Society Regn No. BOM 127/1963 GBBSD*
Public Trust Regn No. F-1166 (BOM)

September-December, 2015
Volume VIII, Issue-3

# NEOCHAP BULLETIN

AN OFFICIAL PUBLICATION OF IAP NEONATOLOGY CHAPTER



*Theme : Nutrition in very low birth weight baby*

## CONTENTS

# IAP NEOCON 2015 MUMBAI


# EDITORIAL

Delivery of a very low birth weight baby is a nutritional emergency. Because the very low birth weight infant has very poor stores of nutrients, providing for nutritional demands at rates which approach what the baby would have received in utero should be considered as high in priority. Inadequate nutrition in the immediate post-natal period is associated with post-natal growth failure and with risk for neurodevelopmental impairment and other morbidities.

Therefore providing appropriate nutrition is necessary to achieve adequate growth and to improve long term neuro-developmental outcomes in very low birth weight infants.

Provision of adequate nutrition is best achieved by enteral feeding. However inappropriate feeding can also increase the risk of necrotising enterocolitis (NEC). The Neonatologist has to balance the need for establishing feeds against the risk of NEC. In some babies enteral feeding is not possible and parenteral nutrition remains the only solution to providing for the nutritional requirements of the baby. We have attempted to review the available evidence and provide the best available answers to maximizing the nutritional requirements of the very low birth weight infant. Dr. Sandeep has reviewed the evidence on best feeding practices and provided evidence based guidelines on feeding of the very low birth weight infant. Dr. Shobana has reviewed the literature on use of parenteral nutrition.

Necrotising enterocolitis (NEC) is a major cause of morbidity and mortality in very low birth weight infants. We have reviewed the clinical manifestations, investigations and treatment for babies with NEC. Dr. Suba has provided a review of the clinical features and management of NEC. In the recent years, there has been lot of interest in the use of probiotics to reduce the risk of necrotising enterocolitis in preterm babies. Dr. Karthikeyan has reviewed the available evidence and made recommendations for practice on the use of probiotics in preterm infants.

Dr. Muzamil Mugloo has provided answers to the appropriate use of micronutrients in very low birth weight infants.

In this bulletin we have aimed to provide best available and practical solutions to the practising paediatrician and neonatologist in the nutritional management of the very low birth weight infant.

Guest Editor
**Dr. K. Sankaranarayanan**
Consultant Neonatologist,
Kanchi Kamakoti CHILDS Trust Hospital, Chennai
E-mail : shankarnk@yahoo.com, Mobile : 8939675579

**IAP NEONATOLOGY CHAPTER SYMPOSIUM**
**PEDICON 2016**
Dates : 23 Jan, 2015, Hall 6, TIME: 08:30 am to 9:45 am

# Current evidence for Probiotics in preterm neonates

**Dr A.G. Karthikeyan**
Consultant Neonatologist, Dr Mehta's Children's Hospital Chetpet, Chennai - 600031
Mobile : 07299861648, E-mail : drkg@mehtahospital.com

Necrotising enterocolitis (NEC) has a high morbidity and mortality in neonates. Inspite of several advances, the incidence of NEC has remained constant over the years. Of interest recently, is the use of probiotics in the prevention of NEC. This article looks at the current available evidence for the use of probiotics in preterm neonates for reducing NEC.

**Terminology**

The World Health Organisation defines **probiotics** as "Live micro-organisms which when administered in adequate amounts confer a health benefit on the host." **Prebiotics** are supplements or foods that contain a nondigestible ingredient that selectively stimulates the growth and/or activity of indigenous bacteria. **Postbiotics** are **non-viable** bacterial products or metabolic byproducts from probiotic microorganisms that have biologic activity in the host. **Synbiotic** is a product that contains both probiotics and prebiotics.

**Gut colonization after delivery**

The pattern of colonization of neonates' gastrointestinal tract varies on the mode of delivery. A neonate who is vaginally delivered is colonized with mothers gastrointestinal bacterial flora - organisms such as lactobacillus, bifedobacter and bacterioids dominate the gut colonization. A neonate who is born by caeserian section is colonized predominantly with skin flora from the mother – organism such as staphylococcus dominate. This results in abnormal colonization of the gut with pathogenic bacteria. Preterm neonates have severe 'dysbiosis' of their gut due to the following reasons –

- Vaginal colonization with Bifidobacter & Lactobacillioccurs as pregnancyadvances. Pretermdeliveryreduces colonisation withtheseorganisms.
- Oftenborn by cesarian section
- Exposed to antibioticspre and postnatallywhichcan alter gutflora
- Exposed to NICU flora
- Multiple procedures –Fed by tube, Aspiration, Intubation
- Lessbreastmilkreceived due to theirseverity of illness

**Clinical implications of abnormal gut colonisation**

Preterm neonates especially those below 1500 grams are colonised predominantly with staphylococcus, Enterobacter and enterococcus. This results in development of late onset sepsis by these organisms. Indian studies have also reported a predominance of gram negative organisms to colonise preterm gut – Eschericia coli, Klebsiella and pseudomonas. These are common causes of late onset sepsis in neonates in India. Hence getting the right pattern of colonisation is critical as soon as possible after birth as abnormal colonisation leads to development of sepsis by these organisms. This becomes the basis for using probiotics in preterm neonates to reduce abnormal colonisation of gut.

**How do probiotics reduce NEC in preterm neonates?**

Probiotics have diverse mechanisms of action to reduce NEC in preterm neonates as outlined in table 1.

| |
|---|
| Normalization of gut microflora |
| Reduction in intestinal permeability |
| Increase in mucosal barrier function |
| Protection of colonization by pathogens |
| Decrease in proinflammatory and increase in anti-inflammatory cytokines |
| Improved enteral nutrition |
| Reduction of sepsis via reduced bacterial translocation |

Table 1 : Mechanism of action of probiotics

**What is the evidence for prebiotics in reducing NEC in preterm neonates?**

Three recent meta-analysis have shown the benefit of probiotic use in preterm neonates. The key results from these meta-analysis is shown in table 2

1. Probiotics reduce the incidence of definite NEC (⩾ stage 2) in preterm neonates by nearly 60%
2. probiotics reduce mortality in preterm neonates and specifically NEC related mortality in preterm neonates
3. There was no reduction in sepsis by use of probiotics in preterm neonates

| | No. of studies | Infants enrolled | Effect size RR (95% CI) |
|---|---|---|---|
| NEC (= stage 2) | 20 | 5529 | 0.43 (0.33–0.56) |
| All cause Mortality | 17 | 5112 | 0.65 (0.52–0.81) |
| NEC related mortality | 7 | 2755 | 0.39 (0.18–0.82) |
| Sepsis | 20 | 5338 | 0.91 (0.8-1.03) |

Table 2: Summary of evidence for probiotics in preterms

**Other beneficial outcomes from probiotic use**

Ten studies showed probiotics administra-tion significantly shortened hospitalization days compared to controls.

Eight studies reported time to full enteral feeds. There was a reduction in time taken to reach full enteral feeds

**Drawback from meta-analysis**

There was variation in the nature of studies included in the meta-analysis – studies had highly variable inclusion criteria with respect to gestational age and birth weight; feeding regimen; timing, dose, formulation of probiotics used; baseline risk of NEC in the control group. Hence applicability of these results to a local unit can be difficult.

**Evidence in neonates < 1000 grams**

The meta-analysis did not reveal a significant reduction in NEC, mortality and sepsis in neonates < 1000 grams (Table 3). Neonates < 1000 grams are most susceptible to NEC, mortality and sepsis. Absence of clear benefit of probiotics in these extremely vulnerable neonates is one of the main reasons why probiotic use has not become a standard of care in neonatal units.

| | No. of studies | Infants enrolled | Effect size RR (95% CI) |
|---|---|---|---|
| NEC (= stage 2) | 2 | 575 | 0.76 (0.37-1.58) |
| Mortality | 2 | 1200 | 0.82 (0.63-1.06) |
| Sepsis | 2 | 1199 | 0.94 (0.58-1.03) |

Table 3: Summary of evidence for probiotics in neonates < 1000 grams

**Practical aspects of Probiotic administration**

Dose of probiotics

- Dose is 3 × 109 cfu/day as a single dose for < 32 weeks gestation
- Suggested starting dose is 1.5 × 109 cfu/day for ELBW neonates until they reach enteral feeds of 50 to 60 ml/kg/day
- Adequate dilution is necessary to avoid hyperosmolarity–not exceeding 600 mOsm/L
- Diluent: Breast milk or water
- Volume: 1-1.5 ml per dose

**Strain selection**

- Single species Vs multispecies
- Bifidobacteria and lactobacilli-combination promotes lactic acid bacteria by formation of short chain fatty acid.
- Saccharomyces boulardii and bifidobacter used alone not useful

- Avoid untested strain combinations as they may be antagonists

**When to start probiotics?**
- Probiotic should be started as early as possible
- In practice , probiotics should be started with the 'first feed'
- Optimal protocol for probiotic administration in ELBW neonates with intrauterine growth restriction needs to be confirmed

**How long to give probiotics?**
- Shedding of probiotic organisms in stool stops about 2 to 3 weeks after the supplement is stopped
- supplementation could be stopped after reaching corrected gestational age of 36 to 37 weeks as risk of NEC is very low after this.

**Clinical monitoring during Probiotic administration**
- Intolerance (higher osmotic load causing abdominal distension, diarrhoea or vomiting)
- Probiotic sepsis
- Adverse effects (flatulence, loose stools) of additives such as prebiotic oligosaccharides need to be monitored Laboratory monitoring during probiotic administration
- Expert microbiological support - exclusion of contaminants and confirmation of colony counts. This ensures good quality control of probiotics used.
- Familiar with Gram stain and phenotypic appearances of the probiotics in different media is essential.
- Molecular methods 16S rRNA sequencing and pulsed-field gel electrophoresis is required as many of the probiotic strains cannot be grown in standard culture media.
- Monitor cross-contamination, resulting in nosocomial acquisition of probiotic strains by other neonates in the neonatal unit
- Antibiotic susceptibility testing of probiotics to provide local guidance for empiric antibiotic prescribing as antibiotics can kill probiotic organisms making it ineffective.

**Role of prebiotics in probiotic use**
- Probiotics and prebiotics, as found in human breast milk, is known to be synergistic
- Further research, such as RCTs of probiotics versus synbiotics, is necessary to evaluate whether addition of prebiotics improves the survival and/or efficacy of probiotic strains in preterm neonates

**Regulatory issues**
- In India, currently probiotics are not classified as medications and not subjected to strict quality control. Hence monitoring for adverse reactions and quality can be difficult. Hence good clinical and laboratory surveillance is essential.

**Probiotics used globally**
Infloran® used in Australian and NewZealand Neonatal units
(bifidobacterium bifidim and lactobacillus acidophilus 250mg capsule)

**Dose and Indications**
- For neonates born at less than 32 weeks gestational age AND receiving at least 1mL feed every 4hrs
- To be continued till 34 weeks corrected age
- Mix one (250mg) capsule with 2mL of expressed breast milk or formula (whatever the neonate is being given). If the supply of breast milk is limited, Infloran® can be made up in sterile water. Give 2 ml if feed volume is > 1 ml/hr and 1 ml if feed volume is $\leqslant$ 1 ml/hr.

**Florababy™**
A mix of 4 bifidobacteria (b breve, bifidum,

infantis and longum) and lactobacillus rhamnosus used in Canadian neonatal units.

**Conclusion**

Probiotics reduce NEC, mortality in preterm neonates but this benefit is not clearly demonstrated in the extremely low birth neonates < 1000 grams. Absence of a good probiotic preparation in our country also makes its use difficult in clinical practice. There are other proven practices of reducing NEC, mortality and sepsis on preterm neonates – infection control practices, following a standardised feeding regimen for preterm neonates, rationalizing antibiotic use and improving nutrition of our neonates. Until more evidence is available for probiotic use in neonates < 1000 grams, we should be optimizing our practice with above mentioned methods for which evidence is clearly available.

**References**


1. Evidence-based guidelines for use of probiotics in preterm neonates. Deshpande et al. BMC Medicine 2011, 9:92
2. Probiotics for Preterm Infants. NeoReviews Vol.6 No.5 May 2005 e227-232
3. Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized ControlleTrial. PEDIATRICS Volume 132, Number 6, December 2013
4. Therapeutic Use of Prebiotics, Probiotics, and Postbiotics to Prevent Necrotizing Enterocolitis: What is the Current Evidence?.Ravi Mangal Patel et al. Clin Perinatol. 2013 March ; 40(1): 11–25.
5. Probiotics for Preterm Neonates: What Will It Take to Change Clinical Practice?. Neonatology 2014;105:64–70
6. A meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Y. Yang et al. Brazilian Journal of Medical and Biological Research (2014) 47(9): 804-810
8. Deshpande G, Rao S, Patole S, Bulsara M: Updated Meta-analysis of Probiotics for Preventing Necrotizing Enterocolitis in Preterm Neonates. Pediatrics 2010, 125(5):921-930.
9. AlFaleh, Khalid; Anabrees, Jasim; Bassler, Dirk; AlKharfi, Turki: Probiotics for prevention of necrotizing enterocolitis in preterm infants Cochrane Database of Systematic Reviews. Issue 3, 2011.
10. Wang Q, Dong J, Zhu Y: Probiotic supplement reduces risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants: an updated meta-analysis of 20 randomized, controlled trials. J Pediatr Surg 2012, 47(1):241-248.
11. South Australian Neonatal Practice Guidelines-http://www. sahealth.sa.gov.au (last accessed on 25/11/2015)

# Enteral Feeding In The Preterm Neonate, Evidence Based Approach

**Dr Sandeep R**
Resident in Neonatology, Kanchi Kamakoti CHILDS Trust Hospital, Chennai
E mail : sandeep_ram21@yahoo.co.in

Provision of optimal nutrition is an important aspect in management of preterm neonate. Enteral route is the preferred method of nutrition delivery. The goal of enteral nutrition is achieving optimal growth and development without any complications like necrotizing enterocolitis. Unfortunately, decisions regarding enteral nutrition, includingtiming of initiation and rate of advancement, as well as indications for discontinuingand the mechanisms for delivery, are controversial and often based on individual or institutional preference rather than scientific evidence.This article summarizes the available evidence for enteral nutrition in preterm neonates.

**Have a feeding policy**

The first step for successful feeding in the preterm neonates is having a feeding policy in the unit. Standardized feeding policy is the single most global tool to prevent NEC in preterms.[1]

**Which milk to start?**

With concerns of NEC and associated morbidity, mother's breast milk is the first choice for feeding. In case mother's milk is not available then donor human milk can be used.[2] If breast milk is not available then enteral feeds should not be withheld for more than 24 hours.[3]

**Preterm or term formula?**

When breast milk is not available( mother /donor milk), feeding should not be delayed for more than 24 hours waiting for breast milk.[3] There is no evidence to support that initiation of feeds should be with standard term formula to prevent NEC. He concerns regarding higher osmolality of preterm formulas are unfounded. Preterm formulas have an osmolality of 400 mosm/kg. There is evidence from studies that osmolality of enteral feeds could be a problem only when it crosses 1000 mosm/kg. There is no difference in mortality and neurodevelopmental outcome when either of them is used[2]. But preterm formula is the preferred diet with higher protein and calorie required for optimal growth.[2]

Initiation and advancement of feeds depends on gestational age and clinical condition. Sick babies like those with hemodynamic instability and extreme preterm feeding can be individualized based.

**When to initiate feeding?**

Enteral nutrition can safely be started soon after birth in most preterm babies. However in sick preterm and ELBW babies feeding should be initiated within 2-3days of life.[3]

**How much milk to start with? What are trophic feeds**

Sick preterm and ELBW babies at birth should be started with minimal enteral nutrition (MEN) also called trophic feeds. It is hypocaloric, low volume (<25ml/kg/day) feeds to promote intestinal maturation and do not contain sufficient calories to sustain somatic growth.[4] There is not enough evidence to recommend the maximum duration of trophic feeding before starting nutritional feeds.

Stable preterm and those above 32 weeks of gestation can be started with 20ml /kg/day and advanced rapidly to reach 60-80ml/kg/day by the end of day[1]. The feeding in each preterm should be individualized based on tolerance and clinical condition.

**Advancement of enteral feeding**

Several randomized controlled trials(RCTs) have compared feeding advancement by

15 to 20 mL/kg per day with advancement by 30 mL/kg per day and have found that those infants who experienced a faster advancement of feedings reached full feedings faster, required fewer days of PN, had a shorter hospital stay, and regained birth weight more quickly without an increased risk of either NEC[4]. There is no evidence regarding feeding in ELBW babies, so their feeding regimen needs to be individualized, with preference of slow advancement i.e. 15-20ml/kg/day.[5] The SIFT (Speed of increasing milk feeds trial) study which is a large RCT s aiming to compare feed increments at 18 ml/kg/day with 30 ml/kg/day. The enrolment into the study has been completed and the results are awaited[6]

The goal is to achieve full feeds i.e 150-180ml/kg/day by 10-14days of life in ELBW babies and much earlier by 7days in VLBW babies.[7]

| | <1000g | 1000g-1500g |
|---|---|---|
| Initiation | Initiate within 2 days with trophic feeds Preferably EBM | Start on day 1 if clinically stable with 20ml/kg/day |
| Advancement | 20ml/kg/day | Advance rapidly to reach 6080ml/kg/ day by the end of day 1 |
| Time to reach full feeds | 14 days | 7 days |

**Mode of feeding**

Common methods of feeding are through nasogastric and orogastric tube. There is no evidence to suggest which mode of feeding is better, with each having their own advantages and drawbacks.[4]

There is no evidence of clear benefit with continuous feeding as compared to intermittent bolus feeding. The latter is more physiological with enhanced gastric emptying and duodenal motor response.[5] However there is no difference in time to reach in full feeds and short term growth. Continuous feeding requires more equipment and personnel and may be difficult in resource poor settings.

**Gastric residuals**

There is no evidence to withhold feeds based on gastric residuals when other symptoms are absent.[2,5,7]

**Management of gastric residuals**

Do not check gastric residuals routinely, if residuals are <50% of previous feed then give it back. If residuals are more than 50% and if there are no other features of intolerance then consider slow infusion feeds.

**When to withhold feeding?**

Gastric residuals and abdominal girth are poor markers of feed intolerance. If the baby has progressive distension, bilious or altered aspirate and tenderness on palpation, then it warrants stoppage of feeds and further investigation.

If abdominal radiograph is not suggestive of NEC and no free air, then restart feeding with increased duration or continuous feeds or decreased volume. Advancement of feeds in these babies must be individualized.

**Fortification of breast milk**

Multicomponent fortification improves post-natal weight gain, head circumference, but has no long term benefits.[2] Concerns of bovine based milk fortifier, as a reason for NEC and feed intolerance exists, unfortunately there is limited evidence to address this.[4,3] However

multiple studies have shown that there is no risk of NEC with addition of Human Milk Fortifier(HMF).

To start HMF, we need not wait till the baby achieves full feed, can be initiated as early as when baby is on 50ml/kg/day of feed volume.[5] WHO recommends HMF to be used in VLBW infants who fail to gain weight despiteadequate breast-milk feeding, preferably thosethat are human milk based.[2]

**Transition to oral feeding**

Oral feeding is not typically initiated inpreterm infants before 32 weeks Post menstrual age(PMA) mainly becausethe coordination of sucking, swallowing, and respiration is not established. 3

Beyond 32 weeks oral feeding should be initiated either by spoon or paladai. After 32 weeks PMA, baby can be allowed to breast feed ( non nutritive sucking), to enhance postnatal maturity of sucking and swallowing co ordination.[8]

**Micronutrient supplements**

1. Preterm are at risk for metabolic bone disease. Hence they need to be supplemented with calcium and phosphorus for adequate mineralization of bones.
   Oral supplementation of calcium (120-140mg/kg/day) and phosphorus (60-90mg/kg/day) is recommended.[2]
   It is advisable to initiate supplements when the baby is on at least 150ml/kg/day.[8]
2. Vitamin D 400 IU/day is recommended to all preterms.[2]
3. Oral iron supplementation should be started as early as 2 weeks postnatally.[2]
4. Routine supplementation of vitamin A and zinc is not recommended.[2,8]

**Gastroesophageal reflux( GER)**

Clinical identification of GER is challenging. Apnea, desaturation, or bradycardia; or behavioral signs, such as gagging, coughing, arching, and irritability, as signs of GER are unreliable.[7]

Placing the baby in left lateral position and head end elevation reduces GER. Domperidone is not advisable due to concerns of cardiac rhythm abnormalities. Erythromycin and thickening of feeds has no role in managing GER.[7]

**Feeding a baby while on Indomethacin or ibuprofen**

There is no evidence to withhold feeds during medical therapy for PDA. There are no RCTs to compare between the 2 drugs, but indirect evidence suggests ibuprofen may be safer.

Blood transfusion

Anecdotal reports of necrotising enterocolitis following blood transfusion have made some neonatologists concerned about feeding during a blood transfusion. At present there is insufficient evidence to stop feeding during blood transfusion. Our unit policy is to continue feeding babies when they are receiving blood transfusion.

Feeding Small for Gestational Age (SGA) Babies with/without History of Absent /Reversed End Diastolic Umbilical Flow (AREDF)

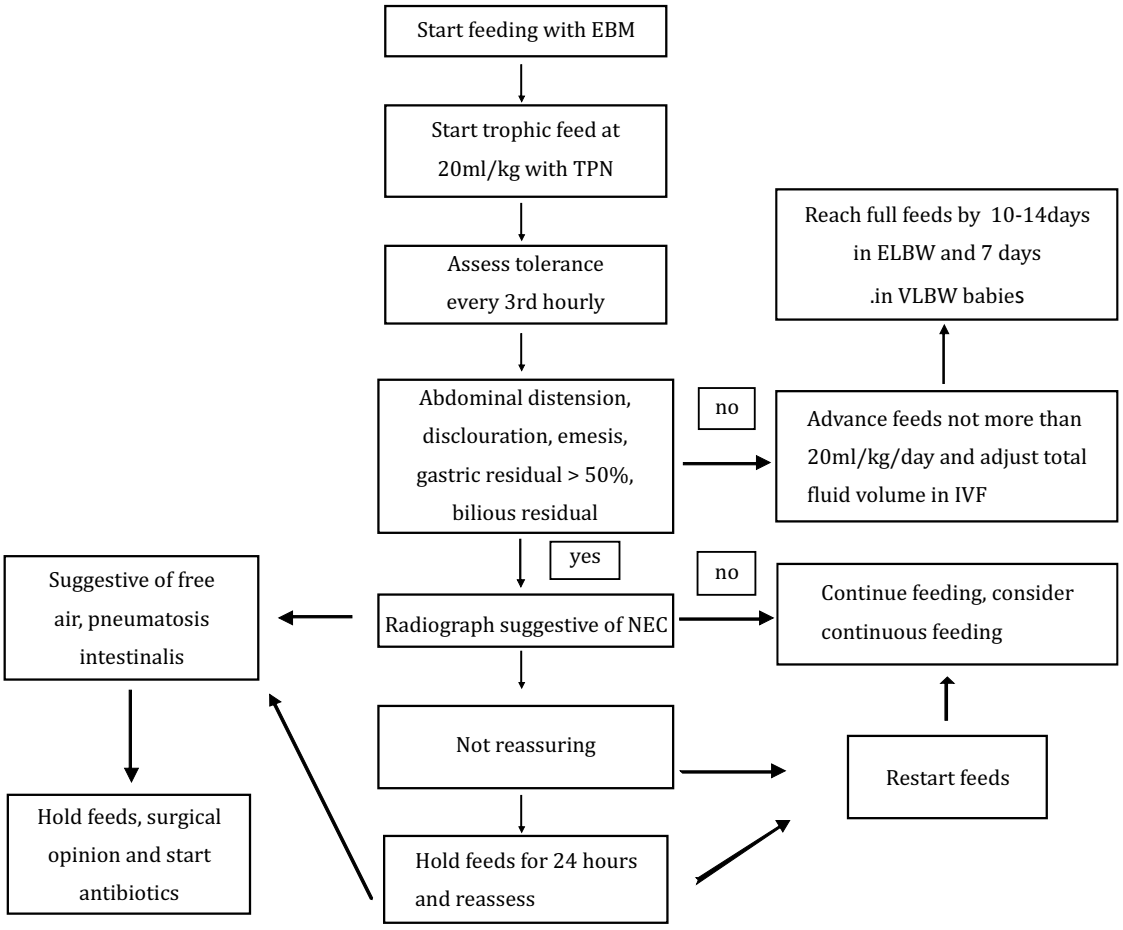
There is evidence to support initiating feeds as early at 24 hours of life in babies with AREDF. Feed increments are done more cautiously. Make every effort to feed human milk, especially in SGA babies with AREDF and gestation <29 weeks.

**REFERENCES**


1. Patole SK. Impact of standardised feeding regimens on incidence ofneonatal necrotising enterocolitis: a systematic review andmeta-analysis of observational studies. Arch Dis Child Fetal Neonatal Ed 2005;90:F147–F151
2. Guidelines on optimal feeding of low birth weight infants in low and middle income countries. World health organization 2011.
3. Torrazza R M, Neu J. Evidence-Based

Guidelines for Optimizationof Nutrition for the Very Low BirthweightInfant. Neoreviews2013;14;e340.
4. Parker L A, Torrazza R M, Neu J. Scientifically Based Strategies for Enteral Feeding in Premature Infants. Neoreviews2013;14;e350
5. Blickstein I, Shinwell ES. Nutritional requirement and provision of nutritional support in premature neonate. In Fanaroff and Martin's Neonatal- Perinatal Medicine. 10th Edition.2015
6. SIFT trial. July 2015. (unpublished)
7. Dutta S et al. Guidelines for Feeding Very Low BirthWeight Infants. Nutrients 2015, 7, 423-442
8. Evidence based clinical practice guidelines. National Neonatology Forum, India. October 2010.

**FEEDING ALGORITHM IN PRETERMS**



# Role of micronutrients in preterm nutrition

**Dr Muzamil Mustafa Mugloo**
M.D. (Peadiatrics)
DNB Neonatology fellow, Kanchi Kamakoti CHILDS Trust Hospital, Chennai

The term micronutrient as used in context of infant nutrition refers generally to any vitamin or mineral that is required for tissue growth and development as well as cellular and tissue function. Extremely preterm infants are frequently growth-restricted at hospital discharge as a consequence of difficulties in the provision of adequate nutrition. The long-term effects of this growth restriction needs to be determined. There is a paucity of studies about the role of minerals, especially micronutrients, in the nutrition of extremely preterm infants.

Extremely preterm infants have low mineral reserves and, as a consequence, may have deficiencies in the postnatal period if they do not receive parenteral or enteral supplementation.

Nutrition must be adjusted on a case-by-case basis, and not based only on birth weight in extremely preterm infants. There are no accurate definitions of their nutritional requirements, so their growth and metabolism must be frequently monitored.

Due to the advanced care preterm infants the survival rate of these infants has increased.. Postnatal malnutrition have been considered in epidemiological studies to play a crucial role in the determination of adult diseases such as diabetes, hypertension and heart diseases. Therefore, neonatologists have a greater responsibility to provide these newborn infants with a nutrition that ensures appropriate physical growth and neuropsychomotor development.

As the role of some minerals has been under investigated, it should be underscored that calcium and phosphorus are the most widely studied minerals in the literature.

**Calcium and phosphorus**

Calcium (Ca) and phosphorus (P) are important to fetal and postnatal bone mineralization. The period of skeletal development and bone mineralization occurs in the third trimester of gestation when the fetus incorporates large amounts of calcium and phosphorus, on average 120 to 140 mg/kg/per day and 60 to75 mg/kg/day, respectively.

Mineralization levels increase exponentially between 24 and 37 weeks of gestation, resulting in 80% of mineral accumulation in the third trimester. As a result, infants born between 24 and 34 weeks will be deprived of the intrauterine supply of calcium, affecting intrauterine and postnatal bone mineralization.

Estimates of calcium requirements in preterm infants are inferred from the chemical composition of fetal tissues. Bone mineral content (BMC) measurement of newborn infants of different gestational ages, determined by photon absorption, shows that the mineral content of the distal third of the radius increases from 25 mg/cm at26 weeks to 65 mg/cm at 36 weeks. BMC and bone area (BA) measured by dual-energy x-ray absorptiometry (DEXA) revealed that both measurements are correlated with body weight, length and gestational age.

DEXA is considered the most accurate noninvasive method to define in vivo bone mineralization.

Metabolic bone disease occurs in approximately 50% of preterm newborn

infants. Calcium deficiency results from the interruption of the placental supply of calcium, from high levels of calcitonin and from the insufficient release of parathyroid hormone, due to the immature response of parathyroid glands.

In the postnatal period, there are some difficulties in providing higher amounts of Ca and P because these extremely preterm infants usually have intercurrent events such as respiratory distress syndrome, peri-intraventricular hemorrhage and chronic lung disease.

Parenteral nutrition is the major source of feeding for extremely preterm infants on the first days of life, until they can tolerate enteral nutrition However, it is difficult to provide sufficient amounts of Ca and P that meet intrauterine requirements through parenteral nutrition. The solubility of calcium in the presence of phosphorus is a limiting factor, in addition to several factors related to the maintenance of the stability of the solution such as: source of calcium, concentration, solution pH, glucose concentration, order of the components, temperature of the solution.

Calcium content in breast milk and formulas:- Studies on breast milk revealed that calcium content in the initial colostrum is on average160mg/l, increasing to 256 mg/l on the third day, and maintaining these values upto third month, when it slowly declines to 176 mg/l around one year. The content of a preterm infants mother's breast milk does not differ from that of a full-term infant's mother's in terms of calcium and phosphorus in the first month of life. These data indicate that the mineral content of breast milk is insufficient to keep postnatal mineralization in very low birth weight infants at the levels observed in the intrauterine period.

In commercially available formulas, an appropriate Ca:P ratio should be observed by proposing a ratio close to 2:1 to ensure optimal absorption.

The evaluation performed by Cochrane Review in 2004 include randomized studies on newborns evaluated only metabolic parameters, showed supplementation with, no differences in serum alkaline phosphatase levels in the short run. The results regarding bone mineralization are discrepant, since only two studies described an increase in the BMC of the radius and an increase in total BMC while two authors did not find differences in total BMC with the supplementation. No fractures, hypercalcemia or any other clinical manifestations were observed.

Other factors in extremely preterm infants that influence bone growth and mineralization are drugs with a hypercalciuric effect; furosemide and methylxanthines.

AAP recommendation for VLBW : Ca 150 220mg / kg/d P 75-140mg/kg/d

**Other minerals: Trace elements or microelements**

Important microelements or trace elements to human nutrition include zinc, copper, selenium, chrome, molybdenum, manganese, iodine and iron. Although they quantitatively represent a small fraction of the total mineral content of the human body, they play a key role in several metabolic pathways. Preterm infants may have deficiencies, even if clinical manifestations are absent, due to low stores at birth, since mineralization occurs in the last trimester of gestation.

**Selenium**

This element has an added importance in all age groups, since it is a constituent part of selenoenzymes withdifferent functions, including glutathione peroxidase, which is an antioxidant enzyme that acts on cell membranes. These enzymes prevent the formation of free radicals,reducing lipid

peroxides and hydrogen peroxide, protecting the body against oxidative insult. Selenium also plays a role in immunocompetence. Neutrophils and macrophages of selenium-deficient animals have a low concentration ofglutathione peroxidase, which may affect their antimicrobial properties. Extremely low birthweight infants are at risk for conditions whose pathophysiology includes free radical damage, as observed in bronchopulmonary dysplasia, retinopathy of prematurity, peri-intraventricular hemorrhage and necrotizing enterocolitis. Also due to the frequency at which they receive oxygen, they are susceptible to oxidative stress and production of reactive oxygen.

In a review article, Klein mentions studies that relate selenium deficiency to diseases of prematurity. Eight preterm newborns who developed respiratory distress syndrome and who did not receive oral or parenteral selenium revealed a quick decrease in serum levels two weeks after birth. The control mechanisms of the mother-to-fetal transfer of selenium have not been clearly defined yet. Transplacental transfer is limited, so selenium concentration is relatively low in the fetus, corresponding in umbilical cord blood to approximately 65% of the maternal serum level. Selenium is stored in fetal liver between the 20th and 40th week.

In preterm infants with respiratory disorders, submitted to parenteral nutrition without selenium supplementation in the first 14 days, there was a relevant decrease in selenium levels in the first days of life. Meta analysis suggest 3 µg/kg/day of selenium in order to maintain concentrations at the umbilical cord blood levels. To increase the concentrations closer to those of breastfed full-term infants, 5-7 µg/kg/day is recommended. .

**Zinc**

Zinc is important to growth, cell differentiation and to the metabolism of proteins, carbohydrates and lipids. It plays a role in hormone structure and in genetic transcription factors. Signs of subclinical zinc deficiency may develop including weight loss, failure to thrive, periorificial dermatitis, glossitis, and enhanced susceptibility to infections. Preterm infants also have an immature gastrointestinal tract, which results in negative zinc balance, with zinc excretion by the intestinal tract. Preterm infants can take up 25% to 40% of dietary zinc. Formula components, such as iron can affect zinc bioavailability in the presence of a high Fe: Zn. Zinc concentration in breast milk quickly decreases after the colostrum, when levels are at their highest. The calculation of dietary zinc in order for optimal growth to occur is equivalent to500 µg/kg/day, with approximately 1,000 g of birth weight and 27 weeks of gestational age; 400 µg/kg/day for newborn infants between 1,500 and 2,000 g (30-32 weeks)

Minerals such as copper, iodine, manganese and molybdenum have been investigated as to the feeding of preterm infants in order to develop special preterm formulas and parenteral nutrition solutions. Clinical manifestations caused by deficiency in the neonatal period are not described, that is why their characteristics are under reported in daily practice.

Among these elements, special attention should be paid to copper, an important element in the constitution of enzymes such as superoxide dismutase, which protects the cell membranes against oxidative damage. This element is stored in fetal liver, being bound to metallothionein in greater amounts than those found in the liver of adult individuals.

Deficiency is rare in the neonatal period, but when present, it causes hypochromic anemia resistant to iron supplementation, neutropenia, osteoporosis, skin manifestations and difficulty in gaining weight. There is a paucity of data about copper requirements in preterm infants. When fed breast milk, they

receive enough quantities. On long-term parenteral nutrition, it is recommendable to use 20μg/kg/day and not use it in the presence of cholestasis, because it is excreted by the bile.

**Vitamins**

Preterm infants do not appear to need supplemental vitamins once they are taking adequate amount of fortified human milk or fortified formula except vitamin D. AAP recommends all infants to receive 200 IU to 400 IU of vitamin D daily.

Further research is required about the role of minerals in preterm nutrition, so that formulas can be more balanced in terms of mineral contents and more appropriate for the requirements of extremely preterm infants, who usually are submitted to parenteral nutrition for a longer period.

**References**


1. Greer FR, Tsang RG. Calcium, phosphorus, magnesium and vitamin D requirements for the preterm infant. In: Tsang RC,editor. Vitamin and minerals requirements in preterm infants. New York: Marcel Deker; 1985. p. 99-136.
2. Rigo J, De Curtis M, Pieltain C, Picaud J, Salle BL, Santerre J.Bone mineral metabolism in the micropremie. Clin Perinatol. 2000; 27: 147-70.
3. Klein CJ. Nutrient requirements for preterm-infant formulas:
4. Minerals: calcium and phosphorus. J Nutr. 2002;132(6 Suppl 1):S1395-577.
5. Salle B, Senterre J, Putet G, Rigo J. Effects of calcium and phosphorus supplementation on calcium retention and fat absorption in preterm infants fed pooled human milk. J Pediatr Gastroenterol Nutr. 1986;5:638-42.
6. Ehrenkranz RA, Gettner PA, Nelli CM. Nutrient balance studies in premature infants fed premature formula or fortified human milk. J Pediatr Gastroenterol Nutr. 1989;8:58-6
7. Schanler RJ, Abrams AS, Garza C. Bioavailability of calcium and phosphorus in human milk fortifiers and formula for very low birth weight infants. J Pediatr. 1988;113:95-100.
8. Rigo J, Salle BL, Picaud JC, Putet G, Senterre J. Nutritional Evaluation of protein hydrolysate formulas. Eur J Clin Nutr. 1995;49 Suppl 1:S26-38.
9. Rigo J, Picaud JC, Lapellone A, Salle LB, Senterre, J. Metabolic balance and plasma AA concentrations in VLBW infants fed a new acidic whey hydrolysate preterm formula. J Pediatr Gastroenterol Nutr. 1997;24:491A.
10. Rowe JC, Goez CA, Carey DE, Horak E. Achievement of in uterus retention of calcium and phosphorus accompanied by high calcium excretion in very low birth weight infants fed a fortified formula. J Pediatr. 1987;110:581-5.

# Necrotizing enterocolitis: A practical approach to diagnosis , management and prevention

**Dr. Suba Karthikeyan**
Consultant Neonatologist, Motherhood, Chennai
DNB, AB (peds), FRCPC, Neonatal fellowship (Canada)

Necrotizing enterocolitis (NEC) is primarily a disease process of the gastrointestinal tract of premature, mainly very low birth weight neonates. It can also affect term neonates. It remains as one of the important causes of morbidity and mortality in the neonatal population

It results in inflammation and bacterial invasion of the bowel wall which might lead to necrosis of the bowel. Early recognition and aggressive treatment of this disorder has improved clinical outcomes.

**Incidence**
It occurs in 1-5% of all neonatal intensive care admissions and 5-10% of all very low birthweight (<1500 g) infants

The incidence and timing of the onset of symptoms varies and is inversely related to gestational age and birth weight .So the median age of onset in infants with a gestational age of less than 26 weeks was 23 days, and for those with a gestational age of greater than 31 weeks,was 11 days and similarly the lower the gestational age higher is its incidence

AETIOLOGY; is multifactorial though the main belief is that NEC arises predominantly from ischaemic injury to the immature GI tract .

some of the other key factors which can contribute to it are

- time of introduction and rate of advancement of enteric feeds
- alterations in the normal bacterial colonization of the GI tract
- bacterial translocation and activation of the cytokine cascade
- mucosal damage from free radical production.

In term neonates polycythemia , exchange transfusion, congenital heart disease, perinatal asphyxia, sepsis, and respiratory disease can be contributing factors

**Clinical Manifestations**
NEC primarily occurs in healthy, growing, and feeding premature infants. It can present with either non specific systemic signs and localized abdominal signs

**Non Specific Signs**

- apnea
- respiratory failure
- poor feeding
- lethargy
- temperature instability

**Abdominal Signs**

- Abdominal distension
- Prefeed aspirate significant
- Bilious aspirates /vomiting
- Rectal bleeding
- Abdominal tenderness
- Abdominal wall edema/discoloration

**Staging**
The Bell staging criteria defines the different stages of NEC based upon the severity of clinical findings (table 1). Modified by Walsh et al in 1986.

**Diagnosis**

The diagnosis of NEC is based upon the presence of the characteristic clinical features as listed above and the abdominal radiographic finding suggestive of it. At times, radiographic findings may be equivocal and treatment decision should be based upon clinical suspicion and findings.

**Modified Bell's Staging Criteria for Necrotizing Enterocolitis**

| STAGE | SYSTEMIC SIGNS | INTESTINAL SIGNS | RADIOLOGIC SIGNS | TREATMENT |
|---|---|---|---|---|
| I. Suspected | | | | |
| A | Temperature instability, apnoea, bradycardia | Elevated pregavage residuals, mild abdominal distension, occult blood in stool | Normal or mild ileus | NPO, antibiotics x 3 days |
| B | Same as IA | Same as IA, plus gross blood in stool | Same as IA | Same as IA |
| II. Definite | | | | |
| A: Mildly ill | Same as IA | Same as I, plus absent bowel sounds, abdominal tenderness | Ileus, pneumatosis intestinalis | NPO, antibiotics x 7 to 10 days |
| B: Moderately ill | Same as I, plus mild metabolic acidosis, mild thrombocytopenia | Same as I, plus absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, right lower quadrant mass | Same as IIA, plus portal vein gas, with or without ascites | NPO, antibiotics x 14 days |
| III Advanced | | | | |
| A: Severely ill, bowel intact | Same as IIB, plus hypotension, bradycardia, respiratory acidosis, metabolic acidosis, disseminated intravascular coagulation, neutropenia | Same as I and II, plus signs of generalised peritonitis, marked tenderness and distension of abdomen. | Same as IIB, plus definite ascites | NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis |
| B: Severely ill: bowel perforated | Same as IIIA | Same as IIIA | Same as IIB, plus pneumoperitoneum | Same as IIA, plus surgery |

**Laboratory Test**

These include Complete blood count , C reactive protein , coagulation work up , Blood,peritoneal fluid and stool cultures, Serum electrolytes ,renal functions and blood gas analysis CBC can have leukopenia and throm-bocytopenia

CRP - can be a marker of infection in the early stages and persistent elevation can indicate presence of necrotic bowel and in the late stages can indicate stricture

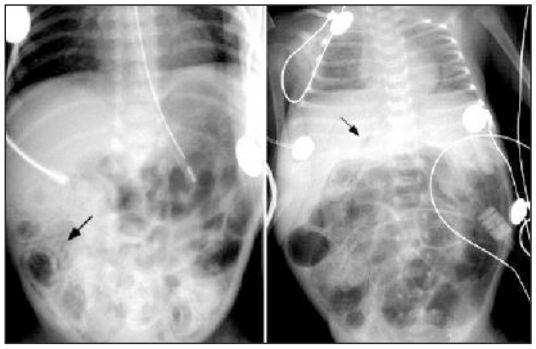
Blood and other cultures - guides us on the choice of antibiotics to continue

Serum electrolytes– can reflect hyponatremia ( if there is third spacing of fluid) and hyperkalemia and acidosis (with necrotic bowel segments)

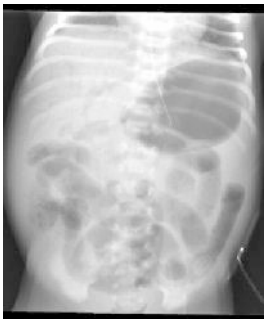
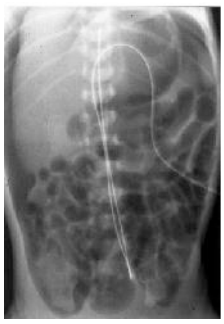
- Blood gas and serum lactate – will reveal metabolic acidosis and elevated lactate can indicate ischaemic bowel
- PT/PTT – can be altered in fulminant bacteremia or sepsis

**Radiographic Signs**

- The xray findings in NEC can be varied based on the staging . It includes ileus, dilated or fixed intestinal loops, air in the intestinal wall or free air in the abdomen.
- Dilated bowel loops
- Pneumatosis intestinalis–air in the intestinal wall



- Portal venous air – air in the portal venous system Pneumoperitoneum

- Persistent fixed loop-sentinel loop can signify necrotic bowel and is an important sign
- Peritoneal fluid
- Pneumoperitoneum A substantial amount of intraperitoneal air may result in the "football" sign on a supine radiograph. This sign consists of a large hypolucent area in the central abdomen with markings from the falciform ligament

**Differential Diagnosis**

The differential diagnosis includes other conditions that cause rectal bleeding, abdominal distension, or intestinal perforation. These include

- spontaneous intestinal perforation of the newborn
- infectious enterocolitis
- benign diagnoses of pneumatosis coli
- anal fissures

**Medical Management**

Overview - Medical management should be initiated promptly when necrotizing enterocolitis (NEC) is suspected. It consists of the following:

**Supportive care**

- Bowel rest Nil Per Oral NPO
- Decompression using a naso gastric tube suctioning
- Maintain fluid and electrolyte balance to manage third spacing
- Total Parentral Nutrition
- Serial monitoring of metabolic and hematological parameters and their management
- stabilize cardiac and respiratory status as some infants require medications to maintain blood pressure and respiratory support

**Antibiotic therapy**

Antibiotic therapy should be initiated at the earliest with initial broad specturm antibiotics which covers organisms for late onset sepsis. Anerobic coverage with metronidazole should be added in case of intestinal perforation. Later based on the blood cultures or peritoneal fluid cultures antibiotics can be altered. Duration depends on the clinical condition of the child for about 10-14 days.

Persistently low platelet count, metabolic acidosis, and increasing blood glucose are associated with worsening or persisting NEC and poor outcome.

**When Is Surgical Intervention Needed**

Surgical intervention is required either when intestinal perforation occurs or when there is unremitting clinical deterioration despite optimal medical management, suggesting extensive necrosis.

There are two options for surgical management primary peritoneal drainage (PPD) and laparotomy with bowel excision. Comparing, both options there is no evidence to prove any one of them is superior to the other .

In extremely low birth weight infants (birth weight <1000 g) initial peritoneal drain is placed and the response is monitored by serial abdominal examinations and radiographic studies. An alternative option is laparotomy with bowel excision. If there is persistent deterioration in clinical status with fixed bowel loops on the x rays in spite of a peritoneal drain a laparotomy will be mandatory.

**Complications**

Acute complications are listed above

Late complications -The most common late complications of NEC are intestinal narrowing (ie, stricture formation) and short bowel syndrome

**Prevention**

Advances in antenatal and neonatal care have resulted in increased survival of extremely preterm neonates. So an effective preventative strategy for NEC is needed.

- the use of antenatal corticosteroids to enhance maturation in case of preterm delivery
- use of breast milk or even donor human milk as compared to formula
- early initiation of trophic feeds and judicoius advancement of enteric feeds15-20ml/kg/day)
- the avoidance of hypertonic formulas and hypertonic medications
- prompt treatment of polycythemia
- Avoiding H2 blockers
- judicious use of antibiotics and shortening the courses whenever possible.
- Probiotics have shown to reduce the risk of NEC in some limited clinical trials in preterm infants. Further studies are required to confirm the optimal administration (type, timing, duration, and dosing of probiotic therapy) of this intervention, before they can be routinely recommended.
- No significant evidence for the use of arginine and glutamine supplementation

**Prognosis**

Prognosis has improved with earlier recognition and treatment, with increased survival rates of infants. In addition, approximately one-half of the survivors are normal. Long-term sequelae include gastrointestinal complications like short bowel syndrome, intestinal strictures, and increased frequency of bowel movements with loose stools and impairment of growth and neurodevelopmental outcome

**References**


1. Yee WH, Soraisham AS, Shah VS, Aziz K, Yoon W, Lee SK, Canadian Neonatal Network: Incidence and timing of presentation of necrotizing enterocolitis in preterm infants.Pediatrics. 2012; 129(2) :e298
2. Uauy RD, Fanaroff AA, Korones SB, Phillips EA, Phillips JB, Wright LL. Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. 1991; 119 (4):630
3. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1
4. Hällström M, Koivisto AM, Janas M, Tammela O. Laboratory parameters predictive of developing necrotizing enterocolitis in infants born before 33 weeks of gestation. J Pediatr Surg. 2006;41(4):792
5. Shah D, Sinn JK. Antibiotic regimens for the empirical treatment of newborn infants with necrotising enterocolitis. Cochrane Database Syst Rev. 2012; 8:CD007448.
6. Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database Syst Rev. 2011
7. Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2011
8. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol. 2007;27(7):428

# Parenteral nutrition in the preterm neonate

**Dr Shobana Rajendran**
Consultant Neonatologist, Kanchi Kamakoti CHILDS Trust Hospital
Chennai - 600034 | Email : shobi_raj@yahoo.co.uk

Effective nutritional support of premature especially the ELBW neonates in the early postnatal period are largely dependent on parenteral nutrition. The supply of nutrients to the extreme preterm is rarely sufficient leading to major deficits after birth.

**Goals of parenteral nutrition in the preterm neonates**

To support optimal growth and neuro development at the rate of a foetus of the same gestational age, or along a growth curve consistent with the birth weight.

Bridging the nutritional requirements until the gastrointestinal tract matures anatomically and functionally to allow enteral feedings to be used for optimal support without complications.

Minimising both short and long term early enteral feeding complications including Necrotising enterocolitis, failure to thrive and feed intolerance.

**Intravenous protein and amino acid requirements**

Normal human foetal development is characterised by rapid rate of growth and accretion of protein. At 28 weeks the gestation the foetus accretes approximately 350 mg of nitrogen /kg/day which declines to 150mg of nitrogen/kg/day at term. Post-natal nitrogen loss decreases from 180mg/kg/day at 27-28 weeks to 120mg/kg/day in term neonates.in the absence of intravenous amino acids the protein loss is approximately two folds higher in ELBW than term neonates.

Protein requirements extrapolated from foetal nitrogen accretion rates and post natal losses have been estimated to be approximately 2.5-3.5gm/kg /day for premature neonates and 1.9-2.5gms / kg/ day in term neonates. As the protein losses are inversely proportional to the gestational age protein requirements are likely to be higher in extreme preterm neonates. Hence in just few days of premature birth the gap between the protein utero and postnatal loss of nitrogen widens leading to quick protein deficiency. Provision of 1gm/kg/day of amino acid can reduce this disparity and achieve net protein balance close to zero where as providing 3gm/kg/day results in net protein gain that approximates that of a reference foetus.

**Evidence supporting early nutritional support with parenteral amino acids**

Rivera et al and Van den Akar demonstrated that administration of 1.5gm/kg/day of amino acid beginning from day one increased protein synthesis.

An RCT to assess the safety and efficacy of higher amino acid immediately after birth 1gm/kg/day versus 3gm/kg/day revealed that higher amino acid intake produced significantly greater protein accretion without evidence of adverse effects. A negative nitrogen balance was seen in babies who did not receive amino acids.

A constant nitrogen intake, increasing non protein energy from 50kcal/kg/day to 80kcal/kg/day resulted in increased nitrogen retention and weight gain. Whereas at a low energy intake of 50kcal/kg/day increasing nitrogen intake from 3 to 4 gm/kg/day had no effect on nitrogen retention or weight gain. However at a higher energy intake the increase in the nitrogen intake resulted in significant weight gain and nitrogen retention.

**Composition of Commercial Parenteral Amino Acid Solutions**
**Concentration: mg/dL**

| Amino Acid* | Aminosyn-PF (Abbott) | TrophAmine (B.Braun) | Primene (Baxter) | Premasol Baxter) |
|---|---|---|---|---|
| Histidine | 312 | 480 | 380 | 480 |
| Isoleucine | 760 | 820 | 670 | 820 |
| Leucine | 1200 | 1400 | 1000 | 1400 |
| Lysine | 677 | 820 | 1100 | 820 |
| Methionine | 180 | 340 | 240 | 340 |
| Phenylalanine | 427 | 480 | 420 | 480 |
| Threonine | 512 | 420 | 370 | 420 |
| Tryptophan | 180 | 200 | 200 | 200 |
| Valine | 673 | 780 | 760 | 780 |
| Alanine | 698 | 540 | 800 | 540 |
| Arginine | 1227 | 1200 | 840 | 1200 |
| Proline | 812 | 680 | 300 | 680 |
| Serine | 495 | 380 | 400 | 380 |
| Taurine | 70 | 25 | 60 | 25 |
| Tyrosine | 44 | 240 | 45 | 240 |
| Glycine | 385 | 360 | 400 | 360 |
| Cysteine | — | <16 | 189 | <16 |
| Glutamic acid | 820 | 500 | 1000 | 500 |
| Aspartic acid | 527 | 320 | 600 | 320 |

Long term effects of early parenteral nutrition found an association between early higher energy nitrogen energy intake and Bayley Mental Development Index score. Improved weight gain at 36 weeks. Early higher amino acids intake of 3gms/kg/day with in first 5 days of life improved growth outcomes such as weight length and head circumference.

**Compositions of Amino acid Mixtures**

The ideal composition of intravenous amino acid mix is unknown. However the ultimate goal is to achieve plasma amino acid concentration in response in response to parenteral nutrition that optimize both growth and neurodevelopment without toxicity.

The first parenteral casein hydrolysate amino acids use was reported to cause acidosis and hyper ammonia. The second generation crystalline amino acid mixture has high quality dietary protein with large amounts of glycine and alanine. They lack essential amino acids such as glutamate, aspartate, tyrosine and cysteine due to poor solubility. None of the currently used amino acids was designed to meet the needs of ELBW. Future efforts should be directed at designing the needed for the most vulnerable group.

**Energy**

The initial goal of parenteral nutrition is to provide sufficient energy to match energy expenditure in order to preserve body energy stores. Energy expenditure in premature

infants have ranged between 30-70kcal / kg/ day. An intake of 70kcal/kg/day may achieve neutral or slightly positive energy balance. To support normal rates of growth a positive energy balance of 20-25kcal/kg/day .This requires 100-110kcal/kg /day in a ELBW and 90-100kcal / kg/day in VLBW . Recommendations for the energy intake is shown below.

**Intravenous glucose requirement**

Foetal glucose use in utero matches the umbilicus glucose uptake which implies that gluconeogenesis and glycogenolysis are minimal in foetus. This is due to high insulin receptors, blunted pancreatic B-cell regulation of insulin secretion and relative Glucagon resistance. As the gestation advance hepatic glycogen synthesis is increased and at delivery the glucagon level rises and insulin falls, causing lipolysis. Thenew born must be able to initiate gluconeogenesis as the glycogen store can sustain only for several hours after birth.

The new born brain uses glucose as the primary energy substrate and the neural tissue makes up a greater proportion of body weight leading to higher glucose oxidation than adults. Theglucose production rate in a term neonate is 3-5mg/kg/min and in a ELBW is 8-9mg / kg / min. The premature with higher basal metabolic use and with additional concerns of hypothermia and sepsis, early administration of glucose is critical. In ELBW a reasonable approach is to start a GIR of 6mg/kg/min with gradual advancement to 10-12mg/kg/min without causing hyperglycaemia.

The cut off levels for hyperglycemia in ELBW is debatable, widely practised levels> 150mg /dl. Reducing fluid needs and minimising insensible water loss can reduce glucose intake or lower the concentration of dextrose to not less than 2.5%.

Routine use of insulin to facilitate tolerance of parental nutrition is not supported as they may lead to lactic acidosis with no net effect on anabolism or other outcomes. Insulin at a dose of 0.05-0.1U/kg/hr may be used to treat hyperglycemia that is not responsive to effort of reducing GIR.

**Intravenous lipid emulsion**

Intravenous lipid emulsion (LE) are a significant source of non-protein energy and also prevent essential fatty acid deficiency. Lipid particle in the emulsion are similar to endogenously produced chylomicrons .Their clearance are dependent on lipoprotein lipase. In preterm <28weeks gestation the lipoprotein lipase activity and triglyceride clearance is reduced.

Essential fatty acids such as linoleic and linolenic acids cannot be endogenously synthesized and preterm develop deficiency within 72 hours of birth. Supplementing 0.5-1gm/kg/day will reduce their deficiency .Additional intravenous lipids is required to meet energy requirement.

**Choice of lipid emulsions**

The LE are oil in water emulsions consisting of one or more triglyceride containing oils, phospholipid emulsifier and glycerine to adjust tonicity. The oils are plant based (soybean, olive oil) and marine based such as fish oil. The phospholipid emulsifier such as egg phosphatide which is essential to keep mean lipid particle size <0.5micron.

The choice of LE is important as the composition influences peroxidation and fatty acid metabolism. The optimal blend of LE needs to provide essential fatty acids, maintain long chain PUFA, reduce lipid peroxidation and improve immune function.

LE available are soy based oils SO (omega 6 PUFA rich in linoleic acid and susceptible for peroxidation and production toxic hyper peroxides. More LE recent contain blends of soy and olive oils and another which has blends of soy , medium chain triglyceride, olive oils and fish oils(SMOF).

## Content of lipid emulsion

| | SO | OL | SMOF |
|---|---|---|---|
| Soyabean oil | 100% | 20% | 30% |
| Coconut oil (MCT) | - | - | 30% |
| Olive oil | - | 80% | 25% |
| Fish oil | - | - | 15% |
| Egg. Phospholipid g% | 1.2 | 1.2 | 1.2 |
| α-tocopherol μg/ml | 14.5 | 30.3 | 200 |
| Linoleic (C18:2n – 6) % fatty acids | 50 | 17.2 | 37.2 |
| Arachidonic (C20:4n – 6) % fatty acids | 0.3 | 0.5 | 1.0 |
| Alpha – linoleic(C18:3n – 3) % fatty acids | 7.0 | 2.3 | 4.7 |
| Eccosapentanoic EPA(C20:5n – 3) % fatty acids | - | - | 4.7 |
| Docosachexaenoic DHA (C22:6n – 3) % fatty acids | 0.34 | 0.5 | 4.4 |

SO – Soya Oil
OL – Olive Oil
SMOF – Soya Oil, Coconut Oil, Olive Oil and Fish Oil

The available evidence prefers olive oils based LE to soy based LE as it avoids impairment of immune function and depletion of long chain omega-6 PUFA derivatives, decreases oxidative stress and has advantages for glucose metabolism in preterm .It is also shown to be safer and well tolerated. SMOF provides a fast source of energy comparatively, less immunological influence and may reduce cholestasis.

**Monitoring and administration of LE**

Lipid should contribute to 30-40% of non-protein calorie but should not exceed 60%. The LE are available 10%,20%.30%, the recommended concentration is 20% as they have lower phospholipid to triglyceride ratio and liposomal content than 10% resulting in a lower triglyceride phospholipid and cholesterol levels.30% solution may confer a better advantage but awaiting larger evidence.

The rate of lipid infusion is important and plasma clearance is improved when given as a infusion over 24 hours. Lipid infusion of 3-4gm/kg/day are well tolerated by preterm when given over 24 hrs.

**Clinical effect of LE**

**Growth:**

LE use as a part of Parenteral nutrition has helped in supplying the require energy to mimic foetal growth in VLBW neonates and improving positive nitrogen balance.

Provision of Essential fatty acids and long chain PUFA: which has a recognised role in development of neurological tissues including brain and retina.

Undesirable effects with LE: they are mainly described with use of soybean oil based LEs

**Pulmonary:**

Hypoxia secondary to lipid micro emboli in pulmonary capillaries or due to production of prostaglandin altering the pulmonary vasoconstriction both of which leading to ventilation perfusion mismatch. This was seen

with rapid infusion over 4 hrs and was not observed when the infusion was given over 16-24 hrs. Studies in presurfactant era showed an association of early LE with CLD. Cochrane review found no significant incidence in CLD with early initiation of lipids (< 5 days)

**Effect on free bilirubin:**
There is a concern that free fatty acids released during lipid metabolism can displace bilirubin from albumin binding sites and increasing the risk of bilirubin encephalopathy. Hence in neonates with severe unconjugated hyperbilirubinemia, it is advisable to follow FFA/albumin molar ratio and adjust the dose LE to keep the ratio<6.

**Hepatic Effects:**
Prolonged use can lead to PNALD (parenteral nutrition associated liver disease), manifested by elevated bilirubin and possibility to hepatic failure. They may be due to phytosterols derived from soy oils which has led to interest in study of fish oil based lipid emulsions in attempt to reduce PNALD.

Thrombocytopenia may be due to prolonged administration of soy based oils.

Peroxide formation due to excess of carbon double bonds in soy based oils. These peroxides alter arachidonic acid metabolism or form free radicals leading to damage of plasma membrane free radicals have also been implicated to have a role in CLD, ROP and NEC. The peroxidation can be reduced by infusing along with multivitamin preparation through dark tubing and protecting them from ambient and phototherapy lights.

**Effect on Immune function**
Typical soy bean oil has been reported to lead to impaired bacterial clearance and chemotaxis, leading to Coagulase negative staphylococcus and M.furfur infections.

**Electrolytes, Minerals, Trace Elements and Vitamins**

Sodium is low in the first few days and may not be needed until about 3 days because of the expected free water diuresis. It is however necessary to measure the sodium and water balance.2-4meq/kg/day of sodium is usually added after diuresis which may be more in the ELBW due to their large renal sodium losses.
Chloride should never be less than 1meq /kg / day after addition of electrolytes in parenteral nutrition and all chloride should not be omitted when sodium bicarbonate is given to correct acidosis.

Potassium requirement is also low in the first few days and until renal functions are clearly established .2-3meq/kg/day are usually adequate to maintain normal levels.

Calcium and phosphorous addition remains a challenge due to their limited solubility and precipitation. Intake of 60-80 mg/kg/day of elemental calcium and 48-60 mg/kg/day of phosphorus are recommended for preterm babies receiving parenteral nutrition with a calcium phosphorous ratio of 1.7:1 by weight. The solubility can be improved by addition of cysteine to the parenteral nutrition.

Magnesium is also a necessary nutrition and should be supplied at 3-7.2mg/kg/day.

**The recommended parenteral intake of trace elements**
There is consensus on early parenteral zinc supplementation (250mgm/kg/day in term neonates and 400mgm/kg/day for preterm infants. Other trace elements are not needed until two weeks of life. Selenium is added after 2 weeks of age.

In infants with cholestasis copper and manganese should be discontinued .Chromium and selenium should be used in caution in suspected renal dysfunction. Iron is recommended only if the preterm neonates are on exclusive parenteral nutrition for more than 2 months. Currently IV trace elements are not available in India.

**Recommended Parenteral Intake of Trace Elements for Term and Preterm Infants**

| Trace Element | Term (µg/kg/day) | Preterm (µg/kg/day) |
|---|---|---|
| Chromium | 0.20 | 0.2 |
| Copper | 20 | 20 |
| Iron | — | — |
| Fluoride | — | — |
| Iodide | 1 | 1 |
| Manganese | 1 | 1 |
| Molybdenum | 0.25 | 0.25 |
| Selenium | 2 | 2 |
| Zinc | 250 | 400 |

**Vitamins**

Paediatric designed MVI are not available in India. The adult MVI preparation may be used at a dose of 1ml/kg/day. They are deficient on Vit K, Biotin,B12 and folic acid hence warranting a weekly dose of Vit K 0.5-1ml/kg I.M and Vit B12 10 micro grams/kg I.M.The risk of vitamin peroxidation may be reduced by adding them to Lipid emulsion rather Amino acids.

| | Term (daily dose) | | Preterm (dose/kg/day) | |
|---|---|---|---|---|
| **Vitamin** | **Recommended** | **MVI-Pediatric (1 vial: 5 mL)** | **Recommended** | **MVI-Pediatric (40% of vial:2 mL/kg/day)** |
| **Fat soluble** | | | | |
| Vitamin A (IU) | 2300 | 2300 | 1640 | 920 |
| Vitamin D (IU) | 400 | 400 | 160 | 160 |
| Vitamin E (IU) | 7 | 7 | 2.8 | — |
| Vitamin K (µg) | 200 | 200 | 80 | 80 |
| **Water soluble** | | | | |
| Vitamin B6 (µg) | 1000 | 1000 | 180 | 400 |
| Vitamin B12 (µg) | 1 | 1 | 0.3 | 0.4 |
| Vitamin C (mg) | 80 | 80 | 25 | 32 |
| Biotin (µg) | 20 | 20 | 6 | 8 |
| Folic acid (µg) | 140 | 140 | 56 | 56 |
| Niacin (mg) | 17 | 17 | 6.8 | 6.8 |
| Pantothenate (mg) | 5 | 5 | 2 | 2 |
| Riboflavin (µg) | 1400 | 1400 | 150 | 560 |
| Thiamin (µg) | 1200 | 1200 | 350 | 480 |

**Use of parenteral nutrition -a practical approach**

EUGR extra uterine growth retardation defined as the discharge weight less than the 10$^{th}$ percentile, is common after very preterm birth and is associated with adverse neurological and metabolic outcomes. Aggressive parenteral nutrition is defined as parenteral nutrition commenced with hours of birth and graded up early to meet recommended intakes with aim of meeting foetal accretion rates, growth and body composition

The preceding portion has discussed the scientific basis for recommendations regarding provision of parenteral nutrition. The following discussion will present a practical approach to the administration of parenteral nutrition with special emphasis on ELBW neonates.

**Suggested Daily Parenteral Intakes for ELBW and VLBW Infants**

| Component | ELBW | | | VLBW | | |
|---|---|---|---|---|---|---|
| (units/kg/day | Day 0 | Transition | Growing | Day 0 | Transition | Growing |
| Energy (kcal) | 40 – 50 | 70 – 80 | 100 – 110 | 40 -50 | 60 -70 | 90 -100 |
| Protein (gm) | 2-3 | 3.5 | 3.5 -4 | 2-3 | 3.0 -3.5 | 3.0 -3.5 |
| Glucose (gm) | 7 – 10 | 8 – 15 | 13 – 17 | 7 – 10 | 8 – 15 | 13 - 17 |
| Fat (gm) | 1 | 1 – 3 | 3 – 4 | 1 | 1 – 3 | 3 |
| Na (mEq) | 0 – 1 | 2 – 4 | 3 – 7 | 0 – 1 | 2 – 4 | 3 - 5 |
| Pottasium (mEq) | 0 | 0 – 2 | 2 – 3 | 0 | 0 – 2 | 2 - 3 |
| Chloride (mEq) | 0 – 1 | 2 – 4 | 3 – 7 | 0 – 1 | 2 – 4 | 3 - 7 |
| Calcium (mg) | 20 – 60 | 60 | 60 – 80 | 20 – 60 | 60 | 60 - 80 |
| Phosphorus (mg) | 0 | 45 – 60 | 45 – 60 | 0 | 45 – 60 | 45 - 60 |
| Magnesium (mg) | 0 | 3 – 7.2 | 3 – 7.2 | 0 | 3 – 7.2 | 3 – 7.2 |

We recommend starting 3gm/kg/day amino acids on day one of life .once amino acids are initiated advancement can be made to 3.5gm/kg/day on day 2.

Glucose to be supplied in a quantity to maintain normal plasma glucose concentration. The needs in ELBW are usually between 6-8mg/kg/min and can be escalated further in the absence of hyperglycemia.

Lipid to started within first 24 hrs of life 1gm/kg/day and advance by 0.5-1gm/kg/day to a usual maximum of 3gm/kg/day while maintaining serum triglyceride levels< 200mg/dl. Given the advantages 20% lipid emulsion is preferred over 10%.

Caloric goal during parenteral nutrition is less than with enteral feeds. To achieve optimal protein retention approximately 70-80kcal/kg/day is a reasonable goal. The non-protein balance between carbohydrate and lipid should be approximately 60:40.

**Caloric Value of Parenteral Nutrition Solutions**

| Composition | kcal/kg/day | % of Nonprotein Calories |
|---|---|---|
| **Example 1: Total Fluids at 110 mL/kg/day** | | |
| 10% dextrose | 37 | 55 |
| 3 g/kg/day lipid | 30 | 45 |
| 3.5 g/kg/day amino acids | 14 | — |
| Total | 81 | — |
| **Example 2: Total Fluids at 80 mL/kg/day** | | |
| 12.5% dextrose | 34 | 53 |
| 3 g/kg/day lipid | 30 | 47 |
| 3.5 g/kg/day amino acids | 14 | — |
| Total | 78 | — |
| **Example 3: Total Fluids at 140 mL/kg/day** | | |
| 12.5% dextrose | 60 | 67 |
| 3 g/kg/day lipid | 30 | 33 |
| 3.5 g/kg/day amino acids | 14 | — |
| Total | 104 | — |

**Route of administration of parenteral nutrition**

Central venous catheter allows the use of more concentrated solution but incurs greater risk of infections. It should be considered when glucose concentration is more than 12.5% or osmolality of the solution is more than 900mOsm/.Some complications associated with central catheter are extravasation, phrenic nerve injury, chylothorax, liver erosion, pleural effusion.

Peripheral parenteral nutrition is also practised but often faces complications like extravasation and thrombophlebitis. It is often used when central venous access is difficult, recurrent central venous catheter associated sepsis, thrombocytopenia or in situation when it is required for a short term. The conflicting recommendations from various organisation continue complicate the literature on peripheral parenteral nutrition and a need for rational study exists

**Monitoring during parenteral nutrition.**

There is paucity of data related to monitoring laboratory tests during parenteral nutrition. A suggested monitoring is given below. All these tests may not be appropriate in ELBW due to constraints of sampling

**Suggested Monitoring During Parenteral Nutrition**

| Parameter | Frequency |
|---|---|
| Weight | Daily |
| Length and OFC | Weekly |
| Serum glucose | 1×/shift during week 1, then daily |
| Serum Na, K, Cl, BUN, Ca, | 2–3×/week during week 1, then |
| P, Mg, hematocrit | weekly |
| Alkaline phosphatase, ALT - | Weekly |
| (SGPT), GGT, fractionated Bilirubin | |

**Common complications encountered during parenteral nutrition**

Catheter related infections or extravasation
Hyperglycemia
Parenteral nutrition associated liver disease
Trace element deficiency selenium zinc copper, chromium, manganese and molybdenum.
Infections
Metabolic bone disease

**Metabolic acidosis, azotaemia, hyperammonemia**

Weaning of parenteral nutrition
The use of parenteral nutrition should be accompanied by early initiation of enteral feeds .Parenteral nutrition is continued until enteral nutrition are well established and providing 100-110 kcal/kg/day .When enteral nutrition are providing 50% of the total intake ,vitamins , calcium, phosphorus, magnesium and proteins in parenteral nutrition are discontinued. Parenteral nutrition is discontinued when 2/3$^{rd}$ of the calorie requirement is met by enteral feeding.

**Future directions**
Preterm infants require more aggressive nutrition hence specialized specific programs for their parenteral nutrition should exist in all Neonatal units.

RCT evaluation of high parenteral protein in achieving lean muscle mass and reducing adiposity should be evaluated.

**Future research:** To address the optimal quality of nutrition. The balance between short and long term benefits and risk of rapid catch up growth .

**REFERENCES**


1. Brenda B. Poindexter and Scott C. Denne: AVERY'S Diseases of the newborn 9$^{th}$ ed: Parenteral Nutrition, 963-971, 2012.
2. Bauer J, Maier K, Hellstern G, et al: Longitudinal evaluation of energy expenditure in preterm infants with birth weight less than 1000 g, Br J Nutr 89;533-537, 2003.
3. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al: Early insulin therapy in very-low-birth-weight infants, N Eng J Med 359: 1873-1884,2008.
4. Clark RH, Thomas P, Peabody J: Extrauterine growth restriction remains a serious problem in prematurely born neonates, pediatrics 111: 986-990, 2003.

5. Fanaroff AA, Stoll BJ, Wright LL, et al: Trends in neonatal morbidity and mortality for very low birth weight infants, Am J Obstet Gynecol 196:147, 2007.
6. Simmer K, Rao SC: Early introduction of lipids to parenterally -fed preterm infants, Cocbrane Database Syst Rev 2: CD005256, 2005.
7. Thureen PJ, Melara D, Fennessery PV, et al: Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period, Pediatr Res 53:24-32, 2003.
8. Torine IJ, Denne SC, Wright -Coltart S, et al: Effect of late-onset sepsis on energy expenditure in extremely premature infants, pediatr Res 61:600-603, 2007.

# Forthcoming Attractions

## IAP NEONATOLOGY CHAPTER SYMPOSIUM
## PEDICON 2016

| | | |
|---|---|---|
| **Dates** | **:** | **23 Jan, 2015, Hall 6, TIME: 08:30 am to 9:45 am** |
| 15 min | : | Lecture 1= Golden Hour Care in Delivery Room Dr Sanjay Wazir, Gurgaon |
| 15 min | : | Lecture 2= Best practice guidelines for Jaundice management<br>Dr Naveen Bajaj, Ludhiana |
| 45 min | : | Panel Discussion |
| Topic | : | Small babies – Big dreams Challenges in care of VLBW |
| Moderator | : | Dr Sandeep Kadam, Pune |
| Panelist | : | Dr Rajesh Kumar (Ranchi), Dr Nalinikant Panigrahi (Hyderabad),<br>Dr Arjit Mohapatra (Bhuvaneshwar), Dr Binu Ninan (Chennai) |
| Chairperson | : | Dr Rhishikesh Thakre |

**Book Release**
**During PEDICON 2016**

- **Atlas & Synopsis of Neonatology**
- **Protocols in Neonotology**

# PROCEEDINGS OF IAP NEOCON 2015 MUMBAI

## 8th National Conference of IAP Neonatology Chapter

**Inaugural Speech**

It is indeed a matter of pride & privilege to have you all here today for this unique conference. When my team took over in Jan this year we placed priority on "science first" as our moto. The details of the work done is included in the Secretary's report.

With this theme in mind we have for the first time in this conference, 4 organisations under one umbrella, holding hands together, for the cause of the newborn, giving it a big boost. All 6 pre conference workshops including the nursing wshop saw all places being taken up. The scientific program has best of minds, national and international, together, to give us an academic feast. We received more than 100 scientific papers/posters, a huge tussle for the Gold Medal award papers, with record submissions for the IAP Neocon. The IAP Neonatology Chapter continues to advocate, support zonal, single theme workshops, every year. This year we had 4 National workshops across the country which had record attendance. All workshops are supported by an Academic grant by the Chapter. The fellowship training program, the flagship of IAP Neonatology Chapter, now completing a decade, is now reaching 60 centers across the country. We continue to keep our promise of one publication per year. After the Manual of Neonatology, we released the Handbook of Newborn nursing, a first of its kind in India dealing with common and uncommon but practical aspects of newborn nursing.

This year we are releasing the Color Atlas of Neonatology. The next year's publication of Protocols in Neonatology shall be released during the Pedicon in Jan 2016 at Hyderabad.
All this was possible thanks to team efforts of all the office bearers and the support of all the executive board members. My special thanks to Dr Rajan Pejaver, our immediate past Chairperson, Dr Sanjay Wazir/ Naveen Bajaj, Nand kishor Kabra, without which all these efforts would not have seen the light of the day. My sincere thanks to each of you for your immense contribution to the success of this conference. We seek your support in all the future endeavors for the cause of the newborn.
Thank you so much.

**Dr. Rhishikesh Thakre**
Chairperson

**CONFERENCE REPORT**

The team IAPNEOCON 2015/ MAHA NEOCON 2015 / NICE III expresses profound gratitude and thanks to Office Bearers of IAP Neonatology Chapter, Maharashtra State Chapter of NNF, IAP Mumbai Branch, Neonatology Forum Mumbai, Central IAP and NNF Office Bearers, Surya Mother and Child Super-speciality Hospital, all the members of IAP/NNF and delegates for being a part this scientific event. It was our utmost privilege, pride and honor to welcome you all to the unique joint conference: 8th National Conference of IAP Neonatology Chapter – IAPNEOCON 2015, XIIth Annual conference of Maharashtra State Chapter of NNF and IIIrd Annual Conference of Neonatology Forum Mumbai; held on November 6th to 8th 2015 in the City of Mumbai, also known as the Financial Capital of India. We proudly share that this was after many years the city of Mumbai has witnessed a prestigious national event in the field of Neonatology. We would like to thank all of you who have travelled from all over the country and abroad to attend this conference and contributed to its grand success by their sheer presence. This conference unique and

was jointly hosted by 5 organizations, venue was a Hotel Sahara Star, a five star located near Domestic Airport. Our organizing team worked hard with meticulous planning and commitment for almost 6 months. The scientific program with the Theme – "Care of Newborns- An Evidence Based Journey" was designed to address issues related to the common neonatal problems.

On 6th November, we started off in the morning with six parallel workshops. All the workshops were well attended and feedback from delegates was awesomely positive.

1. Non invasive ventilation – LTMG Medical College and Hospital, Sion
2. Point of Care USG and ECHO – Wadia Maternity and Children Hospital, Parel
3. Advanced NRP – TN Medical College and BYL Nair Hospital, Mumbai Central
4. Interpreting Labs – Seth GS Medical College and KEM Hospital, Parel
5. Neonatal Procedures – Sir H N Reliance Foundation Hospital, Girgaon
6. Advanced Ventilation – Surya Mother and Childcare Hospital, Santacruz
7. Neonatal Nursing - Surya Mother and Childcare Hospital, Santacruz

A special mention - Neonatal nursing workshop was attended by 115 nursing colleagues. It was inaugurated by Prof Dr Simin Irani. The workshop was kept as interactive platform, with 6 workstations on – Infection Control in NICU, Developmentally supportive care, Care of newborn on ventilator and CPAP, Thermoregulation and KMC, Feeding of LBW and preterm and care of newborn in delivery room and postnatal ward –"Danger Signals" . Nursing colleagues felt that this was better way to learn than listening to didactic lectures.

On the 2nd day, 7th November the main conference began precisely at 9AM as scheduled in Sapphire Hall at Hotel Sahara Star. The total delegate/faculty attendance was 540. For a delegate it was a devoted opportunity to interact with the best experts in the field of neonatology and to benefit from their knowledge and experience. The conference talks were planned with an intention of putting science first.

The welcome address was given by Dr Bhupendra Avasthi, Organising Chairperson of the conference. The conference was formally inaugurated on 7th November with lighting of the lamp by an ex-24 week premature NICU graduate Rushil Pant and his parents in presence of office bearer of the organizations: IAP Neonatology chapter, Maharashtra State Chapter of NNF, Office bearer of Central IAP and NNF, Mumbai IAP Branch and Neonatology Forum Mumbai. Dr Rhishikesh Thakre, Chairperson of IAP Neonatology Chapter briefly outlined the future plans for the chapter. The Hon. Secretary of Chapter Dr Sanjay Wazir narrated the accomplishment and growth of the chapter in last one year. Dr Pramod Jog – (IAP President 2016), Dr Ajay Gambhir (President NNF), Dr Ruchi Nanavati (President Maharashtra State Chapter of NNF) later addressed the delegates and complimented the organizing team. Dr Pramod Jog and Dr Ajay Gambhir honored the Neonatology Fellowship examination toppers.

A large number of papers were submitted for presentations, 29 papers were submitted in "Gold Medal Award Paper Category", 46 papers in free paper Category and many more in Poster category. Out of the 29 papers submitted for Gold Medal Award Paper category, 3 best papers were selected for platform presentation. There were cash awards of Rs 20,000/ -, Rs 15,000/ -, Rs 10,000/- for the 1st, 2nd and 3rd best papers. Gold medal was awarded to Dr Amruta Pendse from Seth G S Medical College and KEM Hospital Mumbai. 2nd Prize was awarded to Dr Akshay Mehta from Govt Medical College, Chandigarh, Punjab. The third prize was awarded to Dr Tejopratap Oleti from Fernandez Hospital, Hyderabad. In free paper category 14 delegates got opportunity to

present their research. About 100 delegates presented their research in poster form. The first prize (Rs 5000/-) for best poster award went to Dr Shridevi Bisanalli of St John's Medical College and Hospital, Bangalore.
Dr Vinod Paul, Professor and Head, Neonatology, AIIMS, New Delhi, delivered prestigious Dr Simin F Irani Oration. He put his thoughts on improving neonatal care in India "Towards Universal Health Coverage in India". Dr Pramod Jog made everyone laugh a loud and rethink about life by talking on "How to stop worrying and start living".

On the evening of 7th November, there was a cultural program. The program started with stand in comedy on cricket by Mr. Vikram Sathe. This was followed by nonstop comedy show by Sudesh and Krishna (Comedy Circus Fame). The icing on cake was scintillating signing and music program by famous singer Shaan and team. The delegates got to sing, dance and relax in this program. It was wonderful to see young generation and senior citizens enjoying this program alike.
On November 7th and 8th, very critical and evidence based talks were given by faculties from abroad Dr Barbara Schmidt, Dr Haresh Kirpalani, Dr Sanjay Patole, Dr Ganesh Srinivasan, Dr Shripada Rao, Dr Kiran Kumar. In his talk Prof Dr Ashok Deorari emphasized on importance of "Apps on Smart Phones – a training tool on Newborn Health". Senior teacher of teacher, Dr P S Shankar, sensitized delegates on: "How to do research in clinical practice?"

Dr BB Jha's oration delivered by well renowned neonatologist, teacher par excellence, former Dean of LTMG Medical College, founder of first milk bank in India, Dr Armida Fernandez. It was attended not only by all delegates but also by the faculty members. She talked on her thoughts on "Saving newborn lives – a search for solutions".

The delegates got enriched with different symposia, deliberations and debates delivered by renowned neonatologist of the country. The Case based Panel discussion on Neonatal Jaundice and Challenges in Care of ELBW infants were very interactive sessions. The conference was concluded on the evening of 8th November, 2015 with the valedictory function. We finished the conference as scheduled in time!

We would like to convey special thanks to all the faculty members who have travelled far distances and whose presence made it possible to deliver excellent science of neonatology. We are grateful to all delegates whose presence and participation made the conference a grand success. We are also grateful to the Office Bearers of IAP Neonatology Chapter, Maharashtra State Chapter of NNF, IAP Mumbai Branch, Neonatology Forum Mumbai, Central IAP and NNF Office Bearers, and the staff of Surya Mother and Child Super-speciality Hospital in helping us conducting this event smoothly. One person who needs special mention here is Dr Rhishikesh Thakre, who stood behind us as a strong pillar of strength. The spontaneous, overwhelmingly encouraging and enthusiastically affirmative response by faculties, delegates and sponsors by phone, SMS. Email, WhatsApp brought us deep sense of satisfaction. It will be forever treasured in our memory. We look back the year of 2015 with nostalgia to all the excitement and anticipation we experienced during the preparation for this long awaited three days of the IAPNEOCON 2015.

**Dr Nandkishor S Kabra**
(Organising Secretary)

**Dr Bhupendra S Avasthi**
(Organising Chairperson)
For Organising Team IAP NEOCON 2015

# IAP NEOCON 2015 Award Papers

**Gold Medal Winner**

## To compare transcutaneous bilirubin with total serum bilirubin in preterm neonates receiving phototherapy.

**Amruta Pendse, Bonny Jasani, Prof Ruchi Nanavati, Nandkishor Kabra**
Department of Neonatology, KEM Hospital, Parel, Mumbai – 400012.
E-mail : ams9586@gmail.com

**Introduction**
Phototherapy (PT) has become the standard of care for all neonates with severe hyperbilirubinemia. Specific evidence based guidelines are available for initiation of phototherapy. However, there is variability among many units and organisations on threshold for stoppage of phototherapy.

**Methods and results**
This study is designed to determine the incidence and magnitude of post-phototherapy bilirubin rebound in neonates needing phototherapy and to identify the cut off TSB to stop phototherapy for prevention of rebound hyperbilirubinemia. All the neonates born ⩾ 35 weeks of gestation and required phototherapy for 24 hours or more for hyperbilirubinemia are considered eligible for the study. They received phototherapy according to American academy of paediatrics age and risk specific guidelines. A total of 129 neonates were included in the study. Of the 129 neonates enrolled, 66 and 63 neonates were randomized to early and late groups respectively. In Infants randomized to early group, PT was stopped immediately. In infants randomized to late group, PT was continued till two consecutive TSB values (at 12 hour intervals) were less than <12mg/dl. They were evaluated for rebound hyperbilirubinemia at 12 hrs and 36 hrs after stoppage of phototherapy. The mean birth weight of the study population was 2908 (467) grams where as the mean gestational age was 37.6 (1.32) weeks. The mean admission weight and the mean age at enrolment were 2710 (443) grams and 87 (41) hours afer birth respectively. The mean TSB at admission (starting of phototherapy) was 16.8 (± 1.8) mg/dl and mean TSB at randomization 11 (± 0.63) mg/dl. None of the neonates had rebound hyperbilirubinemia. There was no difference in rate of rise of bilirubin among the groups {1(0.65 to 1.65) vs. 1.2 (0.35 to 2.45) mg/dL; p=o.52}.

**Conclusion**
The incidence of rebound hyperbilirubinemia is non-existent when phototherapy is stopped at a single TSB value <12mg/dl for all term and late preterm infants with severe jaundice.

**INTRODUCTION**
The incidence of neonatal hyperbilirubinemia is between 30-60% in full-term neonates and nearly 100% in preterm neonates. [1] Preterm neonates are a unique population who are susceptible to higher risk of kernicterus at lower bilirubin values as well as the adverse effects of frequent blood samplings. Therefore testing their level of jaundice with a non-invasive method is extremely beneficial. TcB testing is a non-invasive technique with the advantages being instantaneous results and avoidance of repeated TSB testing. [2] Evidence has demonstrated a linear correlation of TcB with TSB in preterm neonates. [3, 4] However, the use of TcB after the initiation of PT can give ambiguous results as PT is known to bleach the skin. [5] Few studies have been done to assess the accuracy of TcB values after starting PT in term neonates. Juster-Reicher [6] et al showed a good correlation between TCB and TSB 8 hours after PT in 371 neonates >35 weeks of gestation. Similar correlation was shown by Grabenhenrich J et al. [7] There are limited

studies in a resource poor setting on use of TcB during PT in preterm neonates. [8]

Earlier studies used the older JM 103 device or Bilicheck which is not effective for use in preterm neonates. A newer device JM 105 is currently validated for use in preterm neonates with gestational age as low as 24 weeks.[9] Studies have shown sternum to be a superior site than other sites like forehead, inter-scapular area or abdomen. [10, 11, 12] Hence we decided sternum as the site of choice to be used in our study. We therefore planned to compare TcB with TSB in preterm neonates after initiation of PT over the sternum which is shielded from the PT using the new device JM 105.

**METHODS**

This single center correlational study was conducted in a level III neonatal intensive care unit (NICU) over six months duration from September 2014 to February 2015. The study protocol was approved by institutional ethics committee. Written informed consent was obtained from either of the parents or guardian prior to enrollment in the study.

**Inclusion Criteria**:

Preterm neonates >28 weeks gestation having clinically detectable jaundice were enrolled in the study.

**Exclusion Criteria**:

1. Neonates with conjugated (direct) hyperbilirubinemia clinically detected by high colored urine, clay colored stools
2. Neonates with poor perfusion (capillary refill >3 seconds or low blood pressure measurements)

**Methods:**

Birth weight was recorded in labour room within the first hour of life on a machine with accuracy of $\pm$ 2 grams. Gestational age was determined using first trimester ultrasound. Parents or guardian were approached if the neonate was eligible to be included in the study however the enrollment was done at the onset of clinical jaundice after obtaining informed consent.

The neonates were admitted in the NICU and managed according to the standard guidelines. They were assessed daily in bright daylight for possible development of jaundice. Serum bilirubin was estimated by Diazo method. At the same time, the investigator measured the TcB on sternum using Drager jaundice meter JM 105. Average of 3 consecutive readings was recorded in mg/dl. The device was calibrated before usage according to the manufacturer's recommendations and daily quality control measures were performed.

PT was instituted if the TSB fulfilled the criteria as per AAP 2004 charts and sliding scale for preterm neonates. [13] PT units (CFL or LED) were used during the study. Simultaneously a small patch of skin over the sternum was shielded using a circular barrier (1cm in diameter) made from a maxicor electrode covered with aluminium foil and a transparent semipermeable dressing. (The use of aluminium foil has been proven in the previous study to protect the skin from phototherapy). [14] A repeat TcB assessment was done at 6-12 hours depending on the severity of jaundice after the initiation of PT on the shielded skin area. A simultaneous TSB was sent for lab estimation. Blood collections for serum bilirubin estimation were done every 12 hourly in babies with no risk factors and 6 hourly in those with risk factors as per our NICU protocol. No additional blood investigations were done for the purpose of the study.

PT was discontinued if the level of TSB falls to 1-2 mg/dl lower than the recommended range to initiate the same. Care of the baby under PT followed standard NICU protocols. The skin integrity was assessed with the Neonatal skin condition score (NSCS) for all the enrolled neonates before and after the application of the skin patch. [15] (Refer to Appendix1)

**Outcomes:**

**Primary Outcome**

To compare TcB with TSB in preterm neonates after initiation of phototherapy.

**Secondary Outcome**

To compare TcB with TSB in 28- 32 and >32 weeks gestational age after initiation of phototherapy.

To compare TcB with TSB at <72 hours versus >72 hours of postnatal age.

**Sample Size:**

Sample size was calculated by using formula for correlation coefficient using z transformation. From previous studies in literature the correlation coefficient between TcB and TSB measurement performed at the same time varies between r = 0.5 to 0.9. Assuming alpha error of 0.05, beta error of 0.2 (power =0.8) and r value of 0.5, estimated sample size is 29.

**Statistical Analysis:**

A scatter plot has been used to depict the relationship between TcB and TSB measurement performed at the same time. Correlation coefficients are calculated by using Pearson correlation (parametric test) or Spearman rank correlation (nonparametric test) on the basis of normal/ non-normal distribution of data as appropriate. A p value of <0.05 has been considered as statistically significant.

**RESULTS**

We included a total of 30 preterm neonates in our study. The baseline characteristics of enrolled neonates are shown in Table 1. TCB estimated at sternum correlated significantly with TSB prior to initiation of phototherapy (correlation coefficient 0.903, P = 0.0001). During phototherapy TCB over the shielded area of sternum continues to have a positive correlation with TSB levels (correlation coefficient of 0.918, P = 0.0001) (Table 2) (Figure 1).

We also found that the TcB measurements taken in babies 28-32 weeks of gestation were better correlated with TSB than those taken in neonates >32 weeks. (Table 3)

We compared the TcB with TSB in babies according to their postnatal age. The correlation coefficient was better for neonates <72 hours old than those >72 hours of age. (Table 3)

None of the neonates had any evidence of loss of skin integrity before or after the application of skin patch as assessed by the NSCS. [15]

**DISCUSSION**

Our study showed a positive correlation between TcB and TSB in preterm neonates prior to initiation and after starting phototherapy. There are few studies which have compared TcB and TSB in preterm neonates after the initiation of PT.

Jangaard et al [16] compared a total of 65 healthy term, ill term and preterm neonates receiving phototherapy. TcB measurements were accurate for measuring bilirubin levels in term jaundiced neonates not receiving PT and in those receiving PT if an area of the skin was patched. However, it was not sensitive in preterm neonates.

In a larger study by Zecca et al [17] 364 neonates including 253 preterm were evaluated for accuracy of TcB measurements during PT. They showed a good agreement between TSB and patched TcB, while unpatched TcB underestimated the serum levels. The difference between patched and unpatched values was significantly lower in preterm than in term neonates (2.8 mg/dl vs. 3.6 mg/dl; p<0.001).

Povaluk et al [14] studied 44 neonates 29 of whom were preterm. They found a good correlation between TSB and TcB taken from the patched areas of skin during PT.

We also found that the TcB measurements taken in babies 28-32 weeks of gestation were

better correlated with TSB than those taken in neonates >32 weeks. This difference could be explained by the skin immaturity of very preterm neonates. There are no studies till date which have evaluated the effect of gestational age on TcB measurements after initiation of PT in preterm neonates.
We compared the TcB with TSB in babies according to their postnatal age. The correlation coefficient was better for neonates <72 hours old than those >72 hours of age. We hypothesize that after 72 hours of age as the skin pigmentation increases, correlation begins to decline. However, correlation still stays >80%.

In our study, overall there was a tendency to overestimate TSB which is in agreement with the study done by Sanpavat et al. [18] They found that in the early postnatal age of 1-4 days, TcB readings overestimated TSB.

We took the TcB measurements after an average of 12-14 hours after initiation of phototherapy. Ozkan et al [5] studied dermal bilirubin kinetics during PT and found that bilirubin migration in the patched skin area occurred between 6 to 12 hours of PT after which it remained stable. Hence recording TcB values 12 hours after initiation of phototherapy was expected to yield reliable results.

Till date Bilicheck and JM 103 are the two most common devices used to evaluate the efficacy of TcB in preterm neonates. Our study shows that JM 105 which is validated for use in preterm neonates [9] is reliable in TcB estimation after initiation of PT.

**Strengths and Limitations:**
None of the neonates in the present study had any evidence of loss of skin integrity before or after the application of skin patch as assessed by the NSCS. [15] Our study therefore proves that using a patched area of skin for TcB measurements is a safe intervention.

The present study has some limitations. Firstly a small sample size. Secondly, comparison with other sites like forehead and inter-scapular area should have been done which have been found reliable in preterm neonates. And lastly, taking serial measurements after the initiation of PT could yield a better estimate which could be helpful for clinicians in guiding decisions regarding continuation of phototherapy.

To conclude, TcB correlates significantly with TSB at the patched sternal site after initiation of PT in preterm neonates.

**Acknowledgements:** The authors thank the Dean, Seth G.S. Medical College and KEM Hospital, Mumbai for permitting them to publish the manuscript.
**Conflict of interest: None to declare**
**Funding : None**
**References on Request**

**Table 1 : Baseline characteristics of study population**

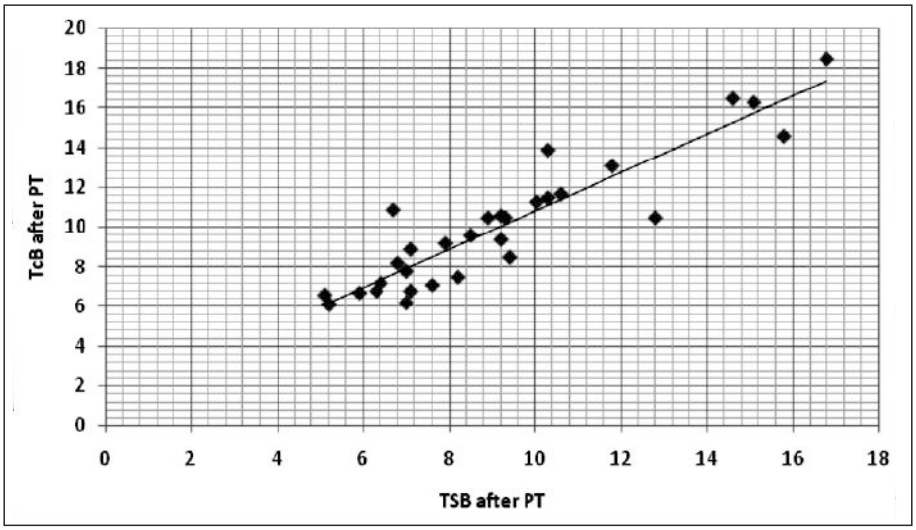
| Baseline characteristics | (n = 30) |
|---|---|
| Birth Weight (grams) | 1680 ± 633.61 |
| Gestational Age (weeks) | 32.93 ± 2.6 |
| Length (cm) | 42.19 ± 5.25 |
| Head circumference (cm) | 29.78 ± 2.45 |
| APGAR at 1 min* | 8 (7-9) |
| APGAR at 5 min* | 9 (8-9) |
| LSCS | 14 (46.7%) |
| SGA | 9 (30%) |
| Male | 13 (43.3%) |
| Age at estimation of bilirubin before PT (hours) | 70.43± 24.93 |
| Average time (hours) of taking TcB after initiation of PT | 12.58 |

**Table 2 : Comparison of TSB with TCB before and during phototherapy**

| Bilirubin | Before Phototherapy | Correlation coefficient** | During Phototherapy | Correlation coefficient** |
|---|---|---|---|---|
| TSB | 12.05 ± 3.49* | 1 | 9.23 ± 3.14 | 1 |
| TcB at sternum | 13.03 ± 3.83* | 0.903 | 10.10 ± 3.30 | 0.918 |

**Table 3 : Correlation of TSB with TcB during phototherapy according to the gestational age and postnatal age:**

| Age (weeks/ hrs) | TcB during phototherapy |
|---|---|
| 28-32 weeks | 0.976 |
| >32 weeks | 0.887 |
| <72 hours | 0.962 |
| >72 hours | 0.826 |




## When to stop phototherapy in neonates with jaundice? - A Randomized Control Trial

**Abstract**

Introduction Phototherapy (PT) has become the standard of care for all neonates with severe hyper-bilirubinemia. Specific evidence based guidelines are available for initiation of phototherapy. However, there is variability among many units and organisations on threshold for stoppage of phototherapy.

**Methods and results**

This study is designed to determine the incidence and magnitude of post-phototherapy bilirubin rebound in neonates needing phototherapy and to identify the cut off TSB to stop phototherapy for prevention of rebound hyperbilirubinemia. All the neonates born ⩾35 weeks of gestation and required phototherapy for 24 hours or more for hyperbilirubinemia are considered eligible for the study. They received phototherapy according to American academy of paediatrics age and risk specific guidelines. A total of 129 neonates were included in the study. Of the 129 neonates enrolled, 66 and 63 neonates were randomized to early and late groups respectively. In Infants randomized to early group, PT was stopped

immediately. In infants randomized to late group, PT was continued till two consecutive TSB values (at 12 hour intervals) were less than <12mg/dl. They were evaluated for rebound hyperbilirubinemia at 12 hrs and 36 hrs after stoppage of phototherapy. The mean birth weight of the study population was 2908 (467) grams where as the mean gestational age was 37.6 (1.32) weeks. The mean admission weight and the mean age at enrolment were 2710 (443) grams and 87 (41) hours afer birth respectively. The mean TSB at admission (starting of phototherapy) was 16.8 (± 1.8) mg/dl and mean TSB at randomization 11 (± 0.63) mg/dl. None of the neonates had rebound hyperbilirubinemia. There was no difference in rate of rise of bilirubin among the groups {1(0.65 to 1.65) vs. 1.2 (0.35 to 2.45) mg/dL; p=o.52}.

**Conclusion**
The incidence of rebound hyperbilirubinemia is non-existent when phototherapy is stopped at a single TSB value <12mg/dl for all term and late preterm infants with severe jaundice.

## To compare transcutaneous bilirubin with total serum bilirubin in preterm neonates receiving phototherapy.


**ABSTRACT**

**Objective:**
Evidence has shown a good correlation between transcutaneous bilirubin (TcB) and total serum bilirubin (TSB) in preterm neonates before initiation of phototherapy (PT). However there is limited data on the reliability of use of TcB after initiation of PT in preterm neonates. Hence the objective of our study was to compare TcB with TSB in preterm neonates after initiation of phototherapy.

**Design:**
Single center correlational study

**Study setting and duration:**
Tertiary care neonatal intensive care unit for 6 months

**Methods:**
30 preterm neonates (gestational age >28 weeks) having clinically detectable jaundice were enrolled. Jaundice was assessed with TcB and TSB before initiation of PT. A small patch was applied over the sternum. A repeat TcB assessment was done at 6-12 hours after the initiation of PT on the shielded skin area along with simultaneous TSB estimation. Correlation coefficients of TcB with TSB were calculated using Pearson correlation and compared according to gestational age and postnatal age.

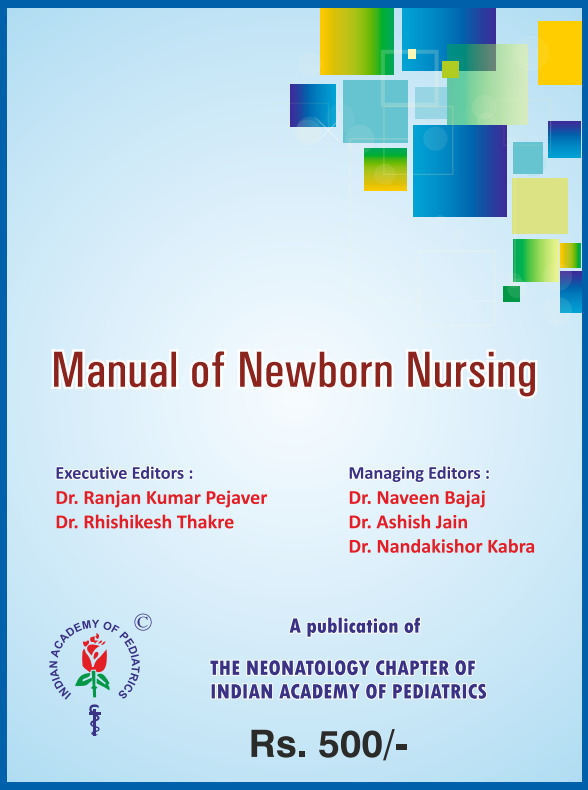
**Results:**
TcB holds a good correlation with TSB both before (r=0.903, p=0.0001) and after initiation of PT. (r=0.918, p=0.0001). Correlation is better for neonates 28-32 weeks gestational age (r=0.976) than >32 weeks (r=0.887). It is also better for lower postnatal age <72h (r=0.962) than >72h (r=0.826).

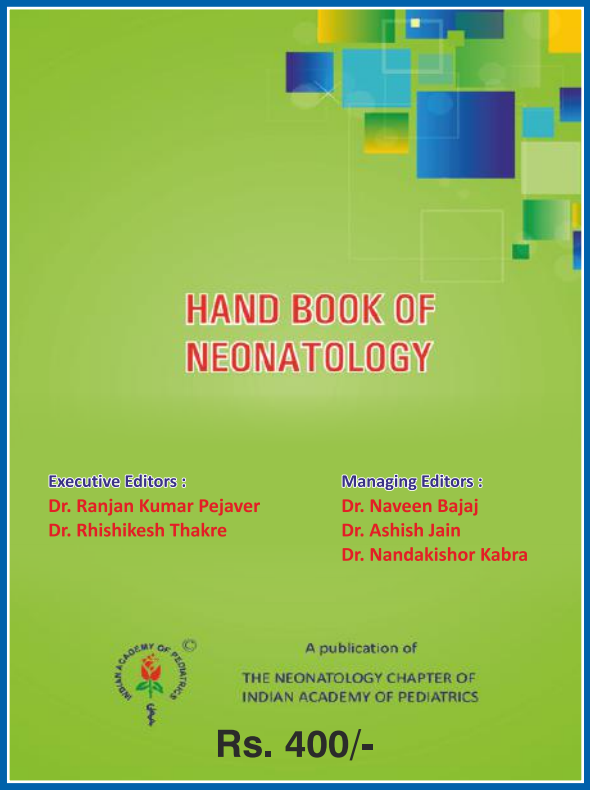
**Conclusion:**
TcB correlates significantly with TSB at the patched sternal site after initiation of PT in preterm neonates.

# IAP NEOCON 2015 MUMBAI








**COMBO OFFER Rs. 750/-**

# THE OFFICIAL PUBLICATIONS OF IAP NEONATOLOGY CHAPTER

**To Purchase Book**
**Visit :- www.iapneochap.org**
**or contact :- Secretary Office**

**Dr. Rhishikesh Thakre**
Neo Clinic 27, Samarth Nagar, Aurangabad - 431 001