pigment-laden macrophages in chorion	>3 hr
Meconium-stained fetal nails	>4–6 hr

Data from Miller PW, Coen RW, Benirschke K. Dating the time interval from meconium passage to birth. *Obstet Gynecol.* 1985;66:459–462.

TABLE 28.12 Grading of Severity of Germinal Matrix–Intraventricular Hemorrhage by Ultrasound Scan

SEVERITY	DESCRIPTION
Grade I	Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (<10% of ventricular area on parasagittal view)
Grade II	Intraventricular hemorrhage (10%–50% of ventricular area on parasagittal view)
Grade III	Intraventricular hemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)
Separate notation	Periventricular echodensity (location and extent)

Answer 13 (iv)

Parasagittal region of the brain is most involved in hypoxic damage in term neonates. The pathogenesis is likely to be due to:

1. Cerebral ischemia
2. Impaired cerebrovascular autoregulation with pressure-passive cerebral circulation
3. Systemic hypotension
4. Parasagittal vascular factors
5. Arterial border zones and end zones

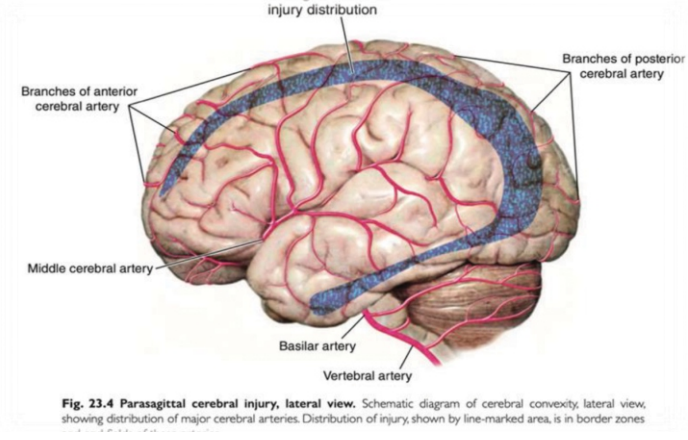
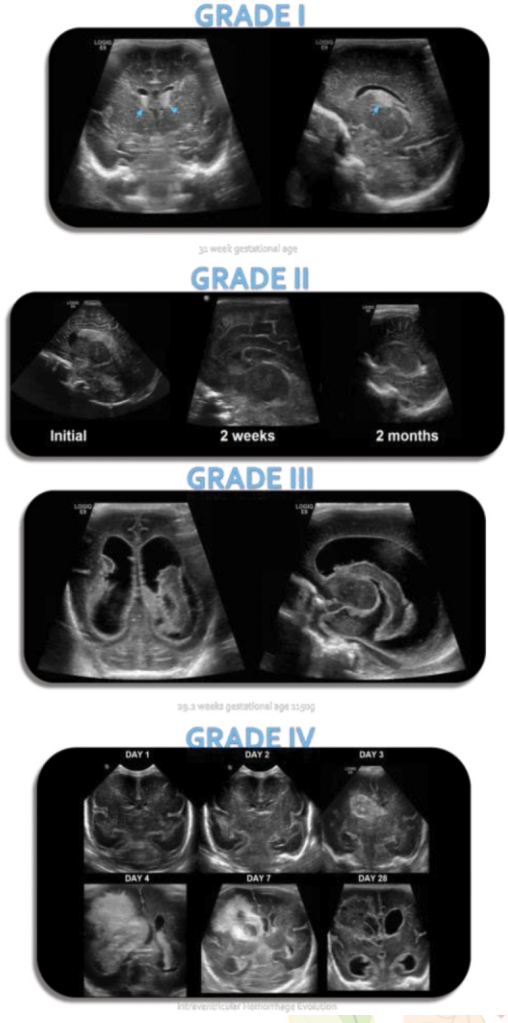


Fig. 23.4 Parasagittal cerebral injury, lateral view. Schematic diagram of cerebral convexity, lateral view, showing distribution of major cerebral arteries. Distribution of injury, shown by line-marked area, is in border zones



Clinical correlates of parasagittal injury are differential tone abnormalities proximal limb weakness > lower limb weakness and long term sequalae of spastic quadriparesis.

Answer 14 (I)

Answer 15 (ii)

As per the position statement by Indian guidelines by NNF 2021, after the HELIX trial these are the criterion for starting therapeutic hypothermia in neonates after birth asphyxia:

Which neonates should be offered TH?

It is recommended that TH should be offered to neonates with HIE with gestational age > 36 weeks, <6 hrs of age of life and with admission temperature 36-37.4oC, IF they fulfil all of the following criteria:

1. pH <7 or BE >-16 on cord or arterial blood gas done within 1 h of life
2. AND

   Apgar score<5 at 10 minutes or at least 10 min of positive pressure ventilation

   AND

(ii) history of acute perinatal event (such as but not limited to placental abruption, uterine rupture, cord prolapse)

3. Evidence of moderate or severe encephalopathy

During preparation for cooling if the neonate's encephalopathy has improved (becomes mild or normal), therapeutic hypothermia may be deferred and neonate observed closely and offered continued supportive care

Prior to initiating TH it must be ensured that parents are provided sufficient information about the benefits and harms of cooling, the details of the procedure and outcomes. A written consent must be obtained from parents/legal guardians. It must be ensured that the neonate's cardio-respiratory status is stable prior to initiating

cooling. It also imperative that cooling is initiated as early as possible and definitely

prior to 6 h of postnatal life.

Which neonates should not receive TH?

Clinical trials have generally excluded the following infants for TH – those who are moribund, have major congenital or genetic abnormalities, neonates with severe intrauterine growth restriction, those with evidence of severe coagulopathy, those with evidence of severe head trauma or intracranial hemorrhage. There is insufficient evidence of the benefit of hypothermia offered beyond 6h of age.

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.

Original Article

Original papers should be structured include a structured abstract with subheadings - aims, materials and methods, results, and conclusions (maximum 250 words).

Main manuscript: Should be typed double-spaced and structured as follows: introduction; materials and methods (including appropriate subsections, e.g. statistical methods); results; discussion; acknowledgements; references (normally 40); legends to figures; tables; and figures. Original manuscripts should be 3,500 words (not including references, tables and figures). Manuscripts should include a maximum of 5 Figures and/or tables.

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 Issue

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 10-15 questions would be included in this section along with answers.

You can contact us at following email addresses:

info@nnfdelhi.org

dr.thakuranup@gmail.com

Please call or Whats App at 8800565956