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From the President's Pen

DR. MAMTA JAJOO

President NNF Delhi

Hello every one
Warm greetings!

At the outset, I want to congratulate our editorial team for their hard work and sincere efforts to bring the "'NeoClips' (Neonatal Clinical Practice)" a journal full of knowledge, research, unique case reports and interesting Quiz and OSCE for our young budding paediatrician and Neonatologists.

We all know that neonates are the most vulnerable group of entire population and is major cause of under 5 mortality in India and most of these deaths are preventable. It has also been estimated that preventable neonatal deaths can be decreased at least 50% through the implementation of scale-up of educational interventions, therefore Delhi NNF is mainly focused to train and impart knowledge in different ways and bringing out "'NeoClips' (Neonatal Clinical Practice)" is one of the efforts towards that only.

Handling a tiny neonate requires both art and science and is very important for every Paediatrician to learn that art of empathy, compassion while treating them and not to do any harmful practices and for that it's important to learn the basics thoroughly especially when you are young, and more importantly to implement these evidenced-based practices in your everyday practice while caring for newborns in NICU.

The new generation of doctors is keen to learn about advanced technologies, ventilation, and many new things, but must always remember that learning the basics is the most important. Starting enteral nutrition especially mothers' own milk, kangaroo mother care, hand hygiene practices, not using unnecessary antibiotics, and developmental supportive care are the best practices which everyone must implement.

Every commitment to advance the health and well-being of newborns is important and embodies the spirit of collective action.

'NeoClips' (Neonatal Clinical Practice) is also a small lamp to light the knowledge of all of us and to improve the newborn health in our country. I am sure that this Journal is going to be an academic feast for all of us with lot of recent evidences, and variety of cases. Once again sincere thanks to our Editorial team of NEOCLIP.

"Extending a hand of assistance to people who are suffering the most is the way to open path for happiness for all"
Daisaku Ikeda

Dr Mamta Jajoo
President, Delhi NNF

From the Secretary's desk

DR NAVEEN PARKASH GUPTA

Secretary, NNF Delhi

Dear Friends,

As the secretary of the National Neonatology Forum, Delhi, I am pleased to announce the launch of the first edition of NeoCliPs (Neonatal Clinical Practice) in the year 2024. You will now see NeoCilPs as a quarterly newsletter.

It is with great enthusiasm that we introduce this quarterly newsletter as a means to spread knowledge and advancements in the field of Neonatology. I welcome and congratulate the new team of NeoCliPs comprising of Dr Kumar Ankur (Chairperson), Dr Anup Thakur (Editor in Chief), Dr Vivek Choudhury (Vice Chairperson) and dynamic members (Dr Pratima Anand, Dr Tapas Badopadhyay and Dr Kumari Gunjan).

My sincere thanks to the efforts of all the authors for working hard in bringing this issue. I am sure that under the dynamic leadership of Dr Kumar Ankur and Dr Anup Thakur, we expect NeoCliPs to touch new heights and get indexed soon.

This year, in addition to the existing contents in the previous issues such as interesting case, Image section, Picture of the month, Journal Scan and OSCE, we are adding neonatal ventilation and medical statistics (each issue will cover one aspect) as a review part. These additions are based on the feedback from the readers and suggestions of the new team. Also, we are adding an original research article in each of the issues.

You can visit our website https://nnfdelhi.org and stay informed about NeoClips editions and upcoming activities by NNF Delhi.

Thank you for your interest and support in our mission to improve neonatal care through research, education, and advocacy. We look forward to your participation in the NeoCliPs and to the meaningful contributions you will undoubtedly make to our shared pursuit of excellence in neonatology.

Should you have any questions or require further information, please do not hesitate to contact me or any member of the NeoCliPs Committee.

Dr Naveen Parkash Gupta
Secretary, NNF Delhi

From the Editor's Desk

DR. ANUP THAKUR

Editor NNF Delhi

"I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

……Sir Isaac Newton

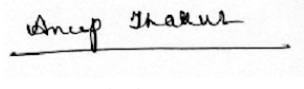
Dear Seniors, Colleagues and Friends,

The confines of knowledge are limitless. How much sand can we hold from the vast shores of knowledge? As our new editorial team begin the task of publishing "NeoClips-the official journal of NNF", we understand that it's a tall order. Well! Let me first congratulate the past editorial team for setting up an excellent benchmark. Next, I would like to thank the office bearers of Central and Delhi NNF for giving me and my team this opportunity. And last but not the least, I am grateful to my editorial team and the authors for their support in bringing out this issue.

As the new editorial team, we have retained the core features of the journal such as Journal review, OSCE, Case report, image section and review article. For review article, we are starting a series of articles on Neonatal ventilation this year. We also understand that our readers include post-graduate and super-specialty students and therefore a section on basics of medical statistics will be published in each issue. Original research articles are essential for any journal to get indexed. From this year, we will publish the journal quarterly and, in each issue, we intent to publish at least one original research article. While the pursuit for excellence may be eluding sometimes, we the editors and the authors have put into our hard work with unfeigned passion to make this journal a small treatise for medical students, residents, pediatricians, nurses and neonatologists to assist them in management of critical and sick neonates ultimately helping them to save these little angels, who are our tomorrow.

We hope the readers enjoy going through the journal articles. We invite the members of Delhi NNF to contribute articles for publication in NeoClips.

विद्यां ददाति विनयं, विनयाद् याति पात्रताम् ।
पात्रत्वात् धनमाप्नोति, धनात् धर्मं ततः सुखम् । ।



On behalf of editorial team
Editor in Chief
Dr Anup Thakur

Bacillus Circulans Sepsis in Neonates- A Case Series

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Abstract

Objective: We report the clinical manifestations, laboratory parameters, management and outcomes of nine cases of Bacillus circulans sepsis in neonates.

Material and Methods: We retrieved data on nine cases of Bacillus circulans sepsis in a level 3 B neonatal intensive care unit of Northern India from May 2019 to February 2021. We collected data on clinical presentation, laboratory parameters, culture sensitivity, management and outcomes of the neonates from the hospital information system. Missing data was retrieved from individual file records. A case of Bacillus circulans was defined as blood culture positivity in two cultures taken at least 24 hours apart.

Results: A total of 9 cases of Bacillus circulans sepsis were identified during the study period. Two neonates developed meningitis. The median (IQR) birth weight and gestation of the neonates were 1500 (870-2710) g and 33 (30.5-36) weeks respectively. Seven neonates were preterm, of which 3 were extremely low birth weight. A cluster of 8 cases occurred from May 2019 to February 2020, with the index case being an extramural neonate. The neonate had 6 consecutive positive weekly cultures despite administration of sensitive antibiotics that included meropenem, vancomycin, ciprofloxacin, cotrimoxazole and chloramphenicol. Median (IQR) time to culture positivity was 15 (14.5-17.5) hours. Median (IQR) duration of antibiotics treatment given was 28 (14-28) days. Of the nine neonates, 2 died and both were ELBW infants.

Conclusion: Bacillus infections although uncommon, can occur especially in preterm neonates. They are resistant to the common first line antibiotics used in NICU and usually require prolonged antibiotic therapy.

Key words: Bacillus circulans, sepsis.

Introduction

Neonates, especially those born premature are immune-compromised due to poor T cell function, deficient antibody response and poorly functioning complement system, therefore rendering them susceptible to infection [1]. Sepsis in neonates is usually caused by bacteria such as Escherichia coli, Klebsiella species, Staphylococcus aureus and Enterobacter [2]. Ubiquitous organisms such as non-anthrax Bacillus are usually considered contaminants and as such disregarded [3]. Nevertheless, in an immune-compromised host, Bacillus species can cause systemic infections. Albeit, Bacillus infection is uncommon, case reports of bacillus cereus infection in neonates have been published [4–7]. Bacillus circulans is another species of this positive spore-bearing family encountered ubiquitously and reported to cause systemic infections such as meningitis, endocarditis, osteoarthritis and end-opthalmitis in adults [8–11]. However, no such cases of systemic infection in neonates have been reported. During the study period, nine neonates in our NICU were diagnosed with Bacillus circulans sepsis. In this case series, we report the clinical manifestation, laboratory parameters, management and outcomes of Bacillus circulans infection in neonates.

Case series

We retrieved data on nine cases of Bacillus circulans sepsis in a level 3 B neonatal intensive care unit of Northern India from May 2019 to February 2021. We collected data on clinical presentation, laboratory parameters, culture sensitivity, management, and outcomes of the neonates from the hospital information system. Missing data was retrieved from individual file records. A case of Bacillus circulans was defined as blood culture positivity in two cultures taken at least 24 hours apart.

During the study period, neonates who had clinical signs of sepsis based on NeoKiss criteria [12] were investigated. Laboratory investigations such as complete blood count, C Reactive Protein (CRP), blood culture and urine culture were done. Lumbar puncture for CSF analysis was performed in all cases. Two blood culture bottles were concurrently inoculated into BactALERT blood culture system. In case, spore bearing gram variable bacilli were reported, blood cultures were repeated from two different sites. Identification of Bacillus circulans was based on lecithinase activity, motility, penicillin susceptibility and crystal formation results. Antibiotic sensitivity was performed by using the disk diffusion method and minimum inhibitory concentration was calculated. Blood culture was repeated every week till the organism was no longer detectable. Sensitive antibiotics were given for duration of 7 days from negative blood culture and for at least 21days in cases with meningitis.

Statistical analysis was done using SPSS version 25. Mean and standard deviation was calculated for data with normal distribution while median and interquartile range was calculated for data with non-normal distribution.

Results

A total of nine cases of Bacillus circulans sepsis were identified during the study period. The clinical profiles of the neonates are described in table 1. Two neonates (Case 4 and 9) developed meningitis. The median (IQR) birth weight and gestation of the neonates were 1500 (870-2710) g and 33 (30.5-36) weeks respectively. Seven neonates were preterm, of which 3 were extremely low birth weight (ELBW). A cluster of 8 cases occurred from May 2019 to February 2020, with the index case being an extramural neonate (Case 1) who had 6 consecutive weekly culture positives despite administration of sensitive antibiotics that included meropenem, vancomycin, ciprofloxacin, cotrimoxazole and chloramphenicol. The neonate needed prolonged ventilation and required antibiotics for 56 days for eradication of infection. The laboratory parameters at diagnosis are depicted in table 2. The median (IQR) time to culture positivity was 15 (14.5-17.5) hours. The antibiogram of the isolated organism are given in table 3. The median (IQR) duration of antibiotics treatment given was 28 (14-28) days. Of the nine neonates, 2 died and both were ELBW infants.

Table 1. Clinical Profile of Neonates with Bacillus Circulans Sepsis

Case no	Inborn/ Outborn	Weight (g)	Gestation (wks)	Presenting symptoms	Day of life	Days after admission	Ventilation Needs	Inotropes	Antibiotics duration	Survived
1	O	1604	33	Apnea	18	0	CPAP	No	52	Yes
2	O	2220	34	Feed intolerance	8	0	No	No	14	Yes
3	O	1500	34	Feed intolerance	8	0	No	No	14	Yes
4	I	860	29	Apnea/ seizures	1	19	SIMV	No	28	Yes
5	I	880	31	Pulmonary bleed	1	30	HFOV	Yes	11	No
6	O	1120	30	Apnea	7	7	CPAP	No	28	Yes
7	I	620	32	Shock	12	12	HFOV	Yes	21	No
8	O	3200	38	Seizures	20	7	No	No	14	Yes
9	O	3440	40	Apnea	6	3	No	No	28	Yes

O -ouborn, I -inborn, CPAP- Continuous positive airway pressure, SIMV -Synchronized intermittent mandatory ventilation, HFO -High frequency oscillation

Table 2. Demographic, laboratory parameters and outcome of neonates with Bacillus Circulans sepsis.

Parameters	
Birth weight, g	1500 (870-2710)
Gestation, wks	33 (30.5-36)
Time to culture positivity, hrs	15(14.5-17.5)
Laboratory parameters at presentation • Total Leucocyte Count (mm3) • Absolute Neutrophil count (mm3) • Platelet count (lacs/mm3) • Creactive Protein (mg/L)	 16,960 (11,690-20,785) 5,635 (4,180-14,196) 1.9 (0.835-3.045) 37.3(26.2-73.4)
Duration of antibiotics (days)	28 (14-28)
Mortality (n, %)	2 (22.2 %)
All values in median (IQR) unless expressed otherwise.	

Table 3. Antibiotic Sensitivity Pattern of isolated organism

Case no	Vancomycin	Piperacillin +tazobactum	Meropenem/ Imipenem	Levofloxacin	Ciprofloxacin	Cotrimoxazole	Amikacin	Chloramphenicol	Ampicillin
1	S	R	S	I	S	S	I	S	R
2	S	S	S	I	S	NT	S	NT	S
3	S	S	S	I	S	NT	S	NT	S
4	S	R	R	S	S	S	I	S	R
5	S	R	R	S	I	S	I	S	R
6	S	R	R	S	S	S	S	S	R
7	S	R	S	S	S	NT	S	NT	S
8	S	R	S	S	S	NT	S	NT	S
9	S	R	S	I	S	NT	S	NT	S
S=Sensitive, R=Resistant, I=Intermediate sensitivity, NT=not tested									

Discussion:

We report nine cases of Bacillus circulans sepsis in neonates, eight of which occurred in a cluster probably by acquiring infection from an index extramural infant. Bacillus circulans meningitis was diagnosed in two cases. The organism was difficult to clear from blood culture and required prolonged sensitive antibiotics. Morbidities included need for mechanical ventilation, inotropes and increased duration of NICU stay.

Bacillus species are gram positive or variable spore producing rods found in soil, water, and air. These organisms can produce a variety of toxins such as hemolysins, phospholipases, emesis-inducing toxins and several enterotoxins [3,13]. Although, non-anthrax Bacillus cereus infection causing meningitis, pneumonia, meningo-encephalitis, and enterocolitis have been described in neonates[14–17], to the best of our knowledge, this is the first case series of Bacillus circulans sepsis in neonates. Bacillus species are known to cause severe symptomatic infection in immune-compromised host [18,19]. In our case series, seven infants were premature, of which three were ELBW neonates. The possible modes of transmission of

bacillus species are by mechanical ventilation, dissemination from the gastrointestinal tract, or are catheter-related [20,21].

There are a few case reports of Bacillus species sepsis in neonates [20,22–24]. Papan et al reported two cases of bacillus cereus sepsis, of which one died of severe pneumonia, despite being weaned from ECMO [25]. Deindl et al reported two cases of Bacillus cereus infection, one extremely preterm who became critically sick and one term born neonate who developed necrotizing enterocolitis [26]. Adler et al reported eight cases of Bacillus species sepsis in neonates. Most neonates were premature, presented with apnea, lethargy or fever, had raised CRP and the isolates were sensitive to vancomycin, Clindamycin and Meropenem [27]. Similarly in our case series, most neonates (7/9) were premature, but apnea and feed intolerance were the most common presenting symptoms. Neonates in our series had raised CRP (median 37mg/l) and most isolates were sensitive to Vancomycin and Ciprofloxacin.

Containment of spread of infection in NICU is of paramount importance. In September 2019, two ELBW infants developed Bacillus sepsis. A team for infection control was formed with the help of hospital infection control committee, NICU nurse in charge, chief neonatologist, and microbiologist. After situational analysis, immediate steps were taken on the recommendation of the team that included isolation of infected infants to a cubicle, dedicated one is to one nursing care, re-emphasizing on use of hand hygiene, routine cleaning of all door handles and computer key boards with bacilol (etanol-10%,2-propanol-9%,1-propanol-6%) in each shift, prohibition of taking out articles such as files and stethoscope of the cubicle to nursing/working stations, prohibition of use of mobile phones in patient care areas and re-visitation of routine housekeeping policies. All these measures were taken in addition to routine infection control practices of the unit. The unit already had in place a strict infection control guideline, quality control checks and monthly audits of processes in place. By June 2020, the spread of infection could be finally contained.

Non-anthax bacillus is widespread in the environment, yet most of these species are usually considered as culture contaminants. Repeat isolation of Bacillus species in symptomatic neonates should be treated. Bacillus infections are resistant to the common first line antibiotics used in NICU and usually require prolonged antibiotic therapy. Preterm neonates are especially at increased risk of morbidity and mortality. Clinicians should be aware about spectrum of bacillus sepsis, its treatment and methods of containment in the NICU.

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Non-invasive ventilation

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Abstract

Non-invasive ventilation (NIV) is provision of respiratory support without endotracheal tube via nasal route using various interface. It includes continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV) and heated humidified high flow nasal cannula (HHHFNC) system. It is a gentler form of ventilation and decreases risk of ventilation induced lung injury. NIV is primary mode of respiratory support in neonates, presenting with mild to moderate respiratory distress. The main indications of NIV support include respiratory distress, apnea and post extubation respiratory support. Neonates on NIV should be monitored comprehensively for adequacy and complications. The newer modes of NIV are non-invasive high frequency ventilation and non-invasive neutrally adjusted ventilator assist (NIV-NAVA).

Introduction

Non-invasive ventilation (NIV) is delivery of mechanical ventilation to lungs without an endotracheal tube or tracheostomy in the airway. Non-invasive ventilation is a gentler form of ventilation. Non-invasive ventilation strategy is increasingly being recognized as primary modality of treatment of respiratory distress in neonates. It has revolutionized the neonatal intensive care management because of its lesser side effects and risk of complications in comparison to invasive ventilation.

The non-invasive ventilation strategy in a neonate includes continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), heated humidified high flow nasal cannula (HHHFNC) system.[1] Nasal CPAP is predominant form of NIV used in neonates. Other forms of NIV i.e. Non-invasive high frequency ventilation and non-invasive neutrally adjusted ventilator assist (NIV-NAVA) are less frequently used. Heated humidified high flow nasal cannula (HHFNC) will be discussed in a separate chapter. Setting up of NIV involves several aspects for its complete understanding. It includes principles of functioning, types of equipment, components of NIV, type of interfaces, setting up and initiation of NIV.

I. Continuous positive airway pressure

CPAP is a mode of non-invasive ventilation in which there is application of positive pressure to the airways of a spontaneously breathing baby throughout the respiratory cycle.[2] CPAP is used predominantly in respiratory conditions where there is tendency of alveoli to collapse or they are filled with fluid. The common conditions in neonates for use of CPAP are respiratory distress syndrome, apnea of prematurity and post extubation. It can also help to stent the airways in case of laryngomalacia, tracheomalacia and bronchomalacia.

Principles of CPAP

CPAP works by several mechanisms.[3] The most important is improvement of oxygenation by maintaining functional residual capacity by preventing alveoli to collapse. The improvement in oxygenation leads to decrease intrapulmonary shunt. The endogenous surfactant is conserved. The airways are stented and the rib cage is stabilized resulting in regular breathing pattern.

In CPAP mode of ventilation, the pressure is generated in expiratory limb of breathing circuit when constant/variable flow is obstructed by constant/variable resistance.[4] Such pressure which is applied to spontaneous respiratory efforts both during inspiration and expiration is continuous positive airway pressure. A schematic diagram for understanding of CPAP function is shown in Figure 1.

CPAP Types

There are two basic types based on the flow pattern

1) **Continuous flow devices**

Pressure is generated by changing the resistance

Flow is constant

Examples: Bubble CPAP and Ventilator CPAP

2) Variable flow devices

Pressure is generated by changing the flow

Resistance is constant

Examples: Infant flow driver CPAP, Arabella system and Viasys

A comparative table for various types of CPAP is given in Table 1.

Components of CPAP

Following are the components of CPAP (Figure 2).

1. Pressure-generating device: Pressure generating mechanism varies according to the type of CPAP.

Continuous flow devices:

- Bubble CPAP- Pressure generated by submerging the expiratory limb into a water chamber and adjusted by altering its depth (Figure 3). Gas flow is increased until continuous bubbling is achieved. The bubbles in the water chamber have been postulated to provide chest vibration which may improve gas exchange.
- Ventilator -Pressure is generated at the exhalation valve (Figure 4). The CPAP level is increased or decreased by varying the ventilator exhalation orifice size. This type of CPAP has an integrated nasal interface and pressure generator.

Variable flow devices:

CPAP level is generated by varying the flow near nasal interface. Special prongs and flow generator are used for variable flow CPAP. A higher gas flow is used in these devices and pressure is generated by increased resistance as gas leaves the nasal device (Coanda effect). Pressure is changed by varying the flow of gas into device (Figure 5). Because of fluidic flip of inspiratory gases during exhalation, work of breathing is decreased in variable flow system.5 In physiological studies variable flow CPAP has been shown to achieve consistent continuous positive airway pressure.6 An example for Variable flow device along with interface has been shown in Figure 6.

2. Heated and humidified circuit: The inspiratory gases delivered to the baby should be heated and humidified as poor humidification results in mucosal injury, mucociliary dysfunction and bronchospasm. Servo controlled humidifiers are preferable.
3. Blended gas source

   For delivery of optimum fractional concentration of inspired oxygen (FiO2) to maintain target saturation in the range of 90-95%, a blender is must. It helps in prevention of free radical oxygen injury, chronic lung disease and retinopathy of prematurity.
4. Patient interface

   The various types of nasal interfaces are:

   a) Nasal prongs

   b) Nasal mask

   c) Nasal cannula

   d) Nasopharyngeal prongs

Amongst all nasal interfaces the short binasal prongs have been shown to be most effective.7 Various types of nasal interface have been shown in Figure 7. The nasal interfaces vary in size, configuration, material and diameter. These factors affect the resistance to flow and may lead to variation in the pressure delivered at baby's nare or nasopharynx.

a) Nasal prongs: The nasal prongs are most commonly used interface for NCPAP. The various types of nasal prongs have been compared by DePaoli et al. for pressure drop for various rate of gas flow.7 It was observed that there was much variation in pressure drop amongst different devices and least pressure drop occurred with the Infant flow system. In a Cochrane review, the authors have concluded binasal short prongs to be more effective than nasopharyngeal prongs for avoiding re-intubation.

b) Nasal mask: Nasal mask have configuration similar to shape of nose. It is helpful when nares are very small to accommodate the nasal prongs. They are also used along with nasal prongs alternatively for an interval to minimize the pressure effects of the prongs on nares.

c) Nasal Cannula: Nasal cannula is generally used for oxygen delivery. It may provide some distending pressure depending on flow rate, size of the cannula, degree of leak, and size of the nares. The RAM Nasal Cannula which was originally designed for oxygen delivery is also found to be a useful NCPAP interface. It bears short binasal prong on larger calibre tubing than the standard oxygen cannula.

d) Nasopharyngeal prongs: Long nasal or nasopharyngeal prongs leads to increased resistance and high work of breathing. It could be either single or bi-nasaopharyngeal prongs. A cut endotracheal tube from nares to nasopharynx may work as single nasopharyngeal prong (Figure 8B). The nasopharyngeal prongs are infrequently used.

Other parts of nasal interface kit include caps, fixing straps and nasal tubings. A comparative table for different types of nasal interface is given in Table 2.

Indications of CPAP

Following are indications of CPAP

a. Respiratory Distress: CPAP is primary mode of respiratory support in case of neonates. The disease wise common indications are respiratory distress syndrome, transient tachypnea of newborn and pneumonia. It can be also used in mild to moderate case of meconium aspiration syndrome as initial respiratory support.

b. Delivery room resuscitation: In the delivery room for neonates with laboured breathing, CPAP can be given by T-piece resuscitator.

c. Apnea: CPAP reduces episodes of apnea. It is indicated when methylxanthine therapy fails. The usual CPAP pressure is 4-6 cm of H2O.

CPAP is contraindicated in upper airway abnormalities, severe cardiovascular instability and poor spontaneous respiratory efforts.

How to set up a CPAP

1. Identify the baby with respiratory distress and in need of continuous positive airway pressure by Respiratory distress scoring (Silverman Anderson score ≥ 3 in preterm babies and ≥ 5 in term neonates).
2. Monitor and record vitals.
3. Connect air and oxygen tubing to pressurized central source or to air compressor and oxygen cylinder. Attach the tubings to blender for controlled FiO2 delivery. Switch on the humidifier.
4. Assemble the sterile CPAP circuit. Disposable circuits are preferable.
5. Inspiratory limb: Components of inspiratory limb are from flow meter to humidifier and then carrying heated and humidified gas from humidifier to patient end at nasal interface.

   Expiratory limb: In case of bubble CPAP, it goes from patient's nasal interface to water chamber where depth of its insertion determines the pressure. In case of ventilator CPAP, the expiratory limb goes from patient's nasal interface to expiratory valve of the ventilator.
6. The most important aspect of CPAP set up is positioning and fixation of nasal interface. The ideal technique of fixation depends on the type of CPAP equipment.
7. Identify the right size prongs and mask with the help of guide by manufacturers. The nasal prong should snugly fit in the nasal cavity to avoid significantly leak. Loose prongs will not deliver CPAP pressure adequately and tight prongs will lead to nasal trauma. A small piece of tegaderm which covers philtrum and nasal septum can help in decreasing nasal injury due to CPAP interface. The same purpose can be done by commercially available cannulaide (Figure 8C). Maintain a 2-3 mm gap between nasal septum and nasal prongs to decrease the chances of trauma to the nasal septum (Figure 8A). A nasal trauma monitoring chart is given in Table 3.
8. Fix the proper size cap. Cap is chosen on the basis of head circumference and weight. Cap should be placed above the eyebrows, passing over the ears and reaching up to the back of the neck.
9. Fix the cap, prongs and interface with the help of fixing straps and velcro. The set pressure may not be delivered to the baby if the mouth remains persistently open. A chin strap or pacifier may be used to counter this. There is increase of pressure in nasopharynx by 2-3 cm of H2O if chin strap is used.
10. Connect the CPAP circuit.
11. Humidifier should be filled with distilled water.
12. Connect the circuit to the nasal interface. Check for any leaks.
13. Orogastric tube should be in situ which helps in gastric decompression and feeding. CPAP is not a contraindication for feedings and normal feeding protocol should be followed in a baby on NCPAP.
14. CPAP delivery in neonates involves giving heated humidified (370C and 100%) oxygen and air mixture with oxygen concentration range of 21 to

100% at a flow of 6-8 litres/ minute to achieve pressure of 4-8 cm of H2O.

Monitoring on NCPAP

A baby on NCPAP should be monitored with following methods:

1. Clinical: Baby should be monitored for severity of respiratory distress using scoring methods: Downe's for term baby and Silvermann Anderson score for preterm babies. The monitoring also includes comprehensive monitoring of other system including vital parameters.
2. Blood gas analysis: Blood gas should be performed to look for adequacy of CPAP in case of clinical worsening.
3. Chest X ray: Chest X ray is usually performed for etiological diagnosis. In case of clinical worsening, repeat Chest X ray should be considered.

Weaning on NCPAP

Weaning on NCPAP should be considered as:

- Observe for improvement in distress score
- Reduce Fio2 gradually to 25% (decrement of 5%)
- Decrease PEEP to 4-5 cm of H2O
- If PEEP 4 cm & FiO2 <25% & clinically well (no respiratory distress, SpO2 > 90% & Normal blood gas): Wean from CPAP

Complications of CPAP

The following complications can occur on NCPAP

- Gastric distension
- Over distension of the lung:
  - i. Air leaks
  - ii. CO2 retention
  - iii. ↓Cardiac output due to increased intrathoracic pressure.
- Nasal damage

Failure of CPAP

Failure of CPAP is indicated by:

- Worsening of respiratory distress
- Recurrent apneas and desaturation
- Increasing oxygen and pressure requirements
- Worsening blood gases

II. Non-invasive positive pressure ventilation (NIPPV)

Non-invasive positive pressure ventilation (NIPPV) is a bridge between CPAP and invasive ventilation. In this form of ventilation, time cycled pressure controlled breaths are delivered through nasal interface. It is given either as synchronized or non-synchronized NIPPV with conventional ventilators. It has been used for apnea of prematurity, post extubation respiratory support and primary management of respiratory distress.9

NIPPV Devices

The devices which can be used to give NIPPV include:

1. Any conventional ventilators with time cycled pressure limited mode which is capable of providing NCPAP and intermittent mandatory ventilation can deliver NIPPV. With this there would be some alarms about leak and low pressure which can be taken care by ventilatory setting adjustments.The devices for Synchronized non-invasive positive pressure ventilation (SNIPPV) are few. SNIPPV can also be delivered with the assist/control (N-A/C) and pressure support (N-PSV) modes to assist every spontaneous breath. SNIPPV can be provided by Servo-I ventilator from Maquet Medical System, Sechrist IV-200 SAVI ventilator and nasalflow synchronized ventilator from Gineveri.

   The method of synchronization involves detection and feedback of patient's inspiratory efforts. The common methods of synchronization are:

a. Graseby pressure capsule is a transducer sensor which is placed on abdomen. It detects abdomen movement as respiratory effort for feedback and synchronization. It is most commonly used method of synchronization.

b. Flow sensors at patient end on nasal interface detect patient's inspiratory efforts. It requires frequent sensitivity adjustments for leak compensation around patient's efforts.

c. Neurally adjusted ventilator assist: It uses electrical activity of diaphragm (EAdi) as inspiratory effort. To detect EAdi, a special sensor is used which is put as orogastric tube.

d. Internal flow sensors: In some ventilators, flow sensor is inside rather than being at patient's end, but its use in NIV is lacking.

2. Devices that cycle between two levels of positive airway pressure at set frequency (BiPAP). These devices generate peak inspiratory pressure typically between 9-11 cm of H2O and uses longer inspiratory time. Examples of BiPAP devices are: The flow-driver "SiPAP" and Infant Flow Driver Advance by Care Fusion.

   SNIPPV has been shown to be better in terms of improved pulmonary mechanics, stability of chest wall, increased tidal and minute volumes thoraco-abdominal motion synchrony and decreased flow resistance and work of breathing.

   NIPPV nasal interface

   Almost all the nasal interface which is used to deliver NCPAP can be used for NIPPV. There are not proper comparative studies to suggest use of one nasal interface over another. In view of the same, the short bi-nasal prongs are recommended given the ease of use, and decreased susceptibility to blockage secondary to secretions as in case of NCPAP.

   Indications of NIPPV

NIPPV is indicated in following conditions \:

- Respiratory distress: NIPPV can be considered in babies with moderate respiratory distress as primary method or in those who fail on NCPAP.
- Apnea: NIPPV can also be considered in babies with persistent apnea even on NCPAP
- Post extubation: NIPPV is an important modality for respiratory support in babies post extubation from invasive mechanical ventilation.

The suggested initial ventilator settings on NIPPV is shown in Table 4.10

III. Neurally adjusted ventilator assist (NAVA)

   NAVA is a form of ventilation which is used in both intubated and non-intubated babies. It uses electrical activity of diaphragm (EAdi) as inspiratory effort. To detect EAdi, miniature electrodes are used which are fixed on conventional feeding tube. The EAdi signal is used to trigger and cycle of the ventilator. The EAdi signal cannot be acquired in case of apnea, deep sedation and poor respiratory drive. NIV-NAVA is possible only in case of good respiratory effort.

IV. Nasal high frequency ventilation (NHFV)

   In this mode high frequency breaths are delivered by nasal interface. It uses smaller pressures and tidal volumes at higher frequencies as compared to other forms of NIV. The ventilators which can apply NHFV are Infrasonics Infant Star and Draegor VN500. The nasal interface are either nasopharyngeal ETT or bi-nasal prongs.

Conclusions

- NCPAP is most common form of NIV used in neonates.
- Important components of CPAP include blended gas source, heating- humidification system, pressure generator and nasal interface.
- There are two types of CPAP: Constant flow and variable flow.
- Secure fixation of nasal interface is very important aspect of CPAP set up
- NIPPV acts as a bridge between CPAP and invasive ventilation.

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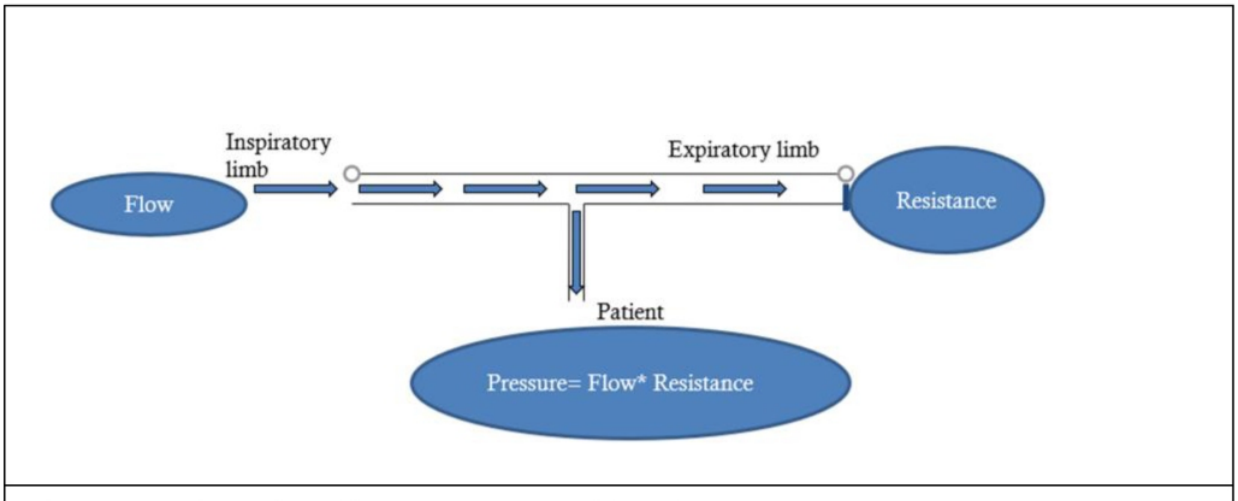

Figure 1: Principles of Continuous positive airway pressure

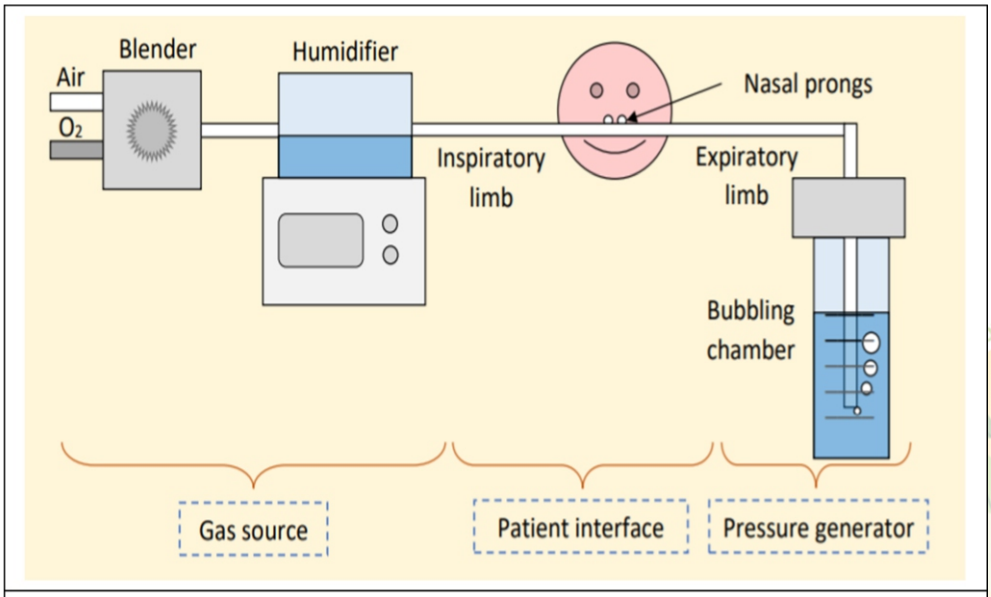

Figure 2: Components of CPAP delivery system

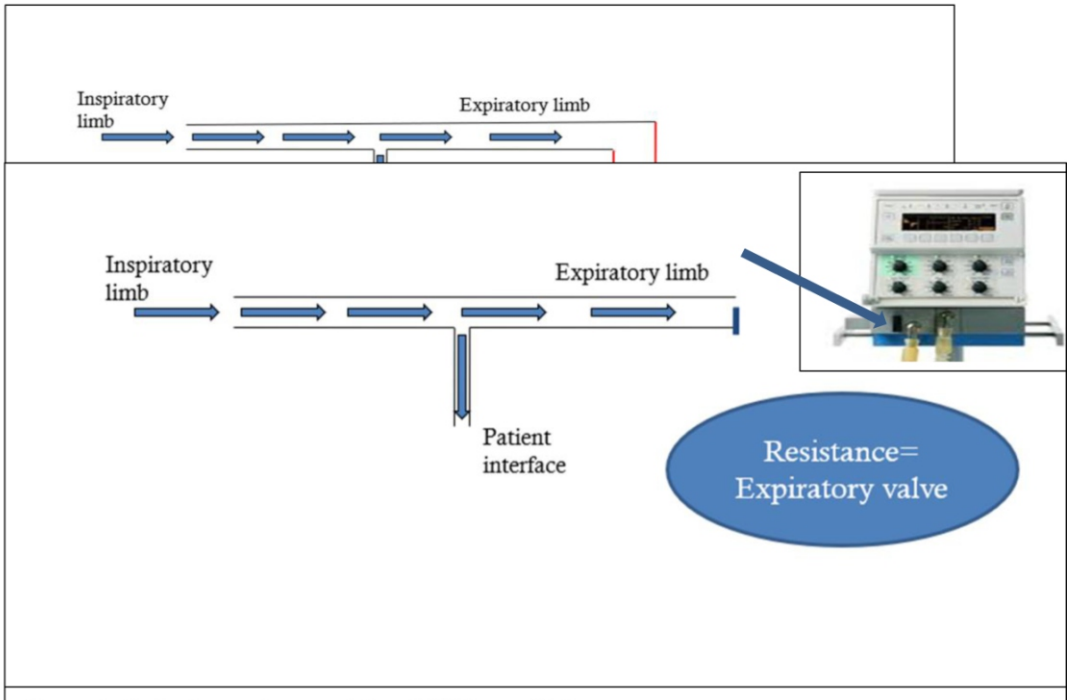

Figure 4: Expiratory valve regulates CPAP in ventilator

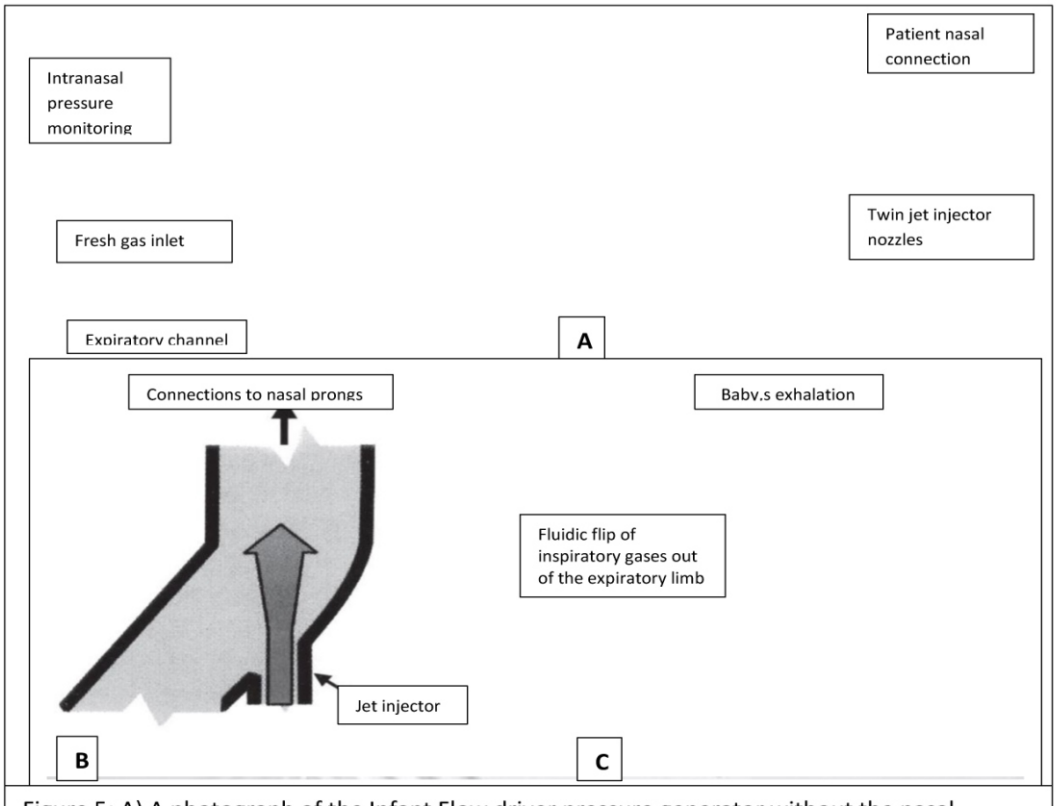

Figure 5: A) A photograph of the Infant Flow driver pressure generator without the nasal prongs. B) & C) Schematic representations of the "fluid flip" of the variable-flow CPAP device.

B) During the child's inspiration, the gas flow is directed toward each nostril due to Bernoulli effect to maintain a constant pressure. C) During the child's exhalation, the Coandă effect causes inspiratory flow to "flip" and leave the generator chamber via the expiratory limb.

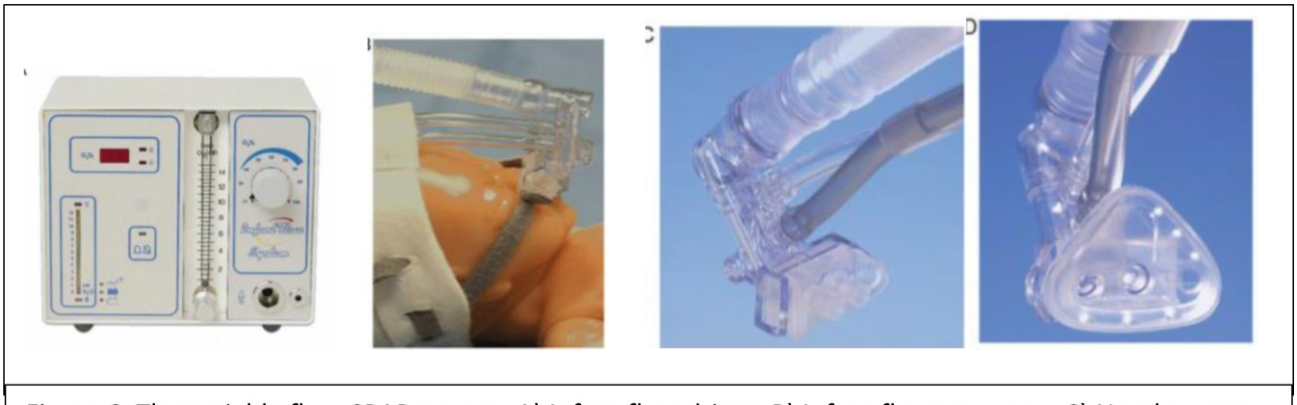

Figure 6: The variable flow CPAP system: A) Infant flow driver; B) Infant flow generator C) Nasal prongs D) Nasal mask

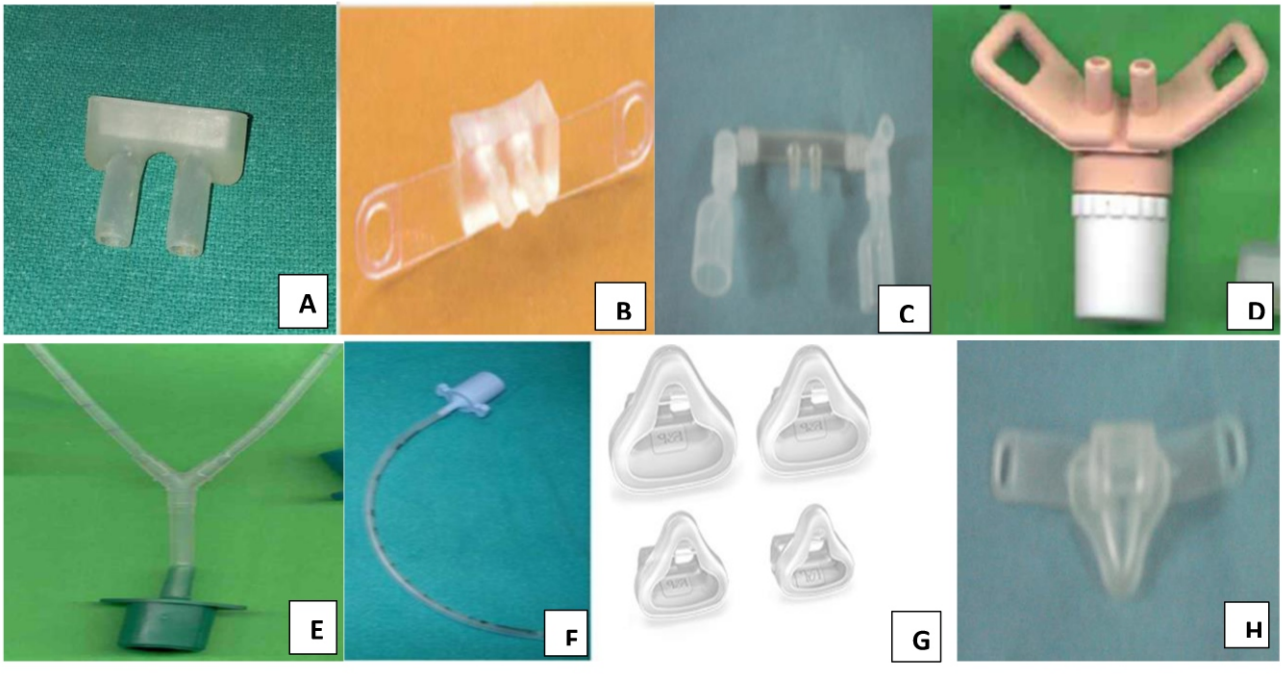

Figure 7: Various types of nasal interfaces. A: Fisher and Paykel Nasal prongs B: Draegor nasal prongs C: Hudson nasal prongs D: Argyle nasal prongs E: Nasopharyngeal prongs F: Endotracheal tube can be used as single nasopharyngeal G: Fisher and Paykel nasal mask G: H: Draegor Nasal mask

Figure 8; A: Secure fixation of Hudson nasal prongs B: Endotracheal tube being used as single nasopharyngeal prong C: Application Cannulaide for decreasing nasal trauma

Table.1: Comparison of different CPAP types

Type of CPAP	VENTILATOR CPAP	BUBBLE CPAP	INFANT FLOW DRIVER
Mechanism	CPAP is generated by expiratory valve	CPAP is generated by the bubble chamber	CPAP is generated just distal to patient prongs
Flow	Constant	Constant	Variable
CPAP level	Change in pressure is by changing the resistance of the valve	Change in pressure is by changing the length of immersion	Change in pressure is by changing the flow
Advantages	1. Changed to ventilator if needed	1. Inexpensive 2. Bubbling produces better gas exchange 3. Leaks can be identified as bubbling stops	1. Reduced work of breathing 2. Maintains uniform CPAP 3. Improved lung recruitment
Disadvantages	Expensive	1. Risk of inadvertent high pressure 2. No reliable pressure monitor display	1. Expensive 2. The physiologic benefits does not translate into improved clinical outcomes

Table 2: Comparison of various CPAP interfaces

Interface type	Advantages	Disadvantages
Nasal prongs e.g. Fisher and Paykel Argyll Hudson Draeger	• Lower resistance • Easily available	• Nasal trauma • Difficult to fix
Nasopharyngeal prongs e.g. cut endotracheal tube	• Easily available • More secure fixation	• More resistance • Easily blocked • Likely to get kinked
Nasal cannula e.g. RAM'S cannula	• Easily applicable	• Unreliable pressure, Fio2. • Large leaks around the cannula
Nasal mask	• Less nasal trauma	• Difficulty in maintaining good seal

Score																							
Date																							
Shift		a.m.	p.m.	Night shift	a.m.	p.m.	Night shift	a.m.	p.m.	Night shift	a.m.	p.m.	Night shift	a.m.	p.m.	Night shift	a.m.	p.m.	Night shift	a.m.	p.m.	Night shift
Internal Nare	Left																					
	Right																					
External Nare	Left																					
	Right																					
Philtrum																						
Septum																						
Total Score																						

Score

0= normal
1= pink/red
2= bleeding/ ulcer/ scab
3= skin tear

Table 3: Nasal trauma scoring chart for babies on CPAP

Table 4: Initial settings in NIPPV

Ventilator variable	Treatment of RDS	Support after extubation
Rate, breaths per minute	40	15-30
PIP, cmH20	2 to 4 > PIP on manual PPV	2 to 4 > PIP on mechanical ventilation
Positive end expiratory pressure, cm H2O	4-6	≤5
Time, inspiratory sec	0.4-0.45	0.3-0.5
Flow rate, L/min	8-10	8-10
Adapted from Bhandari V. Noninvasive respiratory support in the preterm infant. Clin Perinatol. 2012;39(3):497–511. (37)		

Expressing Data and Variable

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- **What are Data and Variables?**

Data is a collection of facts, such as values or measurements that can be processed or analyzed to derive meaningful insights from it. In statistics, we collect, organize, and analyze data from a study, so that we can understand the scenario in a better fashion. So, data is the basic raw material or building block needed for carrying out any research.

Variables are characteristics that takes on different value in different persons, places, or things. When we measure these variables, we get the data which later needs to be organized and analyzed in a certain way according to the type of variable involved in the study.

- **Types of Variables**

There are two types of variables:

A. **Quantitative variable:** They are objective and can be expressed in numbers. Measurements made on quantitative variables conveys information regarding amount. Example: number of children in family, height and weight of preschool children etc.

Quantitative variable is further bifurcated into discrete and continuous variable.

Discrete variable: Discrete variable tend to take an integer or whole number value only. Example: number of babies in NICU, Goal scored in a football match, number of MCQs correctly answered in an exam etc.

Continuous variable: They are measured on a continuous scale and can be recorded as real numbers and hence can have decimal values as well. Example: birth weight, Cord hemoglobin and bilirubin etc.

B. **Qualitative (Categorical) variable:** They cannot be measured in numbers and is expressed in words. Measurements made on qualitative variable conveys information regarding attribute. Example: gender of child (male or female), Cause of death of newborn (Congenital malformation, birth asphyxia, prematurity) etc.

Categorical variable is further broken down into nominal and ordinal variable.

Nominal variable: These are categorical variable where no ranking or order is implied. There is no way to order these categories from highest to lowest. When it comes to nominal variable, every category is equally important, and this property is known as equivalence. When nominal variable has only two categories like yes/no, present or absent, true or false then they are called binary or dichotomous variable. When there are more than two category they are classified as polychotomous variable. We can assign code numbers to the categories of nominal variable. However, the numbers assigned here are just for the purpose of grouping and has no mathematical meaning. Example: Blood groups, gender, colour of hair etc.

Ordinal variable: These are categorical variable which follows some order or hierarchy. Example: Socioeconomic class (poor, lower middle class, middle class, upper middle class, rich), size of clothes (small, medium, large).

For analysis of the available data, variables are also categorized into dependent and independent variables.

1. Independent variable: They are variable which is controlled or manipulated by researcher to see its relation or effects. It is the stimulus /exposure which causes changes in the dependent variable. This is placed on horizontal axis.
2. Dependent variables: They are outcome variable which changes on account of independent variable. A dependent variable is an effect or result and it always depends on another variable. They are not controlled or manipulated in any way but just being measured or registered. This is placed on vertical axis.

   Example: weight of person on different diet-

different diet is independent variable and measured weight is dependent variable. Performance of athlete with different level of training- different level of training is an independent variable and assessed performance is dependent variable.

- **Expression of data and variables:**

A. Qualitative variable: They are expressed either in the form of ratio, rates and proportion.

1. *Ratio:* Comparison of two values when they are independent of each other. Numerator is not a part of the denominator. They are mutually exclusive. Girl to boy newborn ratio in NICU admission, doctor to population ratio.
2. *Proportion:* Proportion is either expressed in percentage or fraction. Numerator is a part of the denominator. If numerator is x and denominator is y, then proportion is (x/x+y). To be expressed in percentage it has to be multiplied by 100.

$$\frac{\text{Number of female newborns admitted in NICU}}{\text{Total number of newborns admitted in NICU}}$$

3. *Rate:* Rate is the measure of frequency with which an event occurs in a definite population over a specified period of time. Rate is basically a proportion, but with added relationship with time. To calculate rate we need numerator, denominator, multiplier and time specification.

$$\text{Death rate} = \frac{\text{Total number of deaths in one year}}{\text{Mid-year population}}$$

$$\text{Infant mortality rate} = \frac{\text{Number of death of children less than one year of age in one year}}{\text{Total number of live birth}} * 1000$$

B. Quantitative variable: This is expressed depending on the distribution of data. Continuous variable with normal distribution is expressed as mean and standard deviation. Skewed data is expressed as median and interquartile range.

1. *Mean:* Mean is calculated by summing up all observation and then dividing it by total number of observations. Mean can either be calculated manually or with a calculator. It can also be done with the help of computer-based application like MS excel or statistical software like SPSS or SAS. An example is given below-

   The serum cholesterol level (mg/dl) of 10 subjects were found to be as follows: 192, 242, 203, 212, 175, 284, 256, 218, 182, 228.

Mean serum cholesterol level of the patients =

$$\frac{192 + 242 + 203 + 212 + 175 + 284 + 256 + 218 + 182 + 228}{10} = \frac{2192}{10} = 219.2 \text{ mg/dl}$$

An outlier is any value that is numerically distant from most of the other data points in a data set. The body weight of 10 students is 48, 52, 46, 58, 60, 59, 54, 104, 62, 50 kg. The outlier in the data set is 104 kg. Mean body weight of 10 students= 59.3 kg while the mean body weight of 9 students excluding the outlier is 54.3 kg. Mean is not a suitable measure for a skewed data set where there is outlier which has values which is numerically distant from other data points. In such cases median is measured.

2. *Standard deviation:* This gives us the idea about dispersion of data set i.e. how much the data is scattered around mean. In a normally distributed data, 68% of the observation lies within 1 standard deviation of mean. Two SDs cover 95% of the observation while 99.7 % of the observation are covered under 3SDs. Standard deviation is the sum of squared deviation divided by the number of values.

   Standard deviation is calculated by the formula:

$$\sigma = \sqrt{[\Sigma(x_i - \bar{x})^2 / (n - 1)]}$$

Although it looks difficult to calculate it manually, it can be easily calculated in MS excel and other software application. We need to choose the function key from toolbar and then can choose STDEV function and subsequently in the bracket we need to select the concerned cells; example: STDEV (B2:B10).

3. *Median:* Quantitative data with non-normal distribution (skewed distribution with outliers) is expressed in the form of median. Median is the middle observation after all values are arranged in ascending or descending order. Median divides the entire data set into two equal parts. In case of odd number of observations, the middle most value is taken, while for an even number of observations, average of two middle values is taken.

   Example: In a data set of [7,14,5,19,26,42,13], rearranged order in ascending fashion become [5,7,13,14,19,26,42]. The median is the middle most observation which in this instance is 14 since there are three numbers on either side.

   In a data set of even amount of number [3,13,2,34,11,17,27,47], the median is the average of two numbers in the middle [2,3,11,13,17,27,34,47] which in this case is 15 {(13+17)/2= 15}

4. *Interquartile range:* Quartile divides the data into 4 equal parts having 25% of data each. The first quartile(Q1) indicates that 25% of the observations lies below this value and 75% above, while the third quartile(Q3) indicates 75% observation lie below this value. Interquartile range is the range of middle 50% of observations (range between 1st and 3rd quartile), (Figure 1).

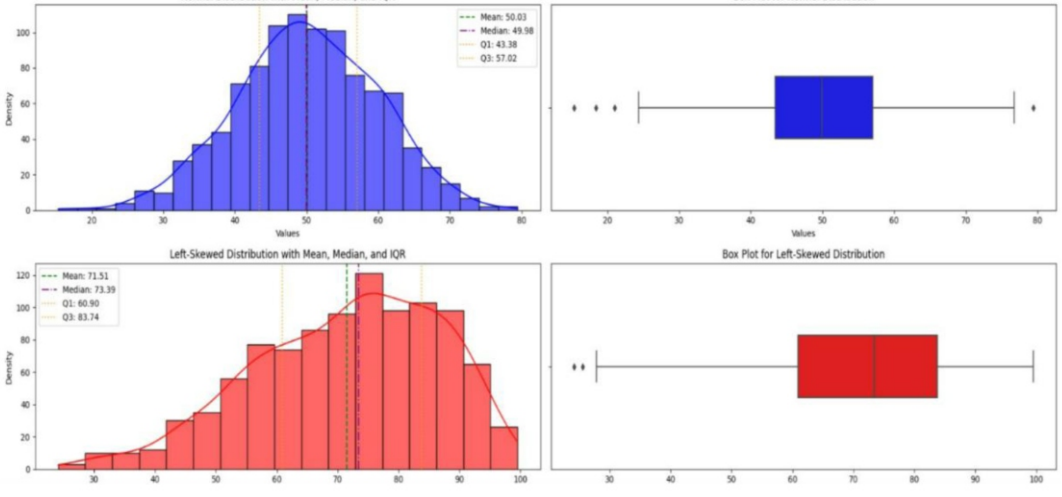

Figure 1: Normal distribution (blue) along with box plot and skewed distribution (red) along with box plot. The vertical lines in box plot show Q1, median and Q3, while whiskers at the end shows lowest and highest value. The width of the box gives the IQR.

- **Distribution of data:** After we collect the data, it is essential to present them in some orderly and logical form so that it provides easily interpretable and meaningful information. Distribution represents graphical representation of data that was collected from a sample or population and typically gives information about spread and pattern of collected data. The distribution for quantitative variable is either normal (gaussian) or skewed. Categorical variables have binomial distribution.

1. Normal distribution: The following are characteristics of a normal distribution-

a. The graph of a normal distribution is bell shaped which is symmetric around the mean value. (figure2).

b. In a normally distributed data mean, median and mode is equal which corresponds to the peak of curve.

c. When mean=0 and standard deviation =1 such distribution is called standard normal distribution.

d. The area under the curve of a standard normal distribution curve covers all the observation and hence it is equal to 1

   Normal distribution is very important because most of the continuous data in nature like height, weight, BP, IQ when compiled and plotted takes the shape of a bell (normal) curve.

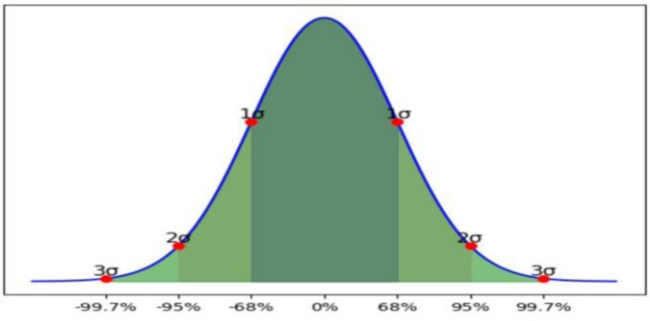

Figure 2: Normal distribution-bell shaped which is symmetric around the mean value.

2. **Skewed distribution:** In this type of distribution, curve obtained is asymmetrical because data is not evenly distributed around the mean. Data is clustered along the shorter tail of the curve. When the long tail of the curve trails towards right it is called positively (right) skewed. Observations are more clustered toward the left side of the curve. (Figure 3a). Examples include scores obtained in a relatively tough exam, income distribution in a state etc.

When the long tail of the curve trail towards left it is called negatively (left) skewed distribution. (Figure 3b). In positively skewed distribution there will be relatively fewer higher values and thus mode<median<mean. In negatively skewed distribution, there will be relatively fewer lower value and hence mean<median<mode

Statistical output gives **skewness of data** during analysis. Skewness >+1 or less than<-1 is considered skewed data and, in such cases, non-parametric statistical test should be considered for comparison.

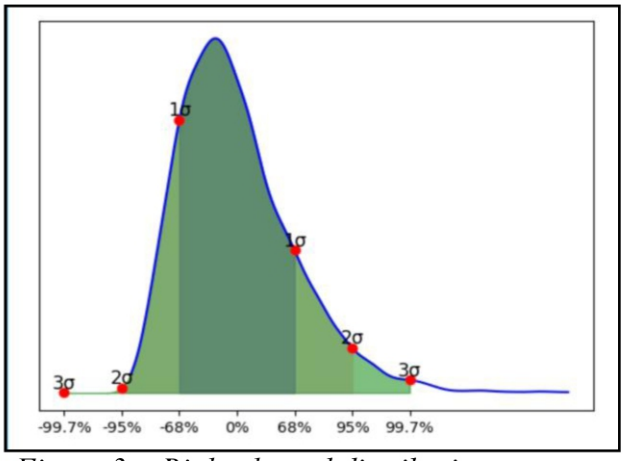

Figure 3a: Right skewed distribution

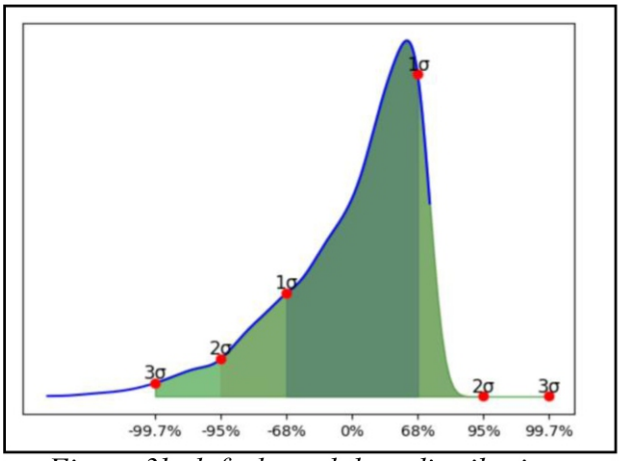

Figure 3b: left skewed data distribution

3. **Kurtosis:** This is derived from a Greek word which means bulginess. It exhibits the extent to which curve is more peaked or flat topped relative to normal distribution (Figure 4). It also tells us about the tail of a distribution. Tail represents how often outlier occurs. A fat tail of distribution contains more outliers as compared to thin tail. Distribution with higher peak and fatter tails relative to normal distribution is called leptokurtic. Here data is more concentrated towards the Centre. The coefficient of kurtosis in these cases is usually more than 3. Kurtosis of a normally distributed data is 3. If the distribution has a lower and fatter peak and thinner tail relative to normal distribution it is called platykurtic. The coefficient of kurtosis is less than 3 in this type of distribution.

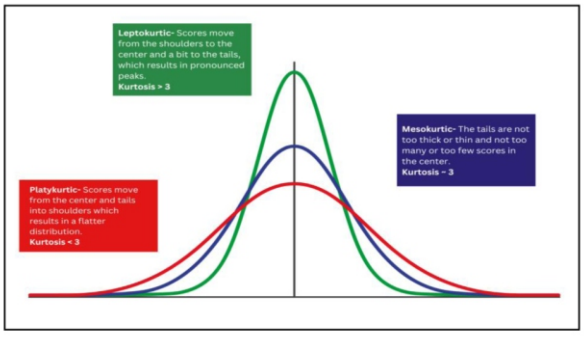

Figure 4: Kurtosis in the normal curve

- **Checking the distribution of data:** The following tests can be used to check the distribution of data-

1. **MK1 eyeballing test:** The quantitative data set is plotted on frequency distribution with the help of SPSS and other statistical packages. We can make an educated guess about the type of distribution by visualizing the graphs and superimposed curve. The normally distributed data can be seen as a superimposed bell- shaped curve on frequency distribution. This method can be misleading if sample size is relatively small, as the bell-shaped curve is often hard to see in smaller samples.
2. **Skew and kurtosis:** As discussed earlier, these can be calculated by using different statistical software. If for a given data, the measured skewness is close to zero, then distribution of data is considered to be normal. For practical purposes a value in the range of -1 to +1 is accepted to classify a data as normally distributed data.
3. **Test of normality:** There are certain tests like Kolmogrov- Smirnov and Shapiro-Wilk test to check the normality of data. Further details of these tests are beyond the scope of this article.
4. **Chi square goodness of fit test:** Frequency observed in a given data is compared to the expected frequencies of a theoretical data. A fitness of good test is applied and the given data is considered as a good fit if p value > 0.05.

- **Statistical test based on the type of distribution:** The type of the statistical test to be used for quantitative data depends on the type of distribution. In case of normally distributed data, parametric tests are applied. Non-parametric tests are chosen if the given data has significant skewness or kurtosis. If we are not mindful while choosing the type of statistical tests, p values tend to be inaccurate. The flowchart below can be used to choose the appropriate statistical test in a given situation (Figure 5).

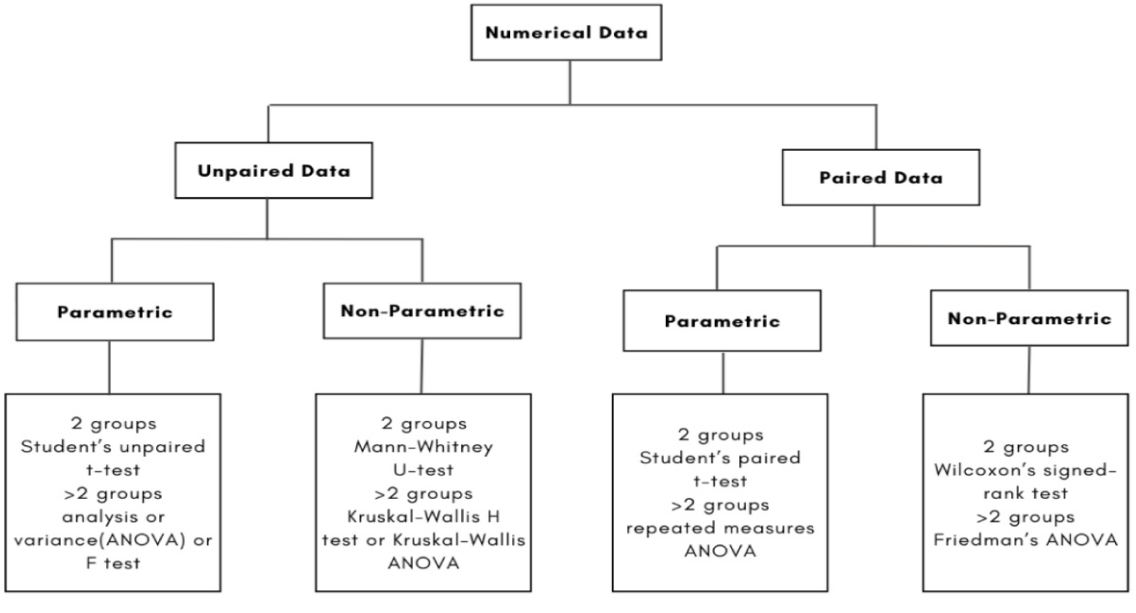

Figure 5: Statistical tests to compare quantitative data for difference

Key points:

- Variables are characteristics that takes on different value in different persons, places, or things. Measuring variables gives us the data which is the basic raw material for any research.
- There are two types of variables: Quantitative variables which are expressed in numbers and qualitative variables which are expressed in words.
- Quantitative variable depending on the type of distribution of data is expressed either as mean and SDs or median and IQR.
- Qualitative data is expressed as ratio, proportion or rates
- Distribution of data gives information about gives information about spread and pattern of collected data.
- The graph of a normal distribution is bell shaped which is symmetric around the mean value.
- Curve obtained in skewed distribution asymmetrical because data is not evenly distributed around the mean.
- Kurtosis measures the peaked-ness of curve relative to normal distribution.

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Journal Scan

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Selective Early Treatment of Patent Ductus Arteriosus with Ibuprofen

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N Engl J Med. 2024 Jan 25;390(4):314-325

1. Research Question:

Does selective treatment of echo-cardiographically confirmed large PDA in extremely preterm babies with ibuprofen within 72 h of birth reduce the incidence of death by 36 weeks postmenstrual age, or moderate or severe BPD at 36 weeks postmenstrual age?

2. Hypothesis

Population	Extreme preterm babies (23+0 - 28+ 6 weeks' gestation) with echo-cardiographically confirmed large PDA within the first 72 hours of life
Intervention	Ibuprofen administered parent-erally as a loading dose of 10 mg/kg of body weight, followed by two doses of 5 mg/kg at least 24 hours apart. Only one course of ibuprofen or placebo was given
Comparator	Placebo administered as an equal volume of 0.9% sodium chloride Only one course of placebo was given
Outcome	Composite outcome of incidence of death by 36 weeks postmenstrual age, or moderate or severe BPD at 36 weeks postmenstrual age

3. Methodology

3.1 *Study design:* Multicenter, double-blind, randomized, placebo-controlled trial

3.2 *Setting:* 32 neonatal intensive care units in the United Kingdom

3.3 *Study period:* July 2015-December 2020

3.4 *Study Participants:*

3.4a Inclusion criteria

All of the following must be present:

a. Born at 23+ 0–28+ 6 weeks' gestation

b. Less than 72 h old

c. Confirmed by echocardiography to have a large PDA which

- at least 1.5 mm in diameter,

AND

- unrestrictive pulsatile (left to right) flow (ratio of flow velocity in PDA Maximum (Vmax) to Minimum (Vmin) > 2:1) or, growing flow pattern (< 30% right to left), and no clinical concerns of pulmonary hypertension

d. Written informed consent is obtained from the parent (s).

3.4b Exclusion criteria:

If any one of the following is present:

- No realistic prospect of survival
- Severe congenital anomaly
- Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen
- Other conditions that would contraindicate the use of ibuprofen (active bleeding especially intracranial or gastrointestinal bleeding, coagulopathy, thrombocytopenia (platelet count < 50,000), renal failure, life-threatening infection, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC)
- Indomethacin, ibuprofen, or paracetamol administration after birth

3.5 Randomization, Allocation Concealment and Blinding

Dynamic randomization was performed with a secure Web-based system that was created and hosted by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit with 24/7 telephone backup, ensuring concealment of the group assignments.

The randomization program used a probabilistic minimization algorithm and assigned patients in a 1:1 ratio to one of the two groups to ensure balance with respect to the size of the PDA, gestational age at birth, age, sex, trial site, whether the infant was from multiple births, mode of respiratory support, and whether inotropes were received. The treatment allocation was blinded to study clinicians, the baby's family, or the trial outcome assessors (Double-blind)

3.6 Sample size

The incidence of the primary outcome was predicted to be 60% in the placebo group. A sample of 730 infants was calculated to be required in order to detect a clinically important absolute risk reduction of 12 percentage points (i.e., an incidence of 60% in the placebo group and an incidence of 48% in the ibuprofen group) with 90% power and a type I error of 5% under the assumption that 1% of infants would be lost to follow-up.

3.7 Statistical Analysis

Analyses were performed according to the intention-to-treat principle. Analyses were adjusted for size of the PDA at randomization, gestational age at birth, age at randomization, sex, infant from multiple births, mode of respiratory support at randomization, receiving inotropes at the time of randomization, and trial site. The trial site was treated as a random effect in the models, and all other factors were treated as fixed effects. Binary outcomes were analyzed using mixed effects. Poisson regression with a robust variance estimator; risk ratios and 95% confidence intervals are reported. Continuous outcomes were analyzed with the use of linear regression models; mean differences and 95% confidence intervals were reported. Stata/SE, version 15 (Stata Corp), was used for all analyses.

4. Results

653 infants underwent randomization; 326 assigned to the ibuprofen group and 327 to the placebo group. A primary-outcome event occurred in 220 of 318 infants (69.2%) in the ibuprofen group and 202 of 318 infants (63.5%) in the placebo group (adjusted risk ratio, 1.09; 95% confidence interval [CI], 0.98 to 1.20; P = 0.10). A total of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 infants (10.3%) in the placebo group died (adjusted risk ratio, 1.32; 95% CI, 0.92 to 1.90). Among the infants who survived to 36 weeks of postmenstrual age, moderate or severe bronchopulmonary dysplasia occurred in 176 of 274 (64.2%) in the ibuprofen group and 169 of 285 (59.3%) in the placebo group (adjusted risk ratio, 1.09; 95% CI, 0.96 to 1.23). No significant difference in any other prespecified secondary outcomes.

5. Strength of the study

- Largest randomized clinical trial assessing the role of "selective early treatment" versus "expectant management" approach for PDA closure in extremely preterm neonates.
- Stricter echocardiography criteria to identify babies whose PDA are unlikely to close spontaneously as compared to the previous studies.1
- Approximately half the enrolled infants were born at less than 26 weeks' gestation, the cohort at greatest risk for a hemodynamically significant PDA making the results of the study more meaningful.
- Aimed to reduce open-label treatment of ibuprofen by setting up clinical and echocardiography thresholds that need to be met before considering treatment of a symptomatic PDA.
- The study outcomes were adjusted for several minimization factors which could have potentially reduced the risk of bias by balancing the important prognostic factors as compared to the previous studies.

6. Study Limitations

- Open-label ibuprofen therapy was received by 14% of the infants in the ibuprofen group and 29.8% of the infants in the placebo group, making it more difficult to identify between-group differences in clinical outcomes. Further, 15 infants in the ibuprofen group and 33 infants in the placebo group received open-label treatment without satisfying pre-specified clinical and echocardiography thresholds that need to be met before considering treatment of a symptomatic PDA (protocol violation).
- The trial failed to achieve the target enrollment goal of 730 babies, reducing the power of the study.
- The first dose of ibuprofen or placebo was administered at a median of 57.5 hours (43.1–65.6) and 56.8 hours (43.9–66.7) after birth, which was later than in other, similar trials.2,3 However, it is possible that earlier intervention would have achieved more effective ductal closure.
- The mortality data is only reported up to 36 weeks and not overall mortality. Hence, it doesn't really answer whether early ibuprofen treatment of a large PDA has any effect on survival.
- Long-term neurodevelopmental outcomes were not assessed

7. Reviewer comments

In this multicenter, double-blind, randomized, placebo-controlled trial evaluating whether a targeted, prophylactic approach to duct closure with parenteral ibuprofen in extremely preterm babies (23+0 -28+ 6 weeks' gestation) with a large PDA (diameter of ≥1.5 mm and pulsatile flow on echocardiography) would reduce mortality and the risk of moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age. By selectively identifying infants within the first 72 hours of life who were deemed most at risk for a symptomatic PDA, the authors hypothesized that they would limit unnecessary drug exposure while optimizing outcomes.

The results of the trial indicated that early, targeted use of ibuprofen offered no benefit in reducing the risk of death or moderate or severe bronchopulmonary dysplasia as compared to placebo. The results remained non-significant even after adjustment for important prognostic factors. More sobering, some secondary outcomes are numerically higher with ibuprofen than with placebo, including the risk of severe intraventricular hemorrhage, cystic periventricular leukomalacia, and clinically significant pulmonary hemorrhage.

To date, RCTs and their meta-analysis comparing "selective early treatment" versus "expectant management" of ductus have uniformly failed to demonstrate any significant improvement in clinical outcomes as shown in Table 1.1-9 However, even minor variations in the timing of drug delivery, non-standardized dosing regimens and routes of administration, receipt of open-label treatment, and exposure to drugs that affect duct patency all contribute to the difficulty in interpreting results in even the most well-designed trials.

Based on the evidence generated from previous RCTs and the two recently published good-quality RCTs with adequate sample size as shown in Table 1 the most prudent approach to the PDA probably, appears to be to just leave it alone.

Table 1: Clinical trials assessing the role of "selective early treatment" versus "expectant management" approach for PDA closure in preterm neonates

S.No.	Author/Year	Population	Inclusion criteria	Primary Outcome	Result	Remarks
1.	Merritt/ 19814	Birth weight ≤ 1.35 kg N=24 IV indomethacin vs Fluid restriction and/or furosemide	Severe RDS requiring MV within 1 hr after birth and clinical symptoms of PDA along with left atrium to aortic root ration > 1.2; demonstration of PDA on retrograde aortogram	Death or BPD by 6 months of age	Significant reduction in the combined outcome of death or BPD Among individual outcomes there was significant reduction in the incidence of BPD with no effect on mortality	a. High open label indomethacin treatment in the control arm (84.6%) b. Only fewer clinically relevant outcomes were assessed
2.	Lin/2012 (Chinese)[5]	≤ 32 weeks and < 1500 grams N= 64 Oral ibuprofen vs placebo	Clinical symptoms with hs PDA	Multiple clinically relevant outcomes	No significant difference in mortality	
3.	Kluckow/ 20143	Multicenter RCT <29 weeks, N= 92. Indomethacin vs placebo before 12 h age	Large PDA based on the 50th centile postnatal age cut off from a population-based study	Combined death and/or abnormal cranial ultrasound (Papile Grade ≥2 or cystic PVL) at discharge	18% in the indomethacin group vs 19% in placebo. The individual components showed no significant differences.	Insufficient power due to poor rates of recruitment
4.	DeWaal/ 20196	Multicenter RCT < 29 weeks, n = 72, Site A used IV ibuprofen-lysine and site B used IV indomethacin Placebo as IV normal saline	hs PDA diameter > 1.5 mm with signs of pulmonary volume load and < 72 hours after birth	Recruitment rate and incidence of open label treatment Secondary - Mortality/ BPD	54% gave consent No difference in mortality and/or BPD	Open-label treatment rates not mentioned
5.	El-Khuffash/ 20217	Single center RCT, N = 60 Feasiblity trial IV Ibuprofen vs placebo as normal saline	Based on PDA risk score for developing CLD/death (5)	Death or BPD	No difference in Death or CLD (OR 0.8, 95% CT 0.3-2.1)	8 infants (12%) received open-label treatment in 1st 2 weeks The study was underpowered for the primary outcome
6.	Roze JC/ 20212	< 28 weeks, N = 228 Ibuprofen vs placebo	Large PDA at 6-12 hours of age	Survival without cerebral palsy at 24 months corrected age	No difference (71.3% vs 71.6%) (aRR 0.98, 95% CI 0.83 to 1.16, P=.83	Open-label rescue treatment with xibuprofen occurred in 62.3% infants with placebo and 17.5% infants with ibuprofen (p< .001), at a median age of 4 days.

7.	Hundscheid T/2023	Beneductus trial1 < 28 weeks N = 273 Ibuprofen vs placebo	PDA diameter (> 1.5 mm in first 72 hours of life) Non inferiority trial	Composite of NEC, moderate to severe BPD or death at 36 weeks PMA	46.3% in expectant group 63.5% in early ibuprofen group (aRR -17.2%, upper boundary of 95% CI -7.4, p < 0.001 for non-inferiority) BPD was less in expectant group	a. Enrollment stopped after only 48% of the planned sample size b. PDA diameter was used as the inclusion criteria which is imperfect c. Standard dose of ibuprofen was used as compared to the evidence of benefit for the high dose
8.	Gupta S, Baby Oscar/ 20248	<29 weeks, N=653 Ibuprofen vs placebo	PDA diameter >1.5 mm in first 72 hours of life Superiority trial	Death or BPD at 36 weeks PMA	69.2% in ibuprofen and 63.% in placebo aOR,1.09; 95%CI, 0.98 to 1.20; p = 0.10	As discussed above

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Sudden Unexpected Postnatal collapse

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Introduction:

Sudden Unexpected Postnatal Collapse (SUPC) is a rare but serious event, though relatively new clinical entity. In this, apparently healthy newborn infants (term or near term), otherwise well at birth, collapse unexpectedly, within the first week of life i.e. is discovered in a state of cardiorespiratory arrest such that resuscitation with intermittent positive pressure ventilation is required, and eventually either the baby dies or goes on to require intensive care, or develops an encephalopathy [1]. We report a case of SUPC, where the dramatic chain of events prompted us to extensive workup, and eventually led us to a diagnosis of OMIM disease - D2 hydroxy glutaric aciduria (autosomal recessive) variant of uncertain significance.

Case description:

A baby girl was born at a gestational age of 38 weeks, with birth weight of 3160 g by normal vaginal delivery. Her APGAR scores were 7, 9 at 1 and 5 mins of age, respectively. Breast feeding was initiated and baby was roomed in with mother. At about 2 hours of life, baby was found to be unresponsive, blue and without any breathing efforts. The baby was rushed to the nearest warmer and started on bag and mask ventilation, followed by intubation and chest compression. After extensive resuscitation lasting for many minutes, baby was transferred to the NICU. Blood gas revealed severe metabolic acidosis, and blood sugar was normal. Baby remained on ventilator support for about a month with several failed attempts of extubation, because of poor respiratory drive and mechanical issues like recurrent collapses of lung. Baby also had refractory seizures managed by four anti-epileptic drugs, pyridoxine, folinic acid and biotin. Clinically baby remained hypnotic with encephalopathy. However, MRI Brain done at 2 weeks of life was reported as normal. Complete blood count, liver function tests, renal function tests, blood sugar, calcium, phosphorus, alkaline phosphatase, ECG, echocardiography, repeat blood gases, Tandem Mass Spectrometry (TMS), Urine for Gas Chromatography Mass Spectrometry (GCMS); all were normal. Genetic epilepsy with encephalopathy was kept as a possibility in view of normal MRI and multiple episodes of refractory seizures. Whole exome sequencing revealed OMIM disease - D2 hydroxyglutaric aciduria (autosomal recessive) variant of uncertain significance. Baby was discharged on exclusive breast milk feeding by paladay on anti-epileptic drugs. On follow up, baby continues to gain suboptimal weight with no significant delay in neurodevelopmental parameters.

Discussion:

SUPC is a condition where, apparently healthy newborn babies present with any combination of sudden and unexplained episodes of hypotonia, pallor, apnea, bradycardia and/or cyanosis that requires some form of resuscitation and can evolve into death, or encephalopathy. This event happens typically in first week of life, in babies who have been assigned an Apgar score at 10 min of >7, and are of gestational age >35 weeks. In practice SUPC includes two entities: early Sudden Infant Death Syndrome (SIDS) or Sudden Un-Expected Neonatal Death (SUEND) and early Apparent Life-Threatening Event (ALTE) [2].

On review of literature, the estimates of SUPC seem to be lower than the actual collapses as only the most severe cases are probably reported [3]. Risk factors for SUPC are unattended skin-to-skin care (SSC), SSC when mother is tired/ sleepy or under sedation, use of mobile smartphone during SSC, newborn infants that required any form of resuscitation, or are not stable or have medical complications since birth, preterm infants < 36 weeks gestation, primiparous mother, unattended co-bedding, prone positioning of the infant and hypothermia [2].

Preventive strategies to prevent SUPC are as follows [4,5],

1. Identify healthy, term newborns who are prone for SUPC like those with category III fetal heart rate tracings, births complicated by shoulder dystocia and operative vaginal births, term births in which the newborn required resuscitation, or medications (sedatives) taken by the mother that may affect neonatal condition.
2. Educate mother and support persons about risk factors associated with SUPC. Provide education about frequent newborn color assessment and model safe newborn positioning during breastfeeding and skin-to-skin contact. One should continuously monitor the newborn throughout the first 2 hours after birth and also enable parents to raise concerns. Monitoring should be done during skin-to-skin contact and/or breastfeeding throughout the hospital stay. Consider incorporating pulse oximetry monitoring if available, in the first 2 hours following birth, particularly in high-risk cases. Ensure that there are adequate staff to support effective observation and assessment of the mother/parent/care-giver and the baby.
3. Ensure that delivery room staff and those assigned to assess and monitor newborn babies are competent to provide neonatal resuscitation. Teach safe positioning and monitoring of the newborn during skin-to-skin contact and during breastfeeding. Ensure that the newborn's face is seen at all times, nose and mouth are uncovered, head is held in sniffing position, and turned to one side, neck is straight and not bent, shoulders and chest are flat against mother/parent, legs are flexed, skin color remains pink at all times while being held, and mother is semi- reclined, not flat. There should be a formal mechanism to assess staff, at least annually for clinical competency in SUPC prevention and management.

Management of SUPC should be done in an expeditious manner to prevent neonatal morbidity and mortality. Infants, who suffer SUPC should undergo evaluation to rule out infection, congenital anomaly, metabolic or cardiac disease as an underlying cause for their collapse. The investigations suggested by British association of perinatal medicine to find out the etiology of SUPC are outlined in Box 1. Detailed history including situational events is essential and should be obtained by a senior member of medical staff. Continuous monitoring in NICU is a must with regular blood sugar monitoring, continuous oxygen saturation and ECG monitoring. Non-invasive blood pressure or invasive blood pressure monitoring should be done if there are signs of cardiovascular compromise. Assessment of acid-base and respiratory status should be done by blood gas. Neurological status should be periodically assessed, including cerebral function monitoring (CFM), if signs of encephalopathy develop. Other organs should also be assessed for end-organ hypoxic injury and tests such as renal and liver function tests, echocardiogram, brain MRI should be considered. Option of therapeutic hypothermia should be discussed with parents.

Box 1. Investigations suggested in SUPC

- Placenta- if available, placenta and cord should be sent for pathology and microbiology.
- Maternal specimens:

  Blood: Kleihauer test regardless of maternal blood group, viral titres (frozen serum for acute phase titres and HbA1c.

  Urine for toxicology

  High and low vaginal swabs including enriched culture medium for Group B Streptococcus.
- Neonatal specimens:

  Blood: Dried blood spots, complete blood count, coagulation profile, blood gas, renal and liver biochemistry, glucose, lactate, calcium, magnesium, ammonia, beta-hydroxybutyrate, amino acids, insulin, free fatty acids, acyl carnitine profile, urate, uric acid, cortisol (3 samples at different time points), culture, viral titres and blood spot for cardiolipin analysis.

  Cerebrospinal fluid: Biochemistry, glucose (paired with plasma glucose), culture, virology, lactate and amino acids including glycine.

  Nasopharyngeal aspirate: Bacteriology and virology, including SARS COV 2 sample for PCR.

  Urine: Bacteriology, virology, toxicology, organic acids including orotic acid, and amino acids including urinary sulpho-cysteine.

  Skin biopsy for fibroblast culture and muscle biopsy.

  Specific genetic tests:

  a. Array-based comparative genomic hybridization.

  b. If there is any suspicion that the collapse or death may have been as a consequence of unrecognised hypoventilation/apnoea, then a sample of DNA should be sent for abnormalities of the PHOX2B gene.

  c. Consider testing for genetic anomalies of cardiac conduction.

  d. Consider trio exome testing if multiple malformations with or without growth anomalies (including overgrowth) are present.

SUPC is a rare but catastrophic event. Pediatricians and Neonatologists should be aware of methods to prevent and manage such cases.

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Thrombosis of Torcular Herophili

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Clinical details

30-year-old G2A1 mother presented to our hospital at 36+4 weeks of gestation. She was being followed up for a fetal ultrasound finding of an echogenic lesion (2cm) at the torcula i.e. confluence of sinuses or Torcular Herophili, where the superior sagittal sinus, straight sinus, occipital sinus, and two transverse sinuses connect. This was reported as dural sinus thrombosis at 24 weeks of gestation (Figure 1). Rest of the fetal brain was unremarkable. Maternal coagulation profile, Anti-nuclear antibody, Antiphospholipid antibodies and TORCH profile was normal. Follow up antenatal ultrasound at 30 weeks of gestation showed an increased size of the echogenicity from 2 cm to 4 cm. Fetal ECHO was done which was reported normal. At 32 weeks, fetal MRI confirmed sinus thrombosis in Torcular Herophilus region without any associated brain changes. Follow up ultrasound showed a stable thrombus.

Baby was delivered at 36+4 weeks gestation by elective caesarean section in view of maternal perception of reduced fetal movements. A female baby with birth weight of 2600 g was delivered. She cried immediately after birth and did not require any resuscitation. Apgar scores were 9 and 9 at 1 and 5 minutes of life. Clinical examination was unremarkable. No stigmata of intrauterine infection or congenital malformation were noted. Investigations revealed normal platelet counts and coagulation profile. Postnatal MRI (Figure 2 and 3) showed large region of increased echogenicity in the Torcular Herophili region suggestive of sinus thrombosis. Rest of brain parenchyma and draining sinuses reported normal. Parents were counselled accordingly and were offered treatment with low molecular weight heparin (LMWH) for 4 to 6 weeks.

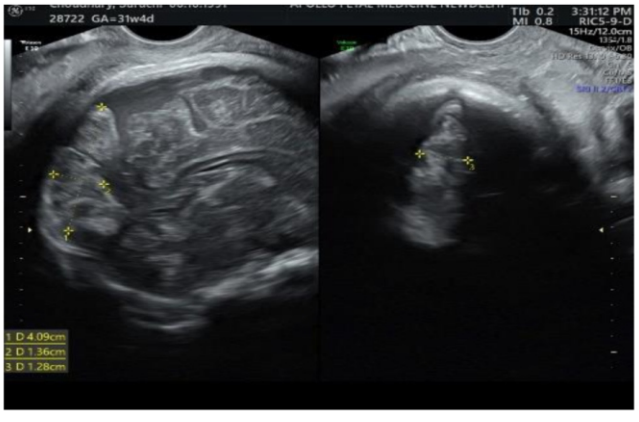

Figure1. Antenatal ultrasound suggestive of the venous sinus thrombosis at 31 weeks

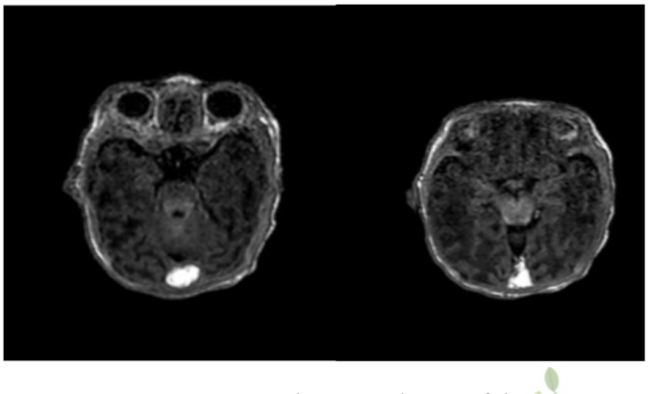

Figure2. Postnatal MRI: Axial views of the thrombus at Torcular Herophilus

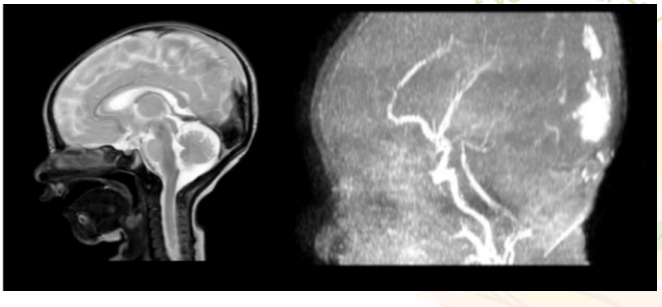

Figure3. Postnatal MRI: Sagittal views of the thrombus at Torcular Herophilus

Review of literature

Torcular Herophilus is the confluence of superior sagittal sinus, straight sinus and the occipital sinus, which join at the level of junction between cerebri and cerebellar tentorium. The low velocity flow in this region of confluence predisposes to formation of thrombosis [1]. Thrombosis of Torcular Herophilus is a rare entity, with only 50 cases reported in literature till date.

A thrombotic event can be precipitated because of local vascular structural anomaly that may cause increased turbulence, trauma, infection or hypercoagulable state, polycythaemia, or intrinsic pro-coagulation disorders. Unlike adults, no specific risk factors are associated with thrombosis, and, in 50% cases, it is idiopathic. The association with environmental exposure and APLA syndrome is also not proven. The distinctive feature on imaging is large intracranial thrombus within a distended torcular herophilia. Anecdotal cases have been treated with low molecular weight heparin [2,3]. Despite the dramatic presentation on imaging, it can be associated with good perinatal outcome, when the thrombosis is an isolated event. Long term follow-up studies are lacking, but it is postulated that without associated morbidities like structural anomalies of brain or hydrocephalus or ventriculomegaly, the prognosis remains good.

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1. Laurichesse Delmas H, Winer N, Gallot D, Lopes K, Perrotin F Fluncker S, Geissler F et al. Prenatal diagnosis of thrombosis of the dural sinuses: report of six cases, review of the literature and suggested management. Ultrasound Obstet Gynecol. 2008;32:188-98.
2. Rayssiguier R, Dumont C, Flunker S, Couture A, Boulot P, Prodhomme O. Thrombosis of torcular herophili: diagnosis, prenatal management, and outcome. Prenat Diagn. 2014;34:1168-75.
3. Wu YW, Miller SP, Chin K, Collins AE, Lomeli SC, Chuang NA et al. Multiple risk factors in neonatal sinovenous thrombosis. Neurology. 2002;59:438-40.

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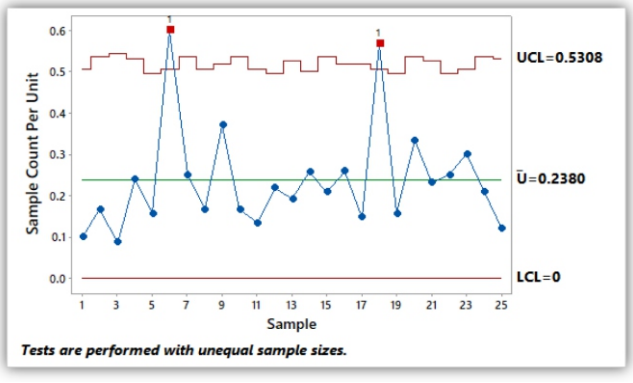
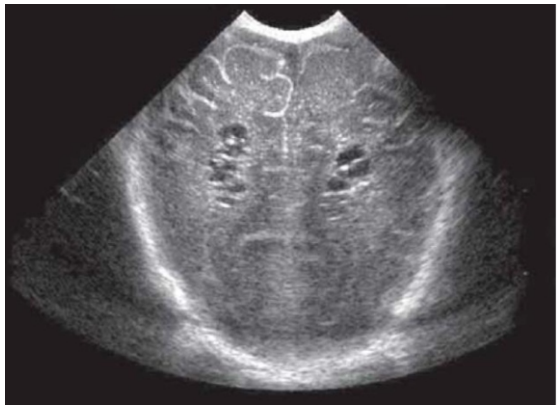
Question 1

Identify the chart depicted in the given picture. In what type of studies are such charts used?



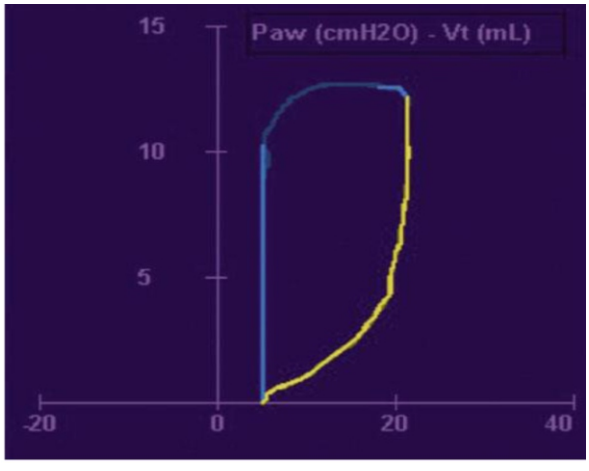
Question 2

Below is the coronal section of cranial ultrasound of 27-week preterm neonate at 4 weeks postnatal age. What are the findings? What could be the long-term sequelae of this condition? How do we grade them?



Question 3

A 40-week male born through MSAF is being ventilated on A/C mode of ventilation for severe MAS. You also saw the adjacent image being displayed on ventilator screen. Identify the abnormality and what should be the first line of management?



Question 4

Which of the following graphs is used for depicting publication bias?

(i) ROC curve

(ii) Bland Altman curve

(iii) Funnel Plot

(iv) Forest Plot

Question 5

Which of the following tests of significance is used to analyse two categorical variables?

(i) Wilcoxon Ranksum test

(ii) Chi Square test

(iii) Student T test

(iv) ANOVA

Question 6

Which of the following diagnostic tests is affected by the prevalence of a disease?

(I) Sensitivity

(ii) Positive predictive value

(iii) Specificity

(iv) All the above

Question 7

An investigator plans to study the risk factors for a rare disease (VACTERAL syndrome) and decides to collect data from the records of the patients diagnosed with this disease in the last ten years and compare the factors from the patients who were not diagnosed disease. Which type of study design is this?

(i) Cohort study

(ii) Cross sectional study

(iii) Case control study

(iv) Randomised study

Question 8

Splitting of monozygotic twins between 8 to 13 days results in which type of twins?

(i) Monochorionic Monoamniotic

(ii) Diamniotic dichorionic

(iii) Diamniotic Monochorionic

(iv) Conjoined twins

Question 9

Significant hypothermia as per WHO is defined as core temperature below?

(i) 36 degrees celsius

(ii) 35 degrees celsius

(iii) 35.5 degrees celsius

(iv) 34 degrees Celsius

Question 10

In CTG, finding absence of baseline variability corresponds to which category of

according to the three-tier classification?

(I) Category 1

(ii) Category 2

(iii) Category 3

(iv) None of the above

Question 11

High placement of umbilical catheter is between which vertebral level?

(i) T 10 to T 12

(ii) T 6 to T 9

(iii) T 8 to T 10

(iv) L1 to L3

Question 12

You are evaluating a 28 weeker at 28 days. His calcium level is 9.4mg/dL, Phosphorus is 4.8 mg/dL and alkaline phosphatase is 925U/L. What is your presumptive diagnosis? What is Tubular reabsorption of phosphate

Question 13

Which app is being used for implementation of LAQSHYA initiative for quality improvement of birthing areas?

Question 14

Baby OSCAR trial involves which preterm illness?

(I) NEC

(ii) RDS

(iii) IVH

(iv) PDA

Question 15

KILKARI is one of the National programs for improving maternal and child health. What is the maximum age of beneficiary as child (mother with child) under the National program "KILKARI"

Answer 1

Control chart

Quality Improvement studies

The control chart is a graph used to study how a process changes over time. Data are plotted in time order. A control chart always has a central line for the average, an upper line for the upper control limit, and a lower line for the lower control limit. These lines are determined from historical data. By comparing current data to these lines, we can draw conclusions about whether the process variation is consistent (in control) or is unpredictable (out of control, affected by special causes of variation).

Answer 2

- **Bilateral cystic periventricular leukomalacia.**
- **Spastic diplegia**

Grading of periventricular leukomalacia

DeVries grading

Grade I: Persistent flare (Usually bilateral) for at least 7 days without cystic evolution

Grade II (cystic PVL), parenchymal lesion persisting for 7 days and evolving into localized small fronto-parietal cysts; lesions not involving occipital cortex

Grade III: Multiple cysts in parieto-occipital area

Grade IV: Intraparenchymal cysts in deep white matter and subcortical region.

Answer 3

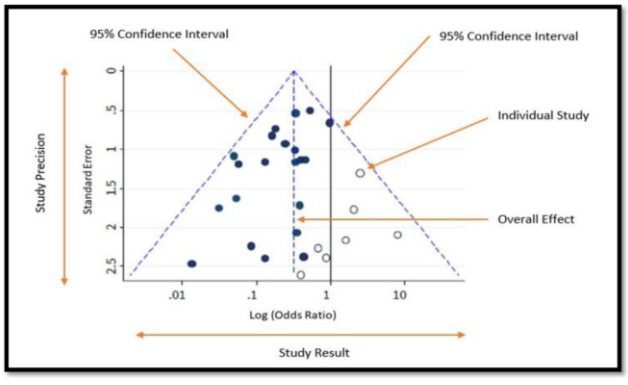
- Air leak- The P-V loop fails to return to the x-axis (0 volume). The deflation limb stops before reaching the PEEP value (the straight solid line is an artifact drawn by the monitor).
- Look for circuit leak and small ET

Answer 4

Funnel plot

A funnel plot is a scatter plot that compares the precision (how close the estimated intervention effect size is to the true effect size) and results of individual studies. It is commonly used in meta-analyses to visually detect publication bias.

The term 'funnel plot' refers to the fact that the precision of the estimated intervention effect increases with the size of the study. Small study effect estimates will typically scatter more widely at the bottom of the graph, with the spread narrowing among larger studies as they are more precise and closer to the true effect.



Each included study is represented as a dot. The y-axis represents a measure of study precision, with standard error being commonly used. Larger studies with greater precision are displayed at the top and studies with lower precision at the bottom. Other measures such as the reciprocal of the standard error, the reciprocal of the sample size, or variance of the estimated effect can also be used as the y-axis. The x-axis displays the study estimated effect size for an outcome. The scale for the x-axis can include risk ratios or odds ratios (which should be plotted on a logarithmic scale), or continuous measures such as mean difference or standardised mean difference.

In the absence of both bias and heterogeneity, 95% of studies would be expected to lie within the diagonal dotted '95% Confidence Interval' lines, as shown in Figure

Answer 5

Chi square test

Statistical tests

A. Between two categorical variables

X is group variable and Y is outcome variable

X=2, Y=2		X>2, Y>2
Unrelated	Related	Unrelated
- Chi square test	McNemar test	- Chi square test
- Fishers Exact test (if cell frequency is <5)	- Fishers Exact test	

B. Between one categorical and one quantitative variable

X=2, Y=normal distribution		X=2, Y=non-normal	
Parametric		Non-Parametric	
Unrelated	Related	Unrelated	Related
Student's test	Paired `t' test	Wilcoxon ranksum/ Mann Whitney test	Wilcoxon signrank
X>2 and Y Normal		X > 2 and Y non-normal	
Unrelated	Related	Unrelated	Related
One way ANOVA	Repeated Measures ANOVA	Kruskal Wallis	Freidmans test

C.Two quantitative variables

X- Normal distribution and Y: Normal distribution (Both should be normal): Pearsons's correlation coefficient

X – Non-Normal or Y: Non-Normal or If one is non-normal and the other is normal: Spearman's rank correlation.

Answer 6

PPV- Positive predictive value

Positive predictive value is the proportion of cases giving positive test results, who are already patients. It is the ratio of patients truly diagnosed as positive to all those who had positive test results (including healthy subjects who were incorrectly diagnosed as patient). This characteristic can predict how likely it is for someone to truly be patient, in case of a positive test result.

Positive predictive value=TP (True positive)/TP (True positive) + FP (False positive)

Since the ratio includes both healthy and patient subjects, predictive values are affected by the prevalence of the disease and can differ from one setting to another for the same diagnostic test. The lower the prevalence of the disease, the higher its negative predictive value. On the other hand, the higher the prevalence of the disease, the higher the positive predictive value.

Answer 7

Case control study

In a case-control study patients who have developed a disease are identified and their past exposure to suspected aetiological factors is compared with that of controls or referents who do not have the disease. This permits estimation of odds ratios (but not of attributable risks). The direction of the study is from outcome to exposure.

A cross sectional study measures the prevalence of health outcomes or determinants of health, or both, in a population at a point in time or over a short period

In a cohort or a longitudinal study, subjects are followed over time with continuous or repeated monitoring of risk factors or health outcomes, or both. The direction of the study is from exposure to outcome.

Answer 8

Monochorionic monoamniotic twins

Answer 9

32.0 degree Celsius

The World Health Organization defines hypothermia in newborns as mild 36.0–36.5°C, moderate 32.0–36.0°C and severe <32.0°C.

Answer 10

Category 3

Category I: Normal.

The fetal heart rate tracing shows ALL the following:

Baseline FHR 110-160 BPM, moderate FHR variability, accelerations may be present or absent, no late or variable decelerations, may have early decelerations.

Strongly predictive of normal acid-base status at the time of observation. Routine care.

Category II: Indeterminate.

The fetal heart rate tracing shows ANY of the following:

Tachycardia, bradycardia without absent variability, minimal variability, absent variability without recurrent decelerations, marked variability, absence of accelerations after stimulation, recurrent variable decelerations with minimal or moderate variability, prolonged deceleration > 2minute but less than 10 minutes, recurrent late decelerations with moderate variability, variable decelerations with other characteristics such as slow return to baseline, and "overshoot".

Not predictive of abnormal fetal acid-base status but requires continued surveillance and re-evaluation.

Category III: Abnormal.

The fetal heart rate tracing shows EITHER of the following:

Sinusoidal pattern OR absent variability with recurrent late decelerations, recurrent variable decelerations, or bradycardia.

Predictive of abnormal fetal-acid base status at the time of observation. Depending on the clinical situation, efforts to expeditiously resolve the underlying cause of the abnormal fetal heart rate pattern should be made.

Answer 11

T6 to T9

The catheter should pass through the umbilicus, travel inferiorly through the umbilical artery, then in the anterior division of the internal iliac artery, into the common iliac artery and then into the aorta. It is essential to ensure that the tip of the catheter is not in a branch of the aorta (where it could block the vessel or instil a high concentration solution directly into an organ-feeding vessel, such as the renal artery).

The tip of the catheter should thus be placed in one of two locations:

1.**high position:** at T6 to T10 level

2.**low position:** at L3 to L5 level

Intermediate positions are generally undesirable due to potential associated thromboses of major aortic branches between T10 to L3.

Answer 12

- Presumptive diagnosis is Metabolic Bone Disease of Prematurity
- **Tubular reabsorption of phosphate (TRP) can be measured as follows: urinary phosphate/serum phosphate × serum creatinine/urinary creatinine-**If serum phosphate is less than 5.5 mg/dL (1.78 mmol/L) and TRP is greater than 95%, this may suggest insufficient phosphorus intake.

Answer 13

Safe delivery app

The Safe Delivery App

The App includes 13 modules focused on evidence-based key interventions for women and newborns around the time of birth (Basic Emergency Obstetric and Neonatal Care (BEmONC)) and preventative procedures aligned with global or national clinical and treatment guidelines. The App was integrated into the QI cycles of the national initiative 'LaQshya'—a labour room QI initiative launched by the Ministry of Health & Family Welfare in Oct 2018.19

Answer 14

PDA

BABY OSCAR trial is a multicentre, randomized, double-blind, placebo-controlled trial evaluating early treatment (≤72 hours after birth) with ibuprofen for a large PDA (diameter of ≥1.5 mm with pulsatile flow) in extremely preterm infants (born between 23 weeks 0 days' and 28 weeks 6 days' gestation) conducted in different units in United Kingdom. The primary outcome was a composite of death, or moderate or severe bronchopulmonary dysplasia evaluated at 36 weeks of postmenstrual age. The risk

of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age was not significantly lower among infants who received early treatment with ibuprofen than among those who received placebo.

Answer 15

One year

The Kilkari program is a mobile based service launched in 2016, for new and expectant mothers aimed at encouraging them to make healthier choices for their newborn messages about Pregnancy, childbirth, and childcare directly to the beneficiaries. It is an audio-based service and hence overcomes the literacy challenges of rural India. Kilkari delivers free, weekly, time appropriate audio messages about pregnancy, childbirth, and childcare via Interactive Voice Response (IVR) to women registered in MCTS/RCH portal.

Messaging begins in the second trimester of pregnancy and continuous until the child is one year old.

The pregnant mother data is fetched from MCTS/RCH portal to Kilkari through web service which has been implemented between both the applications.

Instructions for Authors

Review Article	**The article should be approximately 2-3 pages long with a word count of 2000-2500 words. Author should summarize key practice points at the end. Please include 5-6 references as suggested reading.**
Case Report	**This would be a summary of the case discussed in that months clinical meeting. Interesting cases even if not presented may also be submitted. It should include the clinical presentation and a brief discussion about the condition. Word count should be 1000-1500. Please include 2-3 references at the end.**
Journal Scan	**Some recent research paper of interest to pediatricians and neonatologists. The structure should include Introduction, Research question, Hypothesis, Methods, Results, Limitations and strengths of study, Reviewers comments. Word count should be approximately 1000 words. Please include 2-3 references if needed at the end.**
Picture of Month	**An interesting case related to neonatal practice. It should have a brief case history and a commentary, all fitting on one page along with the pictures.**
Image section	**Any interesting Xray, Ultrasound, CT or MRI of clinical interest. Brief clinical presentation and about the condition should be summarized on one page along with image.**
OSCE	**About 10-15 questions would be included in this section along with answers.**

Contact Us

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

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